Señora
Edna Marcela Ramírez Orozco
Directora de Nuevas Creaciones
Superintendencia de Industria y Comercio
E. S. D.

Referencia: Solicitud de PCT Patente de Invención denominada **COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE UNA SAL DE GLICOPIRROLATO, BUDESONIDA O DIPROPIONATO DE BECLOMETASONA, ETANOL Y 1,1-DIFLUOROETANO (HFA-152A).**

Asunto: Respuesta al Requerimiento No. 16260 del 20 de octubre de 2021.

Expediente No. NC2019/0002556

Juan Carlos Cuesta Quintero, mayor de edad, identificado como aparece al pie de mí firma, obrando en mi calidad de apoderado de **MEXICHEM FLUOR S.A. DE C.V.**, doy respuesta al Oficio No. 16260 del 20 de octubre de 2021, bajo los siguientes términos:

1. DE LA SOLICITUD DE PATENTE

1.1. Título

El examinador objetó el título alegando que no se relaciona con el objeto de la invención. Por consiguiente, se modifica el título como se presenta a continuación:

"COMPOSICIÓN FARMACÉUTICA QUE COMPRENDE UNA SAL DE GLICOPIRROLATO, BUDESONIDA O DIPROPIONATO DE BECLOMETASONA, ETANOL Y 1,1-DIFLUOROETANO (HFA-152A)."

1.2. Reivindicaciones

En respuesta a las objeciones, el Solicitante modifica las reivindicaciones las cuales se pueden evidenciar en el documento adjunto de las reivindicaciones en control de cambios y que encuentran base en la descripción.

De igual forma, se destaca que la reivindicación 1 se ha modificado: - eliminando los términos "al

menos uno” y “al menos”; además se indica que del 90 al 100 % en peso del componente propulsor es HFA-152a (en la página 7, líneas 16 a 18 y en la reivindicación original 19 de la solicitud PCT publicada, se puede encontrar apoyo para el límite superior del 100 % en peso de la cantidad de HFA-152a en el componente propulsor).

Además, se cita el etanol como componente (se puede encontrar apoyo para esta modificación en las reivindicaciones 20 y 21 actuales, en la página 8, líneas 6 a 16 y en las reivindicaciones originales 24 y 25 de la solicitud PCT publicada) y por último se define que la composición farmacéutica es una solución (el apoyo a esta enmienda se puede encontrar en la presente reivindicación 26, en la página 5, líneas 32 a 35 y en la reivindicación original 36 de la solicitud PCT publicada).

Ahora bien, el examinador objetó el uso del término "al menos" en las reivindicaciones 1, 6 a 10, 13, 14 y 17 a 19. Este término se eliminó de las reivindicaciones modificadas adjuntas. En consecuencia, la objeción está superada.

Asimismo, el examinador ha objetado la reivindicación 18 por contener una repetición indebida. Hemos enmendado la reivindicación 18 eliminando las palabras "que comprende al menos un compuesto tensioactivo". En consecuencia, la objeción se supera.
Finalmente, el examinador ha objetado las reivindicaciones 27 a 30 indicando que un envase no debe caracterizarse por la composición que contiene. Hemos eliminado las reivindicaciones 27 a 30. En consecuencia, la objeción se supera.

2. EXAMEN DE PATENTABILIDAD

2.1. Nivel inventivo

El examinador ha mantenido su objeción de que las reivindicaciones carecen de actividad inventiva sobre WO 2012/110770 (D1) y WO 2007/121913 (D2). Discrepamos respetuosamente con el examinador por los siguientes motivos:

El examinador opina que D1 representa el estado de la técnica más cercano y utiliza D1 como punto de partida para rechazar las reivindicaciones por obviedad/falta de actividad inventiva. Afirma que D1 describe una composición que comprende una sal de glicopirrolato, un corticosteroide y 1,1-difluoroetano (HFA-152a), pero no describe los corticosteroides budesonida y dipropionato de beclometasona. Luego recurre a D2 para una descripción de budesonida y dipropionato de beclometasona y concluye que sería obvio usar la budesonida y el dipropionato de beclometasona enseñados en D2 en las composiciones que se describen en D1.

Hemos enmendado la reivindicación 1 que ahora define lo siguiente:

1. Una composición farmacéutica que comprende:

(i) un componente de fármaco que comprende una sal aceptable desde el punto de vista farmacéutico de glicopirrolato, y un corticosteroide seleccionado de budesonida o dipropionato de beclometasona,

(ii) un componente propulsor que comprende entre 90 y 100 % en peso de 1,1-difluoroetano (HFA-152a), y

(iii) etanol,

donde la composición farmacéutica es una solución.

Así, la composición farmacéutica de la nueva reivindicación 1 es una formulación en solución y también incluye etanol.

Por el contrario, D1 evidentemente se refiere a las formulaciones en suspensión. Remitimos al examinador a los ejemplos en D1, todos los cuales estaban relacionados con la preparación de una formulación de suspensión.

Dado que D1 se refiere a las formulaciones en suspensión, consideramos en primer lugar que D1 no sería un punto de partida apropiado para la evaluación de la actividad inventiva de las presentes reivindicaciones. Como un experto en la materia, en galénica en el presente caso, conoce, las propiedades químicas y físicas de las formulaciones en suspensión y las formulaciones en solución son muy diferentes, por lo que las consideraciones técnicas que se aplican al desarrollar una formulación en suspensión son muy diferentes de las que se aplican al desarrollar una formulación en solución. Sin embargo, "*arguendo*", si el experto estuviera motivado para probar la budesonida o el dipropionato de beclometasona en las composiciones que se describen en D1, lo cual cuestionamos, consideramos que no habría llegado a una composición farmacéutica como se reivindica actualmente, ya que las enseñanzas de D1, inevitablemente hubieran dirigido al experto en la materia a preparar una formulación en suspensión y no una formulación en solución como se reivindica actualmente.

Por lo tanto, incluso si el experto en la materia que leyera D1 y D2 se hubiera sentido motivado a probar los corticosteroides descritos en D2 en las composiciones descritas en D1, cosa que afirmamos que no haría, no hay absolutamente ninguna enseñanza en D1 que hubiera motivado y llevado al experto en la materia: - (a) incorporar los corticosteroides de D2 en una formulación de aerosol junto con un propulsor y suficiente etanol para formar una formulación de solución y (b) seleccionar HFA-152a como propulsor. Preparar una formulación en solución sería completamente contrario a la enseñanza clara en D1 de preparar una formulación en suspensión. En resumen, consideramos que no hay una enseñanza clara en D1 y D2 que hubiera llevado y mucho menos motivado al experto en la materia a desarrollar una formulación en solución farmacéutica como se reivindica actualmente.

También nos gustaría reiterar el problema particular que aborda la presente invención.

Se sabe que el bromuro de glicopirronio muestra una estabilidad química deficiente cuando se mezcla con un propulsor para administrarlo mediante un inhalador de dosis medida. Este problema se explica en la página 3, líneas 14 a 19 de la solicitud PCT publicada y es particularmente agudo con las formulaciones en solución. Es el problema de cómo mejorar la estabilidad química el que aborda la presente invención, y que se resuelto inesperadamente usando HFA-152a como propulsor.

Ni D1 ni D2 contienen enseñanza alguna que pudiera haber llevado al experto a resolver el problema técnico de mejorar la estabilidad química que aborda la presente invención usando HFA-152a como propulsor. De hecho, ambos documentos guardan silencio total sobre el problema que aborda la presente invención y ambos documentos carecen de cualquier enseñanza que hubiera llevado, y mucho menos motivado, a la persona experta a usar HFA-152a con el objetivo de resolver el problema de cómo mejorar la estabilidad química. Simplemente no hay expectativas que se deriven de D1 y D2 de que el uso de HFA-152a como propulsor mejoraría la estabilidad química de una sal de glicopirrolato en comparación con la estabilidad que exhibe en HFA-134a.

A mayor abundamiento consideramos además que las propiedades de HFA-152a habrían incluso disuadido activamente al experto que buscaba preparar una composición de glicopirrolato que tuviera una mayor estabilidad química de probar HFA-152a en las composiciones que contienen glicopirrolato de D1.

La mayor polaridad de los propulsores de hidrofluorocarbono y especialmente del HFA-134a en comparación con los propulsores de clorofluorocarbono que alguna vez se usaron en inhaladores de dosis medidas ha dado lugar a problemas de inestabilidad con fármacos particulares. Como evidencia de esto, adjuntamos una copia del documento WO 01/89480 que en la página 2, líneas 6 a 16 dice lo siguiente (traducción nuestra a continuación):

> “Debido a la mayor polaridad de los propulsores HFA, en particular de HFA 134a (constante dieléctrica D > 9,5), con respecto a los vehículos CFC (D < 2,3), las formulaciones de solución HFA pueden sufrir en mayor medida problemas de estabilidad química con respecto a las correspondientes formulaciones de CFC.

En segundo lugar, la mayor polaridad de los propulsores de hidrofluorocarbono los hace significativamente más higroscópicos, y el problema es particularmente agudo para el propulsor de uso común HFA-134a, que tiene una absorción de agua 6 veces mayor que el otro propulsor de uso común HFA-227ea. Como evidencia de esto, adjuntamos una copia de un folleto técnico producido por Daikin sobre los propelentes HFA-134a y HFA-227ea que en la página 20 dice lo siguiente (traducción nuestra a continuación):

> "Hay una diferencia notable en la solubilidad en agua entre HFA 227 y HFA 134a. Como se muestra en la Fig. 17, la absorción de humedad de HFA 134a es seis veces mayor en comparación con HFA 227 (valores medidos) debido a su mayor polaridad. Por lo tanto, se prefiere HFA 227 para formulaciones que pueden cambiar debido a la absorción de agua durante la vida útil del MDI, por ej., para medicamentos como... o formoterol."

Por lo tanto, los expertos en la técnica entenderán que los propulsores de hidrofluorocarbono son significativamente más polares que los propulsores de clorofluorocarbono que reemplazaron, y que esta polaridad más alta puede dar lugar a problemas de absorción de humedad e inestabilidad, especialmente con el HFA-134a más polar.

Esto nos lleva al propulsor HFA-152a que se utiliza en las composiciones de la presente invención reivindicadas, que es más polar y significativamente más susceptible a la absorción de humedad que incluso el HFA-134a. Como prueba de ello, adjuntamos un artículo publicado en el Journal of Physical Chemistry, 1991, 95, 3860-3866 titulado "*Dipole moments of seven partially halogenated ethane refrigerants"* (Momentos dipolares de siete refrigerantes de etano parcialmente halogenados) junto con un estudio sobre la solubilidad del agua en hidrofluorocarbonos.

El resumen del artículo del Journal of Physical Chemistry registra un momento dipolar de 2,262 para HFA-152a en comparación con un momento dipolar de 2,058 para HFA-134a. Por lo tanto, HFA-152a es más polar que HFA-134a.

El estudio fue producido para ASHRAE (Sociedad Estadounidense de Ingenieros de Calefacción, Refrigeración y Aire Acondicionado), que es una organización por supuesto muy respetada, y se puede encontrar en Water solubility & clathrate hydrates in HFC ... - AHRIwww.ahrinet.org › files › RESEARCH › MCLR-Program. El estudio muestra que HFA-152a tiene una afinidad por el agua mucho mayor que HFA-134a. Nos referimos a las Figuras 6, 11 y 16 en las páginas 23, 28 y 33 y los datos asociados en la Tabla B1 (para HFA-134a) y la Tabla B6 (para HFA-152a) en las páginas 53 y 55.

Por tanto, el experto en la materia sabría que HFA-152a es más polar que HFA-227ea y HFA-134a y da como resultado una mayor absorción de humedad y esperaría que diera como resultado una mayor inestabilidad del fármaco. Como resultado, el experto que buscaba resolver el problema técnico que aborda la presente invención de cómo mejorar la estabilidad química de las composiciones que contienen glicopirrolato no habría contemplado usar HFA-152a como propulsor en lugar de los propulsores convencionales HFA-134a y HFA-227ea que se utilizan en D1.

Además, y contrariamente a esta clara expectativa, los presentes inventores encontraron que la estabilidad química de las composiciones farmacéuticas que comprenden bromuro de

glicopirronio mejora cuando se usa HFA-152a como propulsor en oposición al propulsor HFA-134a usado convencionalmente. Remitimos al examinador al Ejemplo 2 ya los datos presentados en las Tablas 7 y 8 de la presente solicitud.

En conclusión, el uso de HFA-152a como el propulsor con una sal de glicopirrolato trae consigo una serie de beneficios muy reales que no solo son sorprendentes sino que son contrarios a las expectativas y claramente respaldan una actividad inventiva.

En este sentido se desea remarcar por último que la GUÍA PARA EXAMEN DE SOLICITUDES DE PATENTE DE INVENCIÓN Y MODELO DE UTILIDAD, Bogotá D. C., Colombia Enero 2014, página 128, señalan lo siguiente:

> *Si la invención tiene nivel inventivo, significa que tiene una ó más características que implican un avance técnico, comparado con el conocimiento existente.*

Por lo tanto, sostenemos que la presente invención implica un avance técnico y las reivindicaciones presentan actividad inventiva sobre D1 y D2.

En consecuencia y luego de haber presentado los argumentos necesarios y haber realizado las modificaciones pertinentes en el capítulo reivindicatorio de la presente invención, queda evidenciado que la invención cumple con los requisitos de patentabilidad definidos en la Decisión 486 de 2000.

Cordialmente,

Juan Carlos Cuesta Quintero.
C.C. 79.339.809 de Bogotá
T.P. 43.273 del C.S. de la J.

Anexos: Comprobante de pago por modificación voluntaria al capítulo reivindicatorio.
Capitulo reivindicatorio modificado en control de cambios.
Capitulo reivindicatorio modificado en limpio.
The journal of physical chemistry – Dipole Moments of Seven Partially Halogenated Ethane Refrigerants.
Daikin Propellants
Water Solubility and Clathrate Hydrates in HFC Refrigerants and Refrigerant Blends-Cavestri and Schafer
WO0189480A1

REIVINDICACIONES

1. Una composición farmacéutica que comprende:

(i) un componente de fármaco que comprende ~~al menos~~ una sal aceptable desde el punto de vista farmacéutico de glicopirrolato, y ~~al menos~~ un corticosteroide seleccionado de budesonida o~~y~~ dipropionato de beclometasona, ~~y,~~

(ii) un componente propulsor que comprende ~~al menos~~ entre 90 y 100 % en peso de 1,1-difluoroetano (HFA-152a), y

(iii) etanol,

donde la composición farmacéutica es una solución.

2. La composición farmacéutica de acuerdo con la reivindicación 1, en donde la composición contiene menos de 500 ppm de agua en función del peso total de la composición farmacéutica.

3. La composición farmacéutica de acuerdo con la reivindicación 2, en donde la composición contiene más de 0,5 ppm de agua en función del peso total de la composición farmacéutica.

4. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde la composición contiene menos de 1000 ppm de oxígeno en función del peso total de la composición farmacéutica.

5. La composición farmacéutica de acuerdo con la reivindicación 4, en donde la composición contiene más de 0,5 ppm de oxígeno en función del peso total de la composición farmacéutica.

6. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde la ~~al menos una~~ sal aceptable desde el punto de vista farmacéutico de glicopirrolato es bromuro de glicopirronio.

7. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde la ~~al menos una~~ sal aceptable desde el punto de vista farmacéutico de glicopirrolato está en forma micronizada.

8. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde el componente de fármaco comprende adicionalmente ~~al menos~~ un beta-2-agonista de acción prolongada (LABA) seleccionado de formoterol y sus sales farmacéuticamente aceptables.

9. La composición farmacéutica de acuerdo con la reivindicación 8, en donde el ~~al menos un~~ beta-2-agonista de acción prolongada está en forma micronizada.

10. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde el ~~al menos~~ un corticosteroide está en forma micronizada.

11. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde el componente de fármaco comprende de 0,01 a 2,5 % en peso del peso total de la composición farmacéutica.

12. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde el componente de propulsor comprende de 80,0 a 99,99 % en peso del peso total de la composición farmacéutica.

13. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde entre ~~al menos~~ 95 y 100 % en peso del componente propulsor es 1,1-difluoroetano (HFA-152a).

14. La composición farmacéutica de acuerdo con la reivindicación 13, en donde al menos 99 % en peso del componente propulsor es 1,1-difluoroetano (HFA-152a).

15. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 1-12, en donde el componente propulsor es 1,1-difluoroetano (HFA-152a) en su totalidad.

16. La composición farmacéutica de acuerdo con la reivindicación 13 o 14, en donde el componente propulsor contiene de 0,5 a 10 ppm de impurezas insaturadas seleccionadas de fluoruro de vinilo, cloruro de vinilo, fluoruro de vinilideno y compuestos de cloro-fluoroetileno.

17. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde entre ~~al menos~~ 95 y 100 % en peso de la composición consiste en los dos componentes (i) e (ii).

18. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, que comprende además un componente tensioactivo ~~que comprende al menos un compuesto tensioactivo~~.

19. La composición farmacéutica de acuerdo con la reivindicación 18, en donde el componente tensioactivo comprende ~~al menos~~ un compuesto tensioactivo seleccionado de polivinilpirrolidona, tensioactivos de polietilenglicol, ácido oleico y lecitina.

~~20. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, que comprende además un excipiente polar.~~

~~21. La composición farmacéutica de acuerdo con la reivindicación 20, en donde el excipiente polar es etanol.~~

~~22. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 1 a 19, la cual está libre de excipientes polares.~~

~~23. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones~~

~~1 a 19, la cual está libre de etanol.~~

20~~24~~. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores~~1 a 23~~, la cual está libre de estabilizantes ácidos.

~~25. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores en forma de una suspensión.~~

~~26. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 1 a 24 en forma de una solución.~~

~~27. Un recipiente sellado y de aerosol presurizado que contiene una composición farmacéutica de acuerdo con lo reivindicado en cualquiera de las reivindicaciones 1 a 26.~~

~~28. El recipiente de acuerdo con la reivindicación 27, el cual es una lata de aluminio no recubierto.~~

~~29. Un inhalador de dosis medida (MDI) equipado con un recipiente sellado de acuerdo con lo reivindicado en la reivindicación 27 o 28.~~

~~30. El inhalador de dosis medida de acuerdo con la reivindicación 29, que comprende un ensamblaje de válvula y boquilla unido al recipiente de aerosol presurizado y una junta hecha de un material elastomérico seleccionado de EPDM, clorobutilo, bromobutilo y gomas de copolímero de olefina cíclica para sellar la unión entre el recipiente y el ensamblaje de válvula/boquilla.~~

REIVINDICACIONES

1. Una composición farmacéutica que comprende:

(i) un componente de fármaco que comprende una sal aceptable desde el punto de vista farmacéutico de glicopirrolato, y un corticosteroide seleccionado de budesonida o dipropionato de beclometasona,

(ii) un componente propulsor que comprende entre 90 y 100 % en peso de 1,1-difluoroetano (HFA-152a), y

(iii) etanol,

donde la composición farmacéutica es una solución.

2. La composición farmacéutica de acuerdo con la reivindicación 1, en donde la composición contiene menos de 500 ppm de agua en función del peso total de la composición farmacéutica.

3. La composición farmacéutica de acuerdo con la reivindicación 2, en donde la composición contiene más de 0,5 ppm de agua en función del peso total de la composición farmacéutica.

4. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde la composición contiene menos de 1000 ppm de oxígeno en función del peso total de la composición farmacéutica.

5. La composición farmacéutica de acuerdo con la reivindicación 4, en donde la composición contiene más de 0,5 ppm de oxígeno en función del peso total de la composición farmacéutica.

6. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde la sal aceptable desde el punto de vista farmacéutico de glicopirrolato es bromuro de glicopirronio.

7. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde la sal aceptable desde el punto de vista farmacéutico de glicopirrolato está en forma micronizada.

8. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde el componente de fármaco comprende adicionalmente un beta-2-agonista de acción prolongada (LABA) seleccionado de formoterol y sus sales farmacéuticamente aceptables.

9. La composición farmacéutica de acuerdo con la reivindicación 8, en donde el beta-2-agonista de acción prolongada está en forma micronizada.

10. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde el corticosteroide está en forma micronizada.

11. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde el componente de fármaco comprende de 0,01 a 2,5 % en peso del peso total de la composición farmacéutica.

12. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde el componente de propulsor comprende de 80,0 a 99,99 % en peso del peso total de la composición farmacéutica.

13. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde entre 95 y 100 % en peso del componente propulsor es 1,1-difluoroetano (HFA-152a).

14. La composición farmacéutica de acuerdo con la reivindicación 13, en donde al menos 99 % en peso del componente propulsor es 1,1-difluoroetano (HFA-152a).

15. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 1-12, en donde el componente propulsor es 1,1-difluoroetano (HFA-152a) en su totalidad.

16. La composición farmacéutica de acuerdo con la reivindicación 13 o 14, en donde el componente propulsor contiene de 0,5 a 10 ppm de impurezas insaturadas seleccionadas de fluoruro de vinilo, cloruro de vinilo, fluoruro de vinilideno y compuestos de cloro-fluoroetileno.

17. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, en donde entre 95 y 100 % en peso de la composición consiste en los dos componentes (i) e (ii).

18. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, que comprende además un componente tensioactivo.

19. La composición farmacéutica de acuerdo con la reivindicación 18, en donde el componente tensioactivo comprende un compuesto tensioactivo seleccionado de polivinilpirrolidona, tensioactivos de polietilenglicol, ácido oleico y lecitina.

20. La composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores, la cual está libre de estabilizantes ácidos.

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Dipole Moments of Seven Partially Halogenated Ethane Refrigerants

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Dielectric constant measurements have been performed on seven partially halogenated ethanes, currently being considered as alternative refrigerants, in the gaseous state over the range 305–415 K in order to determine their dipole moments. Argon was also studied to test the apparatus. Five of the refrigerants have temperature-independent moments: R125 (CF_3CHF_2), $\mu = 1.563 \pm 0.005$ D; R134a (CF_3CH_2F), $\mu = 2.058 \pm 0.010$ D; R143a (CF_3CH_3), $\mu = 2.340 \pm 0.010$ D; R152a (CHF_2CH_3), $\mu = 2.262 \pm 0.008$ D; and R124 (CF_3CHClF), $\mu = 1.469 \pm 0.012$ D. Two refrigerants have conformer-dependent moments, making their time-averaged moments temperature dependent: R134 (CHF_2CHF_2), with a moment ranging from 0.991 ± 0.004 D at 309 K to 1.250 ± 0.004 D at 413 K; and R143 (CHF_2CH_2F), where the moment ranges from 1.680 ± 0.001 D at 309 K to 1.745 ± 0.001 D at 410 K. Accurate estimation of a molecule's temperature-dependent dipole moment requires an independent determination of its polarizability; this determination has been made from index of refraction measurements. Where possible, the present results are compared with earlier determinations of dipole moments. In all but one instance, the agreement is good.

I. Introduction

This paper presents determinations of the dipole moments of seven molecules from dielectric constant measurements. The molecules are partially halogenated ethanes: pentafluoroethane (R125), 1,1-difluoroethane (R152a), 1,1,1,2-tetrafluoroethane (R134a), 1,1,1-trifluoroethane (R143a), 1,1,2,2-tetrafluoroethane (R134), 1,1,2-trifluoroethane (R143), 2-chloro-1,1,1,2-tetrafluoroethane (R124). Here, the names in parentheses are designations for fluorocarbons used by the refrigeration industry.[1] In addition, argon, which has no dipole moment, was studied in order to test the apparatus.

The motivation to measure these dipole moments has come from the recent desire to know the thermophysical properties (the dipole moment has been used in determining the equation of state[2]) of alternative refrigerants that are not harmful to the ozone layer. Six of the refrigerants have zero ozone depletion potential because they have no chlorine. R124 contains chlorine; however, it has a shorter atmospheric lifetime than the fully halogenated chlorofluorocarbons currently used as refrigerants.[3] R134a is the leading alternative to R12 (dichlorodifluoromethane); R125 is a candidate replacement for R502, an azeotropic mixture used in open-case supermarket freezers.

Of the seven refrigerants studied, five (R125, R152a, R134a, R143a, and R124) have temperature-independent dipole moments. Two (R134 and R143) have temperature-dependent moments. The temperature dependence results from the existence of nondegenerate internal-rotation conformers[4] that have different dipole moments.

Section II discusses the purity of the refrigerants used. Section III describes the apparatus and the procedure used in making the measurements, and section IV provides the results of the measurements. A conclusion is given in section V.

II. Purity of Materials

The refrigerants used in this study were obtained from PCR Corp.,[5] with the exceptions of R134a and R124, which were obtained from E.I. DuPont Co.[5] The argon was purchased from Air Products, Inc.[5] The purity of the materials claimed by the manufacturers is listed in Table I. The refrigerants were additionally purified by immersing their containers in liquid nitrogen (thereby freezing them) and then removing the volatile impurities with a mechanical pump.

TABLE I: Purity of Materials

material	purity, %	principal impurities
argon	99.998	nitrogen
R125	99.3	carbon dioxide
R134a	99.9	R125, R143a, R142
R143a	99.3	1,1-difluoroethylene
R152a	99.9	unknown
R134	99.4	perfluorocyclobutane
R143	99.1	unknown
R124	99.9	unknown

III. Apparatus and Procedure

A. Theoretical Method. The dipole moments were determined from dielectric constant measurements of the refrigerants in the gaseous state at various temperatures and pressures. The Debye equation[6] was used to relate the dielectric constant ϵ to the polarizability α and the dipole moment μ of the refrigerants

$$\epsilon^* \equiv \frac{\epsilon - 1}{\epsilon + 2} = \frac{4}{3}\pi N\left(\alpha + \frac{\mu^2}{3kT}\right) \tag{1}$$

where N is the number density, k is Boltzmann's constant, and T is the temperature. The Debye equation is only applicable in the ideal gas limit. At higher values of the molar density d, dielectric virial coefficients must be considered[7]

$$\epsilon^*/d = P + P_1 d + P_2 d^2 + \ldots \tag{2}$$

The parameter P is the molar polarization (the subscript has been dropped to be consistent with the usual notation) and is related to α and μ by combining eqs 1 and 2

$$P = \frac{4}{3}\pi N_0\left(\alpha + \frac{\mu^2}{3kT}\right) \tag{3}$$

where N_0 is Avogadro's number. One may write eq 3 as

$$P = P_\alpha + P_\mu/T \tag{4}$$

where P_α is the molar polarization related to the polarizability and

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(2) Hirshfelder, J. O.; Curtiss, C. F.; Bird, R. B. *Molecular Theory of Gases and Liquids*; J. Wiley: New York, 1954.
(3) McLinden, M. O.; Didion, D. A. *ASHRAE J* **1987**, December.
(4) Mizushima, S. *Structure of Molecules and Internal Rotation*; Academic Press: New York, 1954.
(5) In order to describe materials and experimental procedures adequately, it is occasionally necessary to identify commercial products by manufacturers' name or label. In no instance does such identification imply endorsement by the National Institute of Standards and Technology, nor does it imply that the particular product or equipment is necessarily the best available for the purpose.
(6) Debye, P. *Phys. Z.* **1912**, *13*, 97.
(7) Sutter, H.; Cole, R. H. *J. Chem. Phys.* **1970**, *52*, 132.

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$$P_\mu = 4\pi N_0 \mu^2/9k \quad (5)$$

In practice one measures the pressure p rather than the molar density, yielding

$$\epsilon^*\left(\frac{RT}{p}\right) = P' + P_1'\left(\frac{p}{RT}\right) + P_2'\left(\frac{p}{RT}\right)^2 + \ldots \quad (6)$$

where R is the gas constant. While in general the coefficients in eqs 2 and 6 are not equivalent (although they can be connected by using the virial equation of state), it can be shown that $P' = P$.[7]

In the case where the dipole moment is temperature independent, the moment may be accurately determined by measuring the temperature dependence of P, which arises solely from the $1/T$ dependence of the second term on the right-hand side of eq 3. If the dipole moment is temperature dependent an accurate measurement of μ is difficult without a separate determination of α. Polarizability measurements were made for all the refrigerants by measuring index of refraction.[8] Measurements made with visible light yield only the electronic polarizability α_e

$$\frac{n_\infty^2 - 1}{n_\infty^2 + 2} = \frac{4}{3}\pi N \alpha_e = \frac{N}{N_0} P_{\alpha e} \quad (7)$$

where eq 7 is the Clausius–Mossotti equation and n_∞ is the infinite-wavelength extrapolation of the index of refraction n. The electronic molar polarization $P_{\alpha e}$ is defined in eq 7. The molar polarization not related to the dipole moment P_α is given by $P_\alpha = P_{\alpha e} + P_{\alpha a}$, where $P_{\alpha a}$ is the atomic molar polarization and is frequently between $0.1P_\alpha$ and $0.2P_\alpha$.[8] For the case of temperature-dependent dipole moments there is no convenient way to measure $P_{\alpha a}$, so it must be estimated. Because $P_{\alpha a}$ is so small relative to P, one can make accurate determinations of $\mu(T)$ even with large uncertainties in $P_{\alpha a}$.

B. Capacitance Cell. The dielectric constant was measured in a capacitance cell with vacuum capacitance C_0 such that the measured capacitance C was given by $C = \epsilon C_0$. The three-terminal capacitance cell used in our measurements was loaned to us by Dr. Sandra Greer, who used it to make dielectric constant measurements of Cl_2 near its critical point[9] and more recently of liquid sulfur.[10] The cell has been described in detail previously.[9,10] In brief, it consists of two parallel rectangular plates of area 1×10^{-4} m^2 spaced approximately 1 mm apart. The plates are made of Hastelloy 276C and are mounted in a container made of the same material. Originally one of the walls of the container was a window. It was replaced with an Invar disk of the same dimensions to provide a completely shielded environment. The disk was sealed with a Neoprene O-ring (different from the one used in Greer's experiments) which was cleaned with ethanol before each use. The volume of the container was approximately 7 cm^3, and the vacuum capacitance of the cell was approximately 1 pF. The cell was disassembled and cleaned with acetone before its use in this project.

C. Capacitance Measurement. The capacitance of the cell was measured with a capacitance bridge (General Radio 1615A),[5] using a lock-in amplifier with a sensitivity of 100 nV as the null detector. The excitation of the bridge was 30 V peak to peak and had a frequency of 1 kHz. Self-check procedures performed on the bridge involving zero error and the ratio of the standard capacitors showed it to be performing properly. The output from the null detector was averaged automatically by computer over 100 s for each measurement. A resolution of 3 ppm in the capacitance was easily achieved with this arrangement.

D. Measurement and Control of Temperature and Pressure. The capacitance cell was placed in a temperature controlled oven. The temperature inside the oven was measured by a digital-output platinum resistance thermometer (Guildline 9540)[5] with a specified accuracy of 10 mK. The temperature inside the oven was measured to be constant to within 0.2 K. The pressure was measured with a quartz pressure transducer (Paroscientific 43K-101 Digiquartz) combined with a pressure computer (Paroscientific series 700);[5] this system had a specified accuracy of 0.7 mbar. The refrigerant, which was stored at its saturation pressure at room temperature, was introduced into the cell by opening a valve to the manifold. The refrigerant was removed with a mechanical pump, which was isolated by a nitrogen trap to minimize backstreaming.

E. Experimental Procedure. For each refrigerant, measurements of the molar polarization were made at six temperatures in the range 305–415 K. At each temperature, an initial vacuum capacitance measurement was made. Subsequently, capacitance measurements were made at nine pressures, starting at vacuum and incrementing at constant intervals until the fifth measurement, and then decrementing the pressure so as to repeat the pressures of the first four. The highest pressure was about 3/4 the saturation pressure at room temperature. The dielectric constant was determined by dividing the capacitance by the initial vacuum capacitance measurement. The dielectric-constant data for all materials are found in Table V.

For three of the refrigerants ϵ^* was determined as a function of the molar density rather than as a function of p/RT, since ϵ expressed as the former is more linear than ϵ expressed as the latter. For R134a the second and third PVT virial coefficients measured by Weber[11] were used to make the conversion. The PVT virial coefficients for R143a and R152a were estimated by using those of R134a and the law of corresponding states.[12]

The molar polarization was determined by fitting the functional form of eqs 2 and 6 to the dielectric-constant data (the measurements made at $p = 0$ were omitted). The expansion was

TABLE II: Temperature-Independent Dipole Moments: Molar Polarization as a Function of Temperature

T, K	P, mol/cm³	T, K	P, mol/cm³
	Argon		
309.8	4.21 ± 0.01	367.3	4.19 ± 0.02
327.4	4.18 ± 0.02	388.2	4.27 ± 0.03
349.2	4.20 ± 0.01	411.5	4.20 ± 0.09
	R152a		
308.5	115.15 ± 0.12	367.8	98.76 ± 0.07
326.9	109.19 ± 0.04	389.2	93.88 ± 0.16
348.8	103.33 ± 0.14	413.0	89.61 ± 0.10
	R143a		
308.2	122.20 ± 0.18	368.2	104.44 ± 0.37
329.4	115.33 ± 0.15	389.4	99.76 ± 0.39
350.2	108.87 ± 0.27	412.8	94.74 ± 0.29
	R125		
308.8	62.50 ± 0.06	367.7	54.77 ± 0.07
327.5	59.72 ± 0.03	389.1	52.45 ± 0.10
348.8	57.00 ± 0.05	412.9	50.41 ± 0.10
	R134a		
309.0	97.27 ± 0.02	368.7	83.47 ± 0.03
328.6	92.16 ± 0.02	388.2	80.41 ± 0.10
349.2	87.62 ± 0.02	410.8	76.46 ± 0.04
	R124		
307.9	60.61 ± 0.19	366.6	54.09 ± 0.14
326.1	58.54 ± 0.06	388.4	51.85 ± 0.12
348.1	55.92 ± 0.09	411.3	49.98 ± 0.04

TABLE III: Temperature-Independent Dipole Moments

refrig	$P_{\alpha e}$, mol/cm³	P_α, mol/cm³	μ, D
R125	11.0	14.3 ± 0.3	1.563 ± 0.005
R134a	10.9	13.7 ± 0.7	2.058 ± 0.010
R143a	10.2	13.9 ± 0.8	2.340 ± 0.010
R152a	10.7	14.0 ± 0.6	2.262 ± 0.008
R124	16.2	18.1 ± 0.6	1.469 ± 0.012

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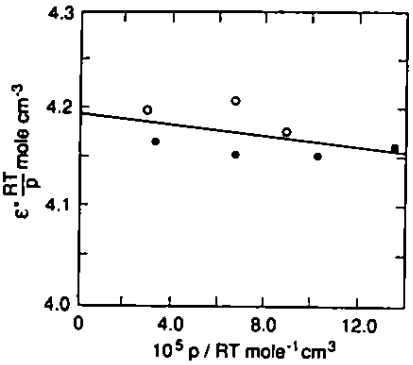

Figure 1. Plot of $\epsilon^* RT/p$ vs p/RT for argon at 349.2 K, where $\epsilon^* = (\epsilon - 1)/(\epsilon + 2)$. The line is the best-fit curve through the points, where the functional form for the curve is given by eq 6 with a truncation at the linear term. The solid (open) circles correspond to increasing (decreasing) pressure.

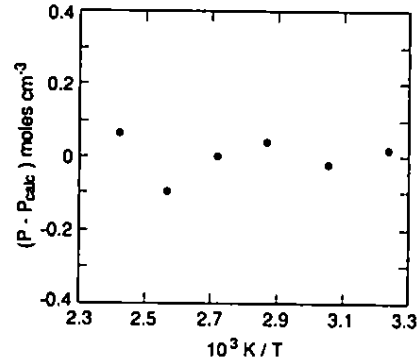

Figure 2. Deviation plot of $P - P_{calc}$ vs $1/T$ for refrigerant R125 (pentafluoroethane), where P is the molar polarization and P_{calc} is the best-fit curve through the points ($P_{calc} = P_\alpha + P_\mu/T$, with $P_\alpha = 14.2$ cm^3/mol, and $P_\mu = 14877.$ cm$_3$ K/mol). The value of P_μ corresponds to a dipole moment of $\mu = 1.563$ D.

truncated at the linear term for most refrigerants; in these cases the addition of a quadratic term increased the uncertainty of P without significantly altering its value. A quadratic term was used for R143a, however. The regression program REGRES of Bevington[5,13] was used to obtain the best-fit value for P and P'. When the same data were fitted to eqs 2 and 6, P' and P were found to agree to within 0.2%. For R125, R134, R143, and R124 eq 6 was used to determine P. The molar polarization as a function of temperature for the refrigerants is shown in Tables II and III.

The temperature-independent dipole moments were determined by fitting eqs 4 and 5 to the molar polarization. The temperature-dependent moments were found by using separately determined values of P_α ($P_{\alpha\epsilon}$ from index of refraction measurements, $P_{\alpha\epsilon}$ from estimation) and inverting eq 3, providing values of $\mu(T)$ for the temperatures at which the measurements were made.

F. Index of Refraction Measurements. Index of refraction measurements were made of all refrigerants except R134 and R152a in the liquid phase at approximately 297 K. Density measurements at that temperature were provided to us by Defibaugh and Morrison.[14] Equation 7 was then used to calculate $P_{\alpha\epsilon}$, which is temperature independent. The index of refraction measurements were made with the apparatus and procedures developed by Chae et al.[15] Their techniques appear in ref 15 together with their results for R134 and R152a.[15] The light source was a He–Ne laser with wavelength $\lambda = 6328$ Å. Because n was not measured with a second wavelength (allowing the infinite-wavelength value to be determined by extrapolation), n_∞ was estimated to be $0.990n$. This relation between n and n_∞ has been found empirically for many liquids,[8] and the estimation procedure has been used before on a number of materials, including fluorinated ethanes.[16] The use of n_∞ rather than n in eq 7 results in a decrease in $P_{\alpha\epsilon}$ of approximately 5%. It should be realized that since n_∞ has been estimated, $P_{\alpha\epsilon}$ is also an estimate. The index of refraction data for all seven refrigerants are tabulated in Table VI, including the measurements made by Chae et al.

IV. Results

A. Argon. Measurements of the molar polarization of argon as a function of temperature were made in order to test the performance of the apparatus. Argon has no dipole moment, so its molar polarization is temperature independent. A typical plot of $\epsilon^* RT/p$ vs p/RT is shown in Figure 1. The data were taken at 367.3 K. The open and solid circles correspond to data taken while the pressure was incremented and decremented, respectively. Hysteresis of about 0.05 cm^3/mol in $\epsilon^* RT/p$ is present in the data; this corresponds to about 12 ppm in the capacitance. The best fit values are $P = 4.19 \pm 0.02$ cm^3/mol and $P_1 = -263 \pm 235$ cm^6/mol^2, where the uncertainties are 1 standard deviation (treating the deviations as if they were due to random scatter). The value of P is 1% higher than the value of 4.136 ± 0.0002 cm^3/mol measured by Orcutt and Cole.[17] The value of P_1 is in satisfactory agreement with that measured by ref 17 (2.1 ± 0.1 cm^6/mol^2). If we consider only the data with the pressure incremented (decremented), we obtain best fit values for P of 4.15 ± 0.02 (4.22 ± 0.03) cm^3/mol. These values deviate from the best-fit value of P obtained by using all data by approximately 0.03 cm^3/mol, an amount comparable to the standard deviation of P. This shows that even though the deviations $\epsilon^* RT/p$ are clearly systematic, the uncertainty values from statistical analysis are repesentative of the uncertainties due to the hysteresis.

The hysteresis shown in Figure 1 was found in all measurements made of $\epsilon^* RT/p$ vs p/RT. The amount of the hysteresis ranged from 0.05 to 0.15 cm^3/mol. We were not able to determine the cause of the hysteresis or its variation from one run to the next. It was not caused by errors in pressure measurements or by allowing insufficient time for equilibrium. Perhaps the spacing between the capacitor plates changed slightly during a set of measurements. The hysteresis shown in Figure 1 could be accounted for by a change of 12 ppm (120 Å). Since the plates were not held apart by spacers this small change might have occurred from slight deformations of the chamber wall to which they were mounted.

We decided to use all seven nonvacuum measurements of $\epsilon^* RT/p$ vs p/RT per isotherm. The values of P vs T for argon are shown in Table II. The average value of P is 4.21 cm^3/mol and is constant to within the resolution of our measurements.

B. Temperature-Independent Dipole Moments. The values of P vs T for the refrigerants with temperature-independent dipole moments are shown in Table II. Figure 2 displays a plot of $P - P_{calc}$ vs $1/T$ for R125, where P_{calc} is the best-fit line with slope 14871 ± 93 cm^3 K/mol and y intercept 14.3 ± 0.3 cm^3/mol. Once again the uncertainties are 1 standard deviation. The scatter is consistent with the uncertainties in the measurement of P. The best-fit values yield $\mu = 1.563 \pm 0.005$ D, and $P_\alpha = 14.3 \pm 0.3$ cm^3/mol, which are in good agreement with the values of $\mu = 1.54$ D, $P_\alpha = 16.0$ cm^3/mol determined by di Giacomo and Smyth using capacitance measurements.[16]

Table III lists the values of the dipole moments determined for all the refrigerants with temperature-independent moments, along with the corresponding values of P_α. All plots of P vs $1/T$ exhibited similar scatter to that shown in Figure 2. The values of $P_{\alpha\epsilon} \equiv 4\pi N_0 \alpha_\epsilon/3$ as determined by the index of refraction measurements are also given in Table III. Note that for all four fluorinated ethanes $P_\alpha \simeq 14.0$ cm^3/mol and $P_{\alpha\epsilon} \simeq 0.80 P_\alpha$.

We found that the dipole moment of R134a was $\mu = 2.058 \pm 0.010$ D. This is consistent with a Stark Effect (spectroscopic) measurement by Ogata and Miki[18] that yielded $\mu = 1.80 \pm 0.22$

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TABLE IV: Temperature-Dependent Dipole Moments

A. Dipole Moment as a Function of Temperature

T, K	P, mol/cm^3	μ, D
	R134[a]	
308.6	33.37 ± 0.15	0.991 ± 0.004
329.3	34.74 ± 0.12	1.059 ± 0.003
349.4	35.61 ± 0.12	1.113 ± 0.003
368.5	36.31 ± 0.10	1.162 ± 0.002
389.5	36.85 ± 0.17	1.209 ± 0.004
412.8	37.04 ± 0.17	1.250 ± 0.004
	R143[a]	
308.8	69.65 ± 0.08	1.680 ± 0.001
326.6	67.36 ± 0.09	1.692 ± 0.001
348.4	64.98 ± 0.06	1.708 ± 0.001
366.9	63.10 ± 0.07	1.720 ± 0.001
388.5	61.09 ± 0.07	1.733 ± 0.001
410.0	59.21 ± 0.05	1.745 ± 0.001

B. Dipole Moments of Individual Conformers

conformer	μ, D
R134 (trans)	0 (by symmetry)
R134 (gauche)	2.45 ± 0.05
R143 (C_1)	1.50 ± 0.15
R143 (C_S)	2.84 ± 0.08

[a] P_α = 14.0 cm^3/mol by estimation.

D. Our value of the moment of R143a is μ = 2.340 ± 0.010 D. It is consistent with the results of Townes et al.,[19] who found μ = 2.35 ± 0.02 D, and of Ghosh et al.,[20] who found μ = 2.27 ± 0.04 D. Both groups used Stark effect techniques. We found the moment of R152a to be μ = 2.262 ± 0.008 D, and P_α = 14.0 ± 0.6 cm^3/mol, values that agree well with μ = 2.24 D and P_α = 14.6 cm^3/mol determined by Gibbs and Smyth also using a capacitance measurement.[21] Reanalysis of published data[21] yields μ = 2.254 ± 0.01 D and P_α = 14.0 ± 0.7 cm^3/mol. Measurements of the dipole moment of R152a have also been made by Kwei and Herschbach[22] using Stark effect techniques. They found μ = 2.30 ± 0.03 D, in agreement with our value. Finally, our value for R124 is μ = 1.469 ± 0.012 D. To our knowledge, no other measurements of this dipole moment have been made.

C. Temperature-Dependent Dipole Moments. Table IV gives the values of P vs T for the refrigerants with temperature-dependent dipole moments, as well as the calculations of the dipole moments at these temperatures. For both R134 and R143 an estimated value of P_α = 14.0 cm^3/mol was used in the determination of the dipole moment. This value is the average value of P_α determined for the four fluorinated ethanes with temperature-independent moments. Using this estimate is equivalent to using the measured values of the electronic polarizability ($P_{\alpha e}$ = 11.2 cm^3/mol and $P_{\alpha e}$ = 10.8 cm^3/mol for R134 and R143, respectively), and estimating the atomic polarizabilities to be $P_{\alpha a}$ = 2.8 cm^3/mol and $P_{\alpha a}$ = 3.2 cm^3/mol for R134 and R143, respectively. Our estimate was based on the consistency of all values of P_α for the temperature-independent moments. As a further justification we cite a variation on Landolt's rule[23] which states that the polarizability of a molecule is the sum of those of its individual bonds. According to the rule, the polarizability of R134 and R143 should be the same as that of R134a and R143a, respectively. Our estimates are consistent with this rule to within experimental uncertainties.

The temperature dependence of the moments of R134 and R143 is due to their multiple conformations. R134 can exist in either gauche (C_2) or trans (C_{2h}) conformations, as shown in Figure 3. The symmetrical trans conformer has no dipole moment and is more stable in the gas phase.[24,25] As the temperature is increased, the population of the doubly degenerate gauche conformer, which has a nonzero moment, increases, resulting in an increasing dipole moment when measured. Figure 3 also shows the C_1 and C_h conformers of R143. The degenerate C_1 conformer has the lower energy of the two. Although the moments of both conformers are nonzero, they are not equal. As the temperature (and C_h population) increases, the dipole moment of the molecule changes.

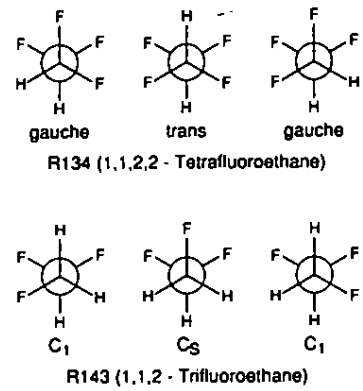

Figure 3. The multiple conformations of R134 (1,1,2,2-tetrafluorethane) and R143 (1,1,2-trifluoroethane). The staggered forms of R134 can exist in either gauche ($\mu > 0$) or trans ($\mu = 0$) conformations, and those of R143 can exist as either C_1 ($\mu > 0$) or C_s ($\mu > 0$) conformations.

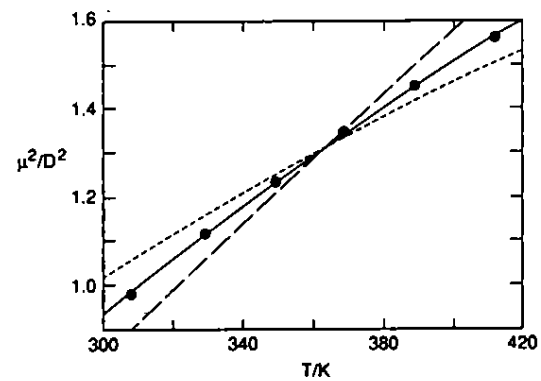

Figure 4. Square of the dipole moment of R134 as a function of temperature. The solid circles are the experimental determinations, and the solid curve represents the best-fit values using the functional form of eq 8 and assigning μ_1 = 0, ω = 2.0. The best-fit parameter values are μ_2 = 2.45 D and ΔE = 5.97 kJ/mol. The long-dashed (short-dashed) curve is a similar best-fit curve, but additionally assigning μ_2 = 2.9 D (ΔE = 4.89 kJ/mol). The placement of the intersection point of the curves reflects the temperature range over which the data was taken, but otherwise holds no significance.

The measured dipole moment is related to the moments of the individual conformers by

$$\mu^2 = \frac{\mu_1^2 + \omega\mu_2^2 e^{-\Delta E/kT}}{1 + \omega e^{-\Delta E/kT}} \tag{8}$$

where μ_1 and μ_2 are the dipole moments of the nondegenerate and degenerate conformers, respectively, and ΔE is the energy difference between the two conformers ($\Delta E = E_2 - E_1$). Here, $\omega = 2f_2/f_1$, where the factor 2 is due to the degeneracy. f_1 and f_2 are the vibrational and rotational partition functions of the nondegenerate and degenerate conformers, respectively.[4] For the case of 1,2-dichloroethane it has been shown[4] that the value of ω varies from 1.90 at 300 K to 1.83 at 400 K.

We have fit our measurements of $\mu(T)$ for R134 and R143 to the functional form of eq 8. Lacking data for the precise determination of ω we have used the approximation ω = 2.0. A discussion of the uncertainty due to this approximation will follow

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TABLE V: Dielectric Constant as a Function of Temperature and Pressure

A. Argon

p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$
		T = 308.8 K						T = 367.3 K			
0.000	0.001	3.686	0.601	1.879	0.308	0.000	0.000	3.113	0.423	2.011	0.277
1.031	0.169	4.183	0.682	1.031	0.169	1.005	0.137	4.114	0.561	0.887	0.122
2.209	0.362	2.890	0.471	0.000	0.001	2.035	0.277	2.704	0.370	0.000	0.000
		T = 326.8 K						T = 388.2 K			
0.000	0.001	3.045	0.467	1.388	0.214	0.000	0.002	3.155	0.410	1.906	0.251
1.109	0.169	4.010	0.614	0.707	0.109	1.213	0.159	4.049	0.526	0.948	0.125
2.138	0.327	2.621	0.402	0.000	0.000	2.283	0.296	2.487	0.326	0.000	0.002
		T = 348.2 K						T = 411.5			
0.000	0.000	3.142	0.454	2.035	0.295	0.000	−0.001	3.133	0.380	1.635	0.202
0.988	0.143	3.964	0.572	1.056	0.153	0.966	0.114	3.981	0.482	1.008	0.128
1.921	0.277	2.788	0.403	0.000	−0.002	2.442	0.293	2.850	0.346	0.000	0.002

B. R125

p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$
		T = 308.8 K						T = 367.7 K			
0.000	0.001	3.102	7.934	2.028	5.106	0.000	0.000	3.123	5.736	2.062	3.761
1.070	2.648	4.030	10.468	1.027	2.545	1.146	2.069	3.998	7.400	1.043	1.887
2.087	5.250	3.044	7.787	0.000	0.001	2.181	3.971	3.054	5.613	0.000	0.003
		T = 327.5 K						T = 389.1 K			
0.000	0.001	3.231	7.385	2.004	4.509	0.000	0.003	2.967	4.903	1.979	3.257
1.138	2.535	4.313	9.997	1.056	2.349	1.215	1.981	4.027	6.711	1.040	1.702
1.954	4.392	3.055	6.968	0.000	−0.001	1.960	3.217	2.640	4.361	0.000	0.003
		T = 348.8 K						T = 412.9 K			
0.000	−0.001	3.581	7.298	2.039	4.094	0.000	0.000	2.991	4.449	1.979	2.935
1.239	2.464	4.729	9.757	1.022	2.033	1.085	1.596	3.258	4.853	1.087	1.609
2.330	4.688	2.697	5.450	0.000	0.000	2.377	3.523	3.004	4.473	0.000	0.004

C. R152a

p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$
		T = 308.5 K						T = 367.8 K			
0.000	0.001	2.001	9.317	1.511	6.981	0.000	0.000	3.368	11.229	2.015	6.634
0.538	2.433	2.498	11.747	0.539	2.448	0.995	3.240	4.034	13.547	0.995	3.247
1.562	7.208	2.025	9.442	0.000	0.004	1.988	6.538	3.030	10.071	0.000	0.005
		T = 326.9 K						T = 389.2 K			
0.000	0.000	3.215	13.537	1.975	8.164	0.000	−0.001	1.544	4.531	0.998	2.922
1.061	4.325	4.142	17.702	1.031	4.206	0.606	1.762	2.007	5.911	0.599	1.749
1.991	8.225	3.030	12.725	0.000	0.006	1.155	3.379	1.521	4.468	0.000	0.008
		T = 348.8 K						T = 413.0 K			
0.000	0.001	2.994	11.041	1.984	7.238	0.000	0.002	3.156	8.376	2.056	5.427
0.984	3.538	4.134	15.458	1.103	3.988	1.478	3.884	4.023	10.741	1.002	2.634
2.156	7.866	3.041	11.223	0.000	0.015	2.347	6.199	3.002	7.969	0.000	0.004

D. R134a

p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$
		T = 309.0 K						T = 368.7 K			
0.000	0.000	1.518	5.917	1.075	4.152	0.000	0.000	1.675	4.647	1.013	2.788
0.603	2.308	2.046	8.055	0.575	2.199	0.547	1.498	2.083	5.804	0.512	1.401
0.954	3.679	1.498	5.833	0.000	0.003	1.270	3.506	1.362	3.766	0.000	0.000
		T = 328.6 K						T = 388.2 K			
0.000	0.000	1.506	5.200	1.011	3.463	0.000	0.001	1.507	3.790	1.020	2.561
0.498	1.693	1.843	6.395	0.496	1.686	0.491	1.226	1.969	4.971	0.523	1.309
1.026	3.514	1.395	4.807	0.000	0.001	1.133	2.840	1.529	3.851	0.000	0.005
		T = 349.2 K						T = 410.8 K			
0.000	0.000	1.663	5.117	1.098	3.356	0.000	0.000	1.531	3.461	1.090	2.457
0.477	1.448	2.070	6.404	0.558	1.696	0.754	1.694	1.954	4.431	0.506	1.137
1.077	3.291	1.527	4.691	0.000	0.003	1.093	2.463	1.500	3.390	0.000	0.001

E. R143a

p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$
		T = 308.2 K						T = 368.2 K			
0.000	0.001	4.551	23.175	2.900	14.402	0.000	0.002	3.558	12.491	1.483	5.133
1.428	6.935	5.413	27.939	1.491	7.261	1.053	3.616	4.235	14.948	1.012	3.487
3.082	15.335	4.257	21.574	0.000	0.005	2.180	7.566	2.773	9.683	0.000	0.002
		T = 329.4 K						T = 389.4 K			
0.000	0.001	3.355	14.653	1.974	8.492	0.000	0.000	3.461	10.892	1.802	5.622
1.123	4.783	4.329	19.123	1.109	4.729	1.061	3.282	4.190	13.248	0.871	2.705
2.155	9.285	2.964	12.892	0.000	0.004	2.257	7.046	2.647	8.302	0.000	0.001
		T = 350.2 K						T = 412.8 K			
0.000	0.001	3.151	12.153	1.814	6.919	0.000	0.000	3.028	8.484	2.007	5.604
1.011	3.816	4.042	15.714	1.063	4.026	1.081	2.996	4.021	11.326	1.150	3.199
1.957	7.460	3.070	11.843	0.000	−0.007	2.549	7.127	2.731	7.650	0.000	0.010

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TABLE V (Continued)

F. R134

p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$
		T = 308.6 K						T = 368.5 K			
0.000	0.001	3.151	4.456	1.982	2.727	0.000	−0.002	3.305	4.070	2.039	2.478
1.287	1.723	4.448	6.521	0.997	1.341	1.011	1.207	4.091	5.094	0.966	1.165
2.247	3.096	3.019	4.256	0.000	0.002	2.520	3.073	2.875	3.527	0.000	0.005
		T = 329.3 K						T = 389.5 K			
0.000	−0.002	3.122	4.214	2.024	2.682	0.000	0.000	3.450	4.045	1.759	2.036
1.159	1.500	4.055	5.584	0.952	1.238	1.306	1.493	3.940	4.646	0.985	1.139
1.919	2.523	3.025	4.083	0.000	0.004	2.052	2.367	2.956	3.458	0.000	0.006
		T = 349.4 K						T = 412.8 K			
0.000	0.001	3.100	3.973	2.011	2.542	0.000	0.000	3.038	3.352	1.999	2.196
0.988	1.223	3.589	4.638	0.990	1.238	1.499	1.627	3.837	4.262	1.073	1.173
2.273	2.875	2.954	3.782	0.000	0.005	2.091	2.283	2.912	3.217	0.000	−0.001

G. R143

p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$
		T = 308.8 K						T = 366.9 K			
0.000	0.000	1.4922	4.218	0.8014	2.221	0.0000	0.001	1.4406	3.033	1.0569	2.216
0.7552	2.091	1.7415	4.961	0.4115	1.130	0.5442	1.132	1.8931	4.013	0.5709	1.192
1.2122	3.400	1.3652	3.845	0.0000	0.002	1.0355	2.168	1.4187	2.988	0.0000	0.003
		T = 326.6 K						T = 388.5 K			
0.0000	0.000	1.5014	3.846	1.0959	2.784	0.0000	0.001	1.5274	2.935	1.0943	2.089
0.5739	1.411	2.1016	5.470	0.4645	1.167	0.5783	1.102	2.0340	3.929	0.5261	1.000
1.1001	2.795	1.4315	3.665	0.0000	0.001	1.2028	2.303	1.5324	2.944	0.0000	0.003
		T = 348.4 K						T = 410.0 K			
0.0000	0.0000	1.4271	3.272	1.0446	2.383	0.0000	0.000	1.4848	2.612	0.8615	1.508
0.5031	1.138	2.1325	4.957	0.4927	1.116	0.5410	0.943	1.9356	3.420	0.5118	0.894
1.0062	2.292	1.5150	3.483	0.0000	0.003	1.0175	1.782	1.2403	2.178	0.0000	0.001

H. R124

p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$	p/bar	$\epsilon^* \times 10^3$
		T = 307.9 K						T = 366.6 K			
0.000	0.000	3.026	7.853	1.911	4.801	0.000	0.000	2.039	3.712	1.406	2.543
1.046	2.553	3.159	8.225	1.009	2.473	0.843	1.508	2.605	4.784	0.669	1.202
2.043	5.139	2.945	7.640	0.000	0.008	1.532	2.768	1.988	3.624	0.000	0.004
		T = 326.1 K						T = 388.4 K			
0.000	0.001	2.422	5.516	1.326	2.951	0.000	0.000	2.482	4.103	1.485	2.432
0.856	1.881	2.625	6.008	0.841	1.853	0.915	1.481	3.222	5.376	0.854	1.390
2.056	4.642	2.070	4.680	0.000	0.008	1.526	2.491	2.389	3.953	0.000	0.004
		T = 348.1 K						T = 411.3 K			
0.000	0.000	2.037	4.066	1.438	2.846	0.000	0.000	2.033	3.009	1.351	1.993
0.766	1.496	2.612	5.266	0.665	1.302	0.617	0.904	2.527	3.755	0.656	0.964
1.425	2.813	2.094	4.189	0.000	0.007	1.845	2.729	2.082	3.088	0.000	0.004

TABLE VI: Results of Index of Refraction Measurements

refrig	T, K	n_∞ (=0.990n)	$N \times 10^{-21}$, cm³/molecules	P_{ex}, mol/cm³
R125	296.2	1.172	6.028	11.0
R134a	296.2	1.203	7.171	10.9
R143a	297.7	1.183	6.920	10.2
R152a[a]	298.2	1.229	8.196	10.7
R134[a]	298.2	1.222	7.584	11.2
R143	296.2	1.249	8.756	10.8
R124	297.7	1.257	6.019	16.3

[a] Data from Chae et al.[12]

shortly. Figure 4 shows a plot of $\mu^2(T)$ for R134. The solid curve is a nonlinear least-squares fit of the data to eq 8 while constraining the moment of the trans conformer to be $\mu_1 = 0$. The best-fit values for the moment of the gauche conformer and the energy difference are $\mu_2 = 2.45 \pm 0.05$ D and $\Delta E = 5.97 \pm 0.15$ kJ/mol. This curve fits the data very well.

Measurements of μ_2 and ΔE have been made using spectroscopic techniques. Mukhtarov and Kuliev[26] have measured the dipole moment of the gauche conformer to be $\mu = 2.9$ D through the Stark effect (no uncertainty provided); this value is not in agreement with ours. We have plotted as the long-dashed curve in Figure 4 a best-fit curve of the data to eq 8 while assigning $\mu_1 = 0$, $\mu_2 = 2.9$ D; the two do not agree well. Studies of infrared and Raman spectra have determined the enthalpy difference between the trans and gauche conformer to be 4.85 ± 0.42 kJ/mol[24] and 4.94 ± 0.42 kJ/mol.[25] Shown as the short-dashed curve in Figure 4 is a best-fit curve of the data to eq 6 while assigning $\mu_1 = 0$, $\Delta E = 4.89$ kJ/mol; the agreement here is also poor.

A possible explanation for the discrepancy between our values of μ_2 and ΔE and those from the spectroscopic measurements might be our approximation of the value of ω. To check this we made a least-squares fit with ω a fitting parameter. The best-fit curve overlapped the solid curve of Figure 4, and the parameter values were $\omega = 9.1 \Omega 3.1$, $\mu_2 = 1.79 \pm 0.16$ D, and $\Delta E = 7.8 \pm 0.5$ kJ/mol. The value of ω is unphysically high, so this fit cannot be relied upon to determine μ_2 and ΔE. A second fit was made constraining μ_2 to have the value measured by ref 26. The quality of the fit was similar to the previous one; it yielded $\omega = 1.13 \pm 0.07$ and $\Delta E = 5.5 \pm 0.2$ kJ/mol. While ΔE is slightly closer to that measured by refs 24 and 25, it is improbable that the value of ω could be so small. A third fit was made constraining ΔE to have the value 4.90 kJ/mol (an average of the values measured by refs 24 and 25). The best-fit curve overlapped the solid curve of Figure 4, and the parameters were $\omega = 0.25 \pm 0.23$ and $\mu_2 = 5.2 \pm 4.8$ D. The value of ω is unphysically low, and the uncertainty in μ_2 is so large as to make the fit useless. From these three fits we conclude that allowing ω to be an adjustable parameter does not help for determining μ_2 and ΔE or explain the discrepancy between our results and the spectroscopic results.

As a final check on the influence of ω we made a least-squares fit with $\omega = 1.8$, a value close to that found for 1,1-dichloroethane at 400 K. The curve overlapped the solid curve of Figure 4 and yielded $\mu_2 = 2.52 \pm 0.06$ D, $\Delta E = 5.9 \pm 0.2$ kJ/mol. These values

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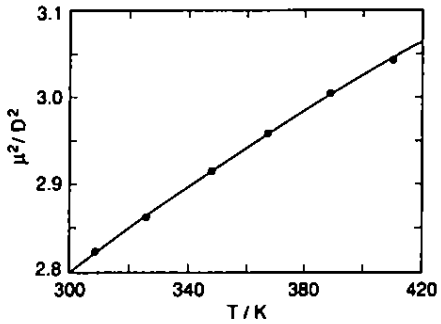

Figure 5. Square of the dipole moment of R143 as a function of temperature. The solid circles are the experimental determinations, and the curve represents the best-fit values using the functional form of eq 8 and assigning $\omega = 2.0$. The best-fit parameter values are $\mu_1 = 2.84$ D, $\mu_2 = 1.50$ D, and $\Delta E = -3.90$ kJ/mol.

are so close to those obtained with $\omega = 2.0$ that we conclude that our approximation of ω cannot account for the discrepancy. We conclude that our results are inconsistent with those of refs 24, 25, and 26.

In Figure 5 we plot $\mu^2(T)$ for R143 along with a best-fit curve of the data to eq 6. The best-fit parameters are $\mu_1 = 2.84 \pm 0.08$ D (C_s conformer), $\mu_2 = 1.50 \pm 0.15$ D (C_1 conformer), and $\Delta E = -3.90 \pm 2.2$ kJ/mol. The fit to the data is very good. Mukhtarov,[27] through the Stark effect, measures $\mu_2 = 1.58 \pm 0.02$ D, in excellent agreement with our fit. When performing the least-squares fit while constraining $\mu_2 = 1.58$ D, we obtain $\mu_1 = 3.00 \pm 0.06$ D, $\Delta E = -5.74 \pm 0.19$ kJ/mol. Kalasinsky et al.[25] have measured with Raman spectra $\Delta E = -4.43 \pm 1.6$ kJ/mol, in agreement with our value.

(27) Mukhtarov, I. A. *Dokl Akad. Nauk. SSSR* **1963**, *151*, 1076.

V. Conclusion

We have measured the dipole moments of R125, R152a, R134a, R143a, R134, R143, and R124. Our measured moments of R125, R152a, R134a, and R143 agree well with previous measurements made on these molecules, and all have uncertainties of less than 1%. We have presented the first measurement of the dipole moment of R124. In addition, we have made the first measurements of the temperature dependence of the dipole moments of R134 and R143 using dielectric-constant measurements. While our value of the moment of the C_1 conformer of R143 agrees well with that obtained from spectroscopic measurements, our value of the moment of the gauche conformer of R134 does not. For both R134 and R143 our value for the energy difference between the two conformers is higher than that measured for the enthalpy difference from spectroscopic measurements.

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Dynamic Instability and Light-Induced Spatial Bifurcation of HgI_2 and External Electric Field Experiments in Two-Dimensional Gel Media

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New results on two-dimensional propagation of a single red/yellow wave of mercuric iodide in gel media in batch, continuous-flow, and gel-ring reactors are reported. The influence of electrolyte concentrations, temperature, thickness of the gel, and type of the reactor on the kinetics of wave propagation has been studied. Light-induced spatial bifurcation of yellow wave into alternate yellow and red bands is observed at low pH of the gel containing mercuric chloride. Experiments to study the precipitation pattern and crystal growth on a thin film of agar–agar gel sandwiched between microslides were carried out. Rhythmicity was observed during red-wave propagation at low [KI]. A new type of continuous-flow reactor has been designed to carry out experiments in the presence of an external electric field. Transitions from yellow to red and red to yellow forms have been observed in the presence of an external electric field. A critical field intensity at 0.283 V cm^{-1} exists at which the yellow form changes into a red variety.

Introduction

There is considerable scientific interest in the crystal growth, development of chemical waves, and rhythmic precipitation in gel media. The subject has been of practical importance for many years. In recent years, a reactivation of experimental and theoretical research in the field of periodic precipitation in gel media can be noticed.[1-8] Light absorption also plays an important role in the macroscopic structure development,[4-6,9-11] and the phenomenon can be influenced in the presence of an external electric field.[11-14] It is possible to stop, reverse, or destroy chemical waves by imposed electric field.[13]

In earlier communications[10,11] we reported results on the one-dimensional propagation of yellow/red mercuric iodide, influence

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DAIKIN | Positively Innovative

SOLKANE™ 227 pharma and 134a pharma

PROPELLANTS

Daikin Industries, Ltd.

has acquired Solvay S.A.'s German-based pharma propellants and refrigerant business effective May 5th, 2015. Daikin will continue the production of HFA propellants 227 pharma and 134a pharma at the Frankfurt works under the Solkane™ trademark, to the same standards as before. Solkane™ is a trademark of the Solvay Group.

SOLKANE™ 227 pharma / SOLKANE™ 134a pharma

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SOLKANE™ 227 pharma / SOLKANE™ 134a pharma

SOLKANE™ pharma – Special Pharmaceutical Grade

- Highest purity guaranteed by manufacture in dedicated facilities according to cGMP
- High-level quality control
- Specifically developed sophisticated analytical methods
- Worldwide Regulatory Affairs support in accordance with drug active substances

HFA Propellants for Use in Medical Sprays

SOLKANE™ 227 pharma and SOLKANE™ 134a pharma, also known as:

- HFA 227, HFC 227 or 1,1,1,2,3,3,3-heptafluoropropane and
- HFA 134a, HFC 134a or 1,1,1,2,-tetrafluoroethane

respectively, are used in medical sprays such as:

- MDIs (Metered Dose Inhalers, also called asthma sprays or pharmaceutical aerosols inhaled by the patient),
- nasal sprays
- foam sprays and
- other oral/topical sprays

to propel the active ingredient which is dispersed or solubilised in the **h**ydro**f**luoro**a**lkane (hereinafter referred to as HFA propellant).

Neither HFA 227 nor HFA 134a contain chlorine and they are thus non-ozone depleting. Furthermore, they are non-flammable and chemically inert. This makes them (from a safety and toxicological point of view) ideal candidates for use in medical products. Moreover, because HFA 227 and HFA 134a have thermodynamic and physical properties closely resembling the **c**hloro**f**luoro**c**arbons CFC 11, CFC 12 and CFC 114 traditionally used in medical sprays, they were proposed to replace these ozone-depleting CFCs currently being phased out under the terms of the Montreal Protocol.

Accordingly, HFA 227 and HFA 134a were developed in a special pharmaceutical grade as SOLKANE™ 227 pharma and SOLKANE™ 134a pharma specifically for use in medical products. They are of the highest quality as required for sensitive routes of administration – in the case of MDIs, via inhalation to the lung.

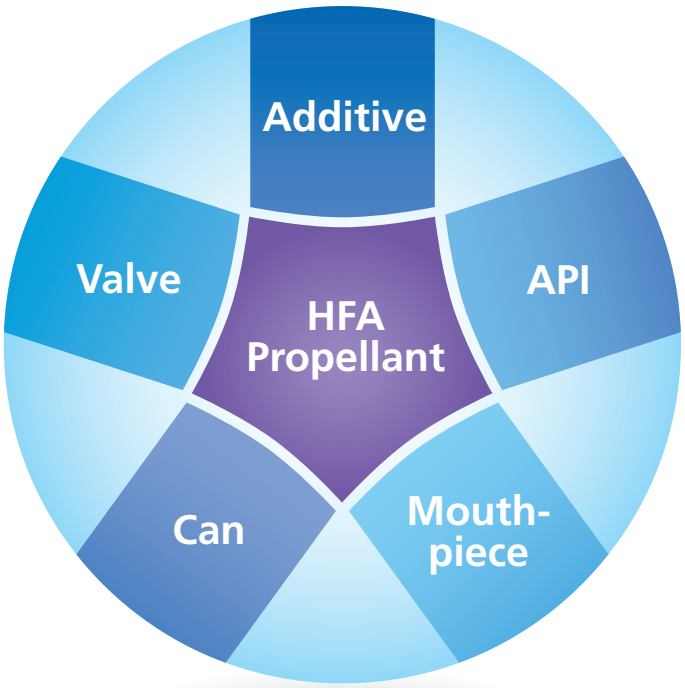


Fig. 1: The world of pressurized Metered Dose Inhalers

The main differences to ordinary "technical grade" SOLKANE™ 227 and SOLKANE™ 134a – predominantly used as refrigerants and fire extinguishing agents – are:

(i) the higher purity obtained by additional manufacturing processes specifically developed and applied to meet the stringent specifications set out for pharmaceutical grade products,

(ii) manufacturing in dedicated facilities according to the current good manufacturing practice guidelines,

(iii) high-level quality control using analytical methods specifically developed to screen more than 60 impurities in the propellants at levels below one part per million,

(iv) registration of the manufacturing processes and quality control systems according to the standards for drug active substances, although both HFA 227 and HFA 134a are classed as exipients.

SOLKANE™ pharma – HFA Propellants for Medical Sprays

Including
- MDIs (Metered Dose Inhalers) also known as pharmaceutical aerosols or asthma sprays for the treatment of asthma, COPD (Chronic Obstructive Pulmonary Disease) and respiratory infections
- nasal sprays for the treatment of allergic rhinitis
- foam sprays
- oral and topical sprays (e.g. nerve sensitisation, tooth vitality, pain relaxation)

to replace the fully halogenated ozone depleting chlorofluorocarbons

- CFC 11, CFC 12 and CFC 114

traditionally used in medical sprays, which are being phased out under the terms of the Montreal Protocol, by the non-ozone depleting hydrofluoroalkanes

- HFA 227, or blends thereof
- and HFA 134a.

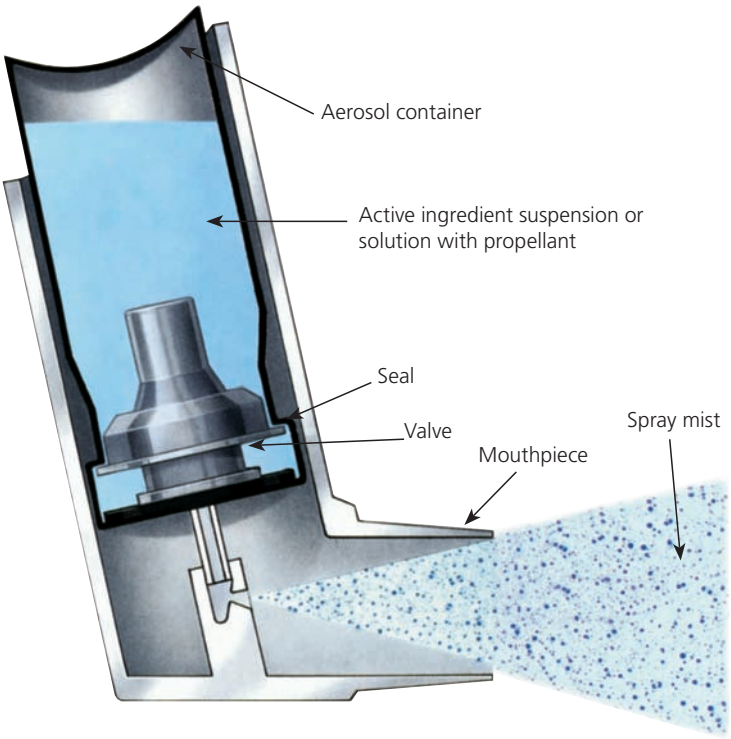


Fig. 2: Metered Dose Inhaler (MDI)

History of the Pharmaceutical Propellants HFA 227 and HFA 134a – IPACT I, IPACT II

When it was confirmed in the 1980s that fully halogenated CFCs harm the ozone layer in the upper stratosphere, extensive investigations were carried out to identify suitable CFC replacement components for various applications including MDIs.

In 1989, a consortium by the name of IPACT I (International Pharmaceutical Aerosol Consortium for Toxicity Testing) formed to investigate HFA 134a as a potential CFC replacement candidate for use in medical sprays. This was followed by IPACT II for HFA 227 in 1990. Both IPACT I and IPACT II comprise major pharmaceutical aerosol manufacturers sponsoring the extensive toxicological tests for HFA 227 and HFA 134a to confirm their use for medical products including MDIs.

The main studies – carried out from 1990 to 1993/4 and laid down in IPACT I/II dossiers submitted to all major countries for support of medical product applications containing HFA 227 and HFA 134a – were reviewed by the European Health Authorities (CPMP – Committee for Proprietary Medicinal Products) and received positive opinions as cited:

SOLKANE™ pharma – History of the Pharmaceutical Propellants HFA 227 and HFA 134a – IPACT I, IPACT II

1989/1990	Formation of two consortia: IPACT I for the toxicological testing of HFA 134a IPACT II for the toxicological testing of HFA 227
1990 – 1993/4	Main toxicological studies carried out with former Hoechst AG, later Solvay, now Daikin, as sole supplier of the pharmaceutical grade HFA 227
July 1994	CPMP positive opinion for HFA 134a with published specifications
September 1995	CPMP positive opinion for HFA 227 "at the specification applied for" for Hoechst, now Daikin-quality; specifications not disclosed
July 1998/April 2001	CPMP reviews of the SOLKANE™ 227 pharma DMFs/Amendments
Dec. 1998/June 2001	Final assessments and CPMP "approval" of all changes received with the final conclusion: **"HFA 227 produced at Frankfurt manufacturing site, SOLKANE™ 227 pharma, is a suitable alternative to CFCs currently used in the formulation of medicinal products, including metered dose inhalers for the treatment of asthma."** [6]

IPACT I International Pharmaceutical Aerosol Consortium for Toxicity Testing of HFA 134a
IPACT II International Pharmaceutical Aerosol Consortium for Toxicity Testing of HFA 227
CPMP Committee for Proprietary Medicinal Products

"The Committee considers that HFA 134a of the specified quality (in annex) could be a suitable alternative to the CFCs currently used in the formulation of medicinal products, incl. metered dose inhalers for the treatment of asthma." [1]. In this report, the specifications for HFA 134a were disclosed in the annex.

The positive opinion for HFA 227 was similar, but did not publish the specifications. Instead, it referred to "the specification as applied for" as follows: "The Committee considers that HFA 227 at the specification applied for is a suitable alternative to the CFCs currently used in the formulation of medicinal products, incl. metered dose inhalers for the treatment of asthma." [6].

Thus, both HFA 277 and HFA 134a can be used in medical products when they comply with the quality assessed by Health Authorities. In the case of HFA 227 it must comply with Daikin's quality standards because all the IPACT II toxicological studies were carried out with Daikin's (formerly Hoechst AG, Solvay) support as the sole supplier of HFA 227. Solvay (formerly Hoechst AG, now Daikin) submitted its Drug Master File (DMF) for the manufacture and quality control of HFA 227 as part of the IPACT II dossier.

In the case of HFA 134a, the quality must comply with the quality standards as disclosed in Europe by the CPMP as referred to above, or for the U.S. market as proposed by the U.S. Food and Drug Administration's Center for Drug Evaluation and Research (FDA CDER) October 1998 Draft Guidance for Industry on MDIs and DPIs (Dry Powder Inhaler)[3].

Since then, Solvay (now Daikin) has optimised its manufacturing processes and quality with many DMF updates, and finally initiated an independently coordinated CPMP review of all amendments. These were finally "approved" in December 1998 and June 2001 with the following conclusion:

Conclusion

The toxicological properties of HFA 227 were previously assessed to an adequate extent (CPMP/391/97).

Comparing the purity of SOLKANE™ 227 pharma with that of the Hoechst test batches used to perform the toxicity tests reported by IPACT II, it can be concluded that SOLKANE™ 227 pharma complies with the pharmaceutical grade specifications for this compound and that it contains less concentrations of the comparable impurities than the Hoechst tox test batches. [...]

Overall Conclusion

HFA 227 produced at Frankfurt manufacturing site, SOLKANE™ 227 pharma, is a suitable alternative to the CFCs currently used in the formulation of medicinal products, including metered dose inhalers for the treatment of asthma."[6]

The approved DMFs were subsequently submitted to all countries for customer support.

As such a review is unique in the case of HFA 227, Daikin is setting the standard for HFA 227 in the medical world.

In the case of SOLKANE™ 134a pharma, Solvay (now Daikin) submitted its Drug Master Files in Canada in 2001, in the USA in 2002, and to the rest of the world, including all European countries in 2003. Hereby Daikin fully complies with all specifications published by the CPMP[1,4,5] as mentioned above and the FDA[3].

Quality Control and Specifications

In the case of HFA 134a, two quality standards have already been published: one by the CPMP as mentioned before[1], and one proposed by the FDA in a draft guideline[3]; accordingly, the quality shall comply with these standards.

In Europe a Norflurane Monograph No. 2257 is available containing Daikins GC-MS (gas chromatography - mass spectrometry) and Non-Volatile Matter Methods. The quality of Daikins Solkane 134a pharma is equal to or even higher than proposed in the published monograph and fully complies with the published CPMP and FDA specifications for use in inhalation products. The latter specifications were developed on the results of the toxicity testing studies by IPACT I, mandatory for safety of the patients inhaling MDI propellant formulations. As a result, HFA 134a pharma specifications in the USA and Europe are still supplier related.

As seen from the table which lists all impurities mentioned in these standards, sophisticated analytical methods are required to identify and detect all impurities without interference from the others. Solvay (now Daikin) has developed a GC-MS method especially for this purpose which allows the control of each of the listed impurities at limits of detection (LODs) below 1 ppm (v/v).

Fig. 3: Cleaning cylinders prior to use for SOLKANE™ 134a pharma according to Standard Operating Procedures (SOPs) in the area designated for SOLKANE™ pharma products only

SOLKANE™ pharma – Impurities of HFA 134a Proposed by CPMP/FDA in Comparison to Daikin Quality

Volatile Related Substance	Limit (ppm) FDA (October 98 draft guidance)	Limit (ppm) CPMP (July 94 press release)	Norflurane Production Batches typical values (ppm (m/m))
CFC 114a	≤ 25	≤ 1000(1)	n.d.
HCC 40	≤ 5	≤ 50	n.d.
HCFC 1122	≤ 5	–	< 0.4
HCFC 124	≤ 100	≤ 1000(1)	n.d.
HCFC 133a	≤ 5	≤ 5	n.d.
HCFC 22	≤ 50	≤ 1000(1)	n.d.
HCFC 31	≤ 5	≤ 5	n.d.
HFC 125	≤ 5	≤ 1000(1)	n.d.
HFC 134	≤ 1000	≤ 1000(1)	15
HFC 143a	≤ 10	≤ 1000(1)	n.d.
HFC 152a	≤ 300	≤ 1000(1)	n.d.
CFC 114	≤ 5	≤ 1000(1)	n.d.
HFC 1234yf	≤ 5	–	n.d.
HFC 1225ye	≤ 5	–	n.d.
HFC 1243zf	≤ 5	–	1
CFC 217ba	≤ 5	–	1
HFC 134a (assay)	≥ 99.9	≥ 99.8	> 99.99
CFC 115	≤ 5	≤ 1000(1)	n.d.
CFC 12	≤ 100	≤ 1000(1)	n.d.
HCFC 1122a	≤ 5	–	n.d.
HFC 245cb	≤ 5	≤ 1000(1)	n.d.
HFC 23	≤ 5	–	n.d.
HFC 32	≤ 5	–	n.d.
HFC 152	≤ 5	≤ 5	n.d.
HFC 1123	≤ 5	–	n.d.
FC 1318my-cis	≤ 5	–	n.d.
FC 1318my-trans	≤ 5	–	n.d.
HFC 1132	≤ 5	–	n.d.
HFC 1336mzz	≤ 5	–	n.d.
HCFC 123	≤ 5	≤ 1000(1)	n.d.
HCFC 123a	≤ 5	≤ 1000(1)	n.d.
HCFC 124a	≤ 5	≤ 1000(1)	n.d.
HCFC 132b	≤ 5	≤ 5	n.d.
HCFC 161	≤ 30	–	n.d.
HCFC 1121	≤ 5	–	n.d.
CFC 11	≤ 5	≤ 1000(1)	n.d.
CFC 12B1	≤ 5	–	n.d.
CFC 13	≤ 5	–	n.d.
CFC 113	≤ 5	–	n.d.
CFC 1112a	≤ 5	–	n.d.
Total unsaturates	≤ 5	≤ 5	1
Sum of others	≤ 50	≤ 50	n.d.
Individual unidentified impurities	≤ 5	–	n.d.
Total unidentified impurities	≤ 10	–	n.d.
Any other identified saturated impurity	≤ 5	–	n.d.
Total impurities	≤ 1000	–	17

(1) Not more than 1000 ppm alone or in combination; n.d.: not detected

Fig. 4: Comparison of the FDA draft proposal for impurity limits in pharmaceutical HFA 134a and CPMP specifications with the SOLKANE™ 134a pharma quality from six production batches

The Daikin specifications for SOLKANE™ 227 pharma and SOLKANE™ 134a pharma are listed as follows:

Daikin Specifications	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Contents	≥ 99.99 % vol.	≥ 99.9 % vol.
Identification	Complies with MS library	Complies with MS library
Water	≤ 10 µg/g	≤ 10 µg/g
Non-volatile Matter	≤ 20 ppm (m/m)	≤ 50 ppm (m/m)
Volatile Related Substances (Impurity Profile)	Described in the Daikin DMF for apaflurane (HFA 227)	Described in the Daikin DMF for norflurane (HFA 134a)
Acidity	≤ 0.1 µg/g (as HF)	≤ 0.1 µg/g (as HCl)

Fig. 5: Electronic bar code scanning of SOLKANE™ 134a pharma cylinders for identification and traceability

Fig. 6: Analytical laboratory of the Daikin Refrigerants Europe GmbH Frankfurt works for the routine quality control of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma

Manufacture of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma by Daikin

The production of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma adhere to the stringent good manufacturing practice guidelines and continuously updated quality standards. For example, the small steel cylinders are thoroughly inspected and flushed according to SOPs prior to filling, and an electronic bar code system is used which allows every consignment to be traced throughout the world.

Daikin's analytical laboratories are state-of-the-art and new analytical methods have been developed and validated for both SOLKANE™ 227 pharma and SOLKANE™ 134a pharma to meet the latest standards. Routine quality controls are carried out at levels of less than 1 ppm for more than 60 impurities in line with CPMP/FDA Guidelines.

Daikin has filed Drug Master Files for both products in all countries for cross-reference to support drug applications containing SOLKANE™ 227 pharma or SOLKANE™ 134a pharma.

The Frankfurt manufacturing site owned by Daikin can look back on more than 25 years of experience in the manufacture and supply of the propellants HFA 227 and HFA 134a for pharmaceutical aerosols and is considered as a center of competence in this field – providing support for its customers in all technical, analytical and regulatory areas.

Fig. 7: Visual inspection of dedicated SOLKANE™ 134a pharma cylinders as part of Daikin's quality control

Fig. 8: Well-trained Daikin personnel at the production site in Frankfurt: Daikin's key to success

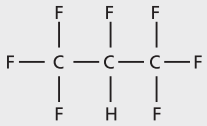
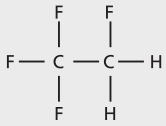
SOLKANE™ pharma – Daikin's Center of Competence

- Extensive experience in pharmaceutical propellants, supplying the pharmaceutical industry with HFAs since 1989
- New validated production facilities established in 1996/2001 in Frankfurt (Germany) meeting the highest quality standards according to cGMP (Current Good Manufacturing Practice)
- Highly qualified staff – continuous personnel training
- Traceability of each consignment via computer-controlled filling operations
- Manufacture of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma in highest purity using patented processes
- Product handling according to SOPs in SOLKANE™ pharma-designated areas only
- All equipment dedicated to SOLKANE™ pharma
- Availability of analytical GC-MS methods to screen more than 60 impurities at LODs < 1 ppm (in-house development)
- Active customer support for technical, analytical, and regulatory issues
- Maintenance of DMFs worldwide with active submission of variation procedures with CPMP/FDA for the establishment of specifications/analytical methods
- Active support of the EDQM/USP (European Directorate for the Quality of Medicines and Healthcare / US Pharmacopeial Convention) working groups and the HFA 227/134a consortia for the establishment of harmonized test methods and specifications

Fig. 9: Electronic bar code scanning of SOLKANE™ 227 pharma one tonne cylinders for identification and traceability

Physical Properties

Nomenclature

	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Structural Formula		
Molecular Formula	C_3HF_7	$C_2H_2F_4$
Chemical Name	1,1,1,2,3,3,3-Heptafluoropropane	1,1,1,2-Tetrafluoroethane
Chemical Family	Fluorinated Hydrocarbon	Fluorinated Hydrocarbon
ASHRAE* Nomenclature/ Laboratory Codes *American Society of Heating, Refrigerating and Air Conditioning Engineers	HFA 227, HFA 227ea HFC 227, HFC 227ea R 227, R 227ea	HFA 134a (**H**ydro**F**luoro**A**lkane) HFC 134a (**H**ydro**F**luoro**C**arbon) R 134a
International Nonproprietary Name (INN)	Apaflurane	Norflurane
Brand Name:	SOLKANE™ 227 pharma HFA 227 pharma	SOLKANE™ 134a pharma HFA 134a pharma

Description

	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Physical Form at 25 °C	Gaseous	Gaseous
Colour	Colourless	Colourless
Odor	Faint ethereal odor	Faint ethereal odor
Flammability	Non-flammable	Non-flammable
Toxicity	No appreciable toxic effect	No appreciable toxic effect
Ozone Depletion Potential (ODP)	Zero	Zero
Global Warming Potential (GWP)[9] related to CO_2 = 1.0 (100 years ITH*) *ITH = integrated time horizon	3,220	1,430
Atmospheric Lifetime[9]	34.2 years	14 years
Storage	Liquefied gas under pressure in steel cylinder	Liquefied gas under pressure in steel cylinder

Physical Data [SI Units]

		SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Chemical Name		1,1,1,2,3,3,3-Heptafluoropropane	1,1,1,2-Tetrafluoroethane
Chemical Formula		$CF_3–CFH–CF_3$	$CF_3–CH_2F$
Molar Mass	g/mol	170.03	102.03
Boiling Point at 1.1013 bar [10]	°C	–16.5	–26.3
Freezing Point [10]	°C	–131	–101
Critical Data: HFA 227 [12]; HFA 134a [11]			
Critical Temperature	°C	101.90	101.15
Critical Pressure	bar	29.52	40.64
Critical Density	kg/l	0.592	0.507
Critical Volume	l/kg	1.69	1.97

Temperature		0 °C	20 °C	40 °C	0 °C	20 °C	40 °C
Pressure of the Vapour	bar	1.96	3.90	7.03	2.93	5.72	10.16
Density of the Liquid	kg/dm³	1.482	1.408	1.322	1.296	1.226	1.148
Density of the Saturated Vapour	kg/dm³	0.0159	0.0310	0.0564	0.0145	0.0280	0.0504
Specific Heat Capacity of the Liquid	kJ/(kg·K)	1.096	1.148	1.222	1.337	1.402	1.505
Thermal Conductivity of the Liquid	mW/(m·K)	65.05	59.45	53.85	94.2	85.7	77.1
Dynamic Viscosity of the Liquid	mPa·s	0.346	0.267	0.210	0.273	0.211	0.162
Surface Tension of the Liquid	mN/m	9.31	6.96	4.80	11.49	8.69	6.06
Dielectric Constant Liquid Phase HFA 227 [14]; HFA 134a [13]		4.6	4.1	3.6	11.3	9.8	8.3

Thermal Stability

	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Temperature Below Which no Evident Degradation Occurs	475 °C [15]	368 °C [16]

Refractive Index

		SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
$n_{20°C}$ [17]	calculated value	1.2207	1.1746
$n_{20°C}$ [18]	measured value	1.2207	n.d.

Physical Data [US/UK Units]

		SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Chemical Name		1,1,1,2,3,3,3-Heptafluoropropane	1,1,1,2-Tetrafluoroethane
Chemical Formula		$CF_3–CFH–CF_3$	$CF_3–CH_2F$
Molar Mass	g/mol	170.03	102.03
Boiling Point at 1 atm [10]	°F	3.9	–15.3
Freezing Point [10]	°F	–203.8	–149.8
Critical Data: HFA 227 [12]; HFA 134a [11]			
Critical Temperature	°F	215.4	214.1
Critical Pressure	psia	424.7	589.4
Critical Density	lb/ft^3	38.77	31.65
Critical Volume	ft^3/lb	0.026	0.032

Temperature		32 °F	68 °F	104 °F	32 °F	68 °F	104 °F
Pressure of the Vapour	psia	28.43	56.56	101.96	42.50	82.96	147.36
Density of the Liquid	lb/ft^3	92.518	87.898	82.530	80.907	76.537	71.667
Density of the Saturated Vapour	lb/ft^3	0.993	1.935	3.521	0.905	1.748	3.146
Specific Heat Capacity of the Liquid	Btu/lb °F	0.262	0.274	0.292	0.319	0.335	0.359
Thermal Conductivity of the Liquid	Btu/hr·ft °F	0.0346	0.0316	0.0287	0.0532	0.0482	0.0432
Dynamic Viscosity of the Liquid	lbf/ft^2	$2.3E^{-04}$	$1.8E^{-04}$	$1.3E^{-04}$	$1.8E^{-04}$	$1.4E^{-04}$	$1.1E^{-04}$
Surface Tension of the Liquid	lbf/ft	$6.4E^{-04}$	$4.8E^{-04}$	$3.3E^{-04}$	$7.9E^{-04}$	$5.9E^{-04}$	$4.2E^{-04}$
Dielectric Constant Liquid Phase HFA 227 [14]; HFA 134a [13]		4.6	4.1	3.6	11.3	9.8	8.3

Thermal Stability

	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Temperature Below Which no Evident Degradation Occurs	887 °F [15]	694 °F [16]

Refractive Index

		SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
$n_{20°C}$ [17]	calculated value	1.2207	1.1746
$n_{20°C}$ [18]	measured value	1.2207	n.d.

Vapour Table Wet Vapour Range SOLKANE™ 227 pharma [19] [SI Units]

t [°C]	p [bar]	rho´ [kg/dm³]	rho´´ [kg/m³]	v´ [dm³/kg]	v´´ [dm³/kg]	h´ [kJ/kg]	h´´ [kJ/kg]	r [kJ/kg]	s´ [kJ/(kg·K)]	s´´ [kJ/(kg·K)]
–60	0.10	1.652	0.94	0.605	1068.06	137.91	285.75	147.84	0.7447	1.4383
–55	0.13	1.641	1.27	0.610	786.40	142.68	288.86	146.18	0.7669	1.4370
–50	0.18	1.628	1.70	0.614	588.58	147.53	292.01	144.49	0.7888	1.4363
–45	0.25	1.616	2.24	0.619	447.16	152.45	295.18	142.74	0.8106	1.4362
–40	0.32	1.603	2.90	0.624	344.47	157.44	298.38	140.93	0.8322	1.4367
–35	0.42	1.589	3.72	0.629	268.78	162.52	301.59	139.07	0.8537	1.4377
–30	0.54	1.575	4.71	0.635	212.21	167.66	304.81	137.15	0.8751	1.4391
–25	0.69	1.561	5.90	0.641	169.39	172.87	308.05	135.17	0.8963	1.4410
–20	0.87	1.546	7.32	0.647	136.57	178.16	311.29	133.13	0.9173	1.4432
–15	1.08	1.531	9.00	0.653	111.14	183.52	314.54	131.02	0.9382	1.4458
–10	1.33	1.515	10.96	0.660	91.22	188.95	317.79	128.84	0.9590	1.4486
–5	1.62	1.499	13.25	0.667	75.46	194.44	321.03	126.59	0.9796	1.4517
0	1.96	1.482	15.90	0.675	62.88	200.00	324.27	124.27	1.0000	1.4550
5	2.35	1.465	18.96	0.683	52.74	205.64	327.50	121.86	1.0204	1.4585
10	2.80	1.446	22.47	0.691	44.51	211.33	330.71	119.38	1.0406	1.4622
15	3.32	1.428	26.48	0.700	37.77	217.10	333.91	116.81	1.0606	1.4660
20	3.90	1.408	31.05	0.710	32.21	222.93	337.08	114.14	1.0806	1.4700
25	4.56	1.388	36.24	0.720	27.59	228.84	340.22	111.38	1.1004	1.4740
30	5.29	1.367	42.15	0.732	23.73	234.82	343.32	108.50	1.1201	1.4780
35	6.11	1.345	48.84	0.744	20.48	240.87	346.37	105.50	1.1397	1.4821
40	7.03	1.322	56.43	0.756	17.72	247.01	349.37	102.36	1.1593	1.4861
45	8.04	1.298	65.05	0.771	15.37	253.24	352.30	99.06	1.1788	1.4901
50	9.16	1.272	74.85	0.786	13.36	259.58	355.15	95.57	1.1982	1.4940
55	10.40	1.246	86.03	0.803	11.62	266.02	357.90	91.87	1.2177	1.4977
60	11.75	1.217	98.85	0.822	10.12	272.60	360.52	87.92	1.2373	1.5012
65	13.24	1.187	113.64	0.843	8.80	279.34	362.99	83.65	1.2570	1.5044
70	14.87	1.154	130.87	0.867	7.64	286.26	365.25	78.99	1.2769	1.5071

Density in g/l

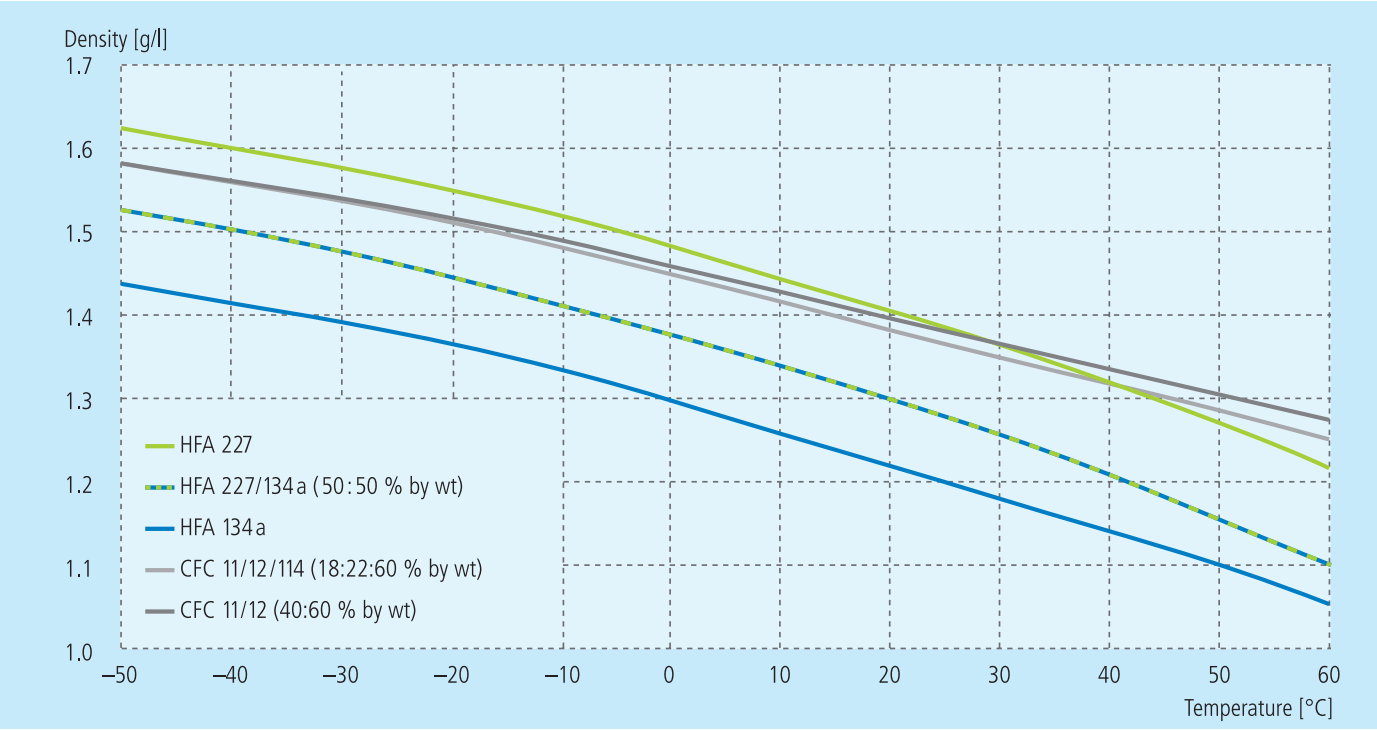


Fig. 10: Density of liquid of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma [19] including a 50:50 blend depending on temperature in comparison to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60) [20]

Vapour Table Wet Vapour Range SOLKANE™ 134a pharma [19] [SI Units]

t [°C]	p [bar]	rho´ [kg/dm³]	rho´´ [kg/m³]	v´ [dm³/kg]	v´´ [dm³/kg]	h´ [kJ/kg]	h´´ [kJ/kg]	r [kJ/kg]	s´ [kJ/(kg·K)]	s´´ [kJ/(kg·K)]
–60	0.16	1.475	0.93	0.678	1078.97	123.16	361.37	238.21	0.6859	1.8012
–55	0.22	1.461	1.25	0.684	802.33	129.49	364.53	235.04	0.7135	1.7904
–50	0.29	1.447	1.65	0.691	606.16	135.75	367.70	231.95	0.7409	1.7808
–45	0.39	1.433	2.15	0.698	464.67	141.98	370.86	228.89	0.7681	1.7722
–40	0.51	1.418	2.77	0.705	361.01	148.21	374.02	225.81	0.7950	1.7645
–35	0.66	1.404	3.52	0.712	283.94	154.47	377.17	222.70	0.8217	1.7576
–30	0.84	1.389	4.43	0.720	225.87	160.77	380.31	219.54	0.8480	1.7515
–25	1.06	1.374	5.51	0.728	181.55	167.13	383.42	216.29	0.8741	1.7460
–20	1.33	1.359	6.79	0.736	147.33	173.56	386.51	212.95	0.8999	1.7412
–15	1.64	1.343	8.29	0.744	120.61	180.06	389.56	209.51	0.9254	1.7369
–10	2.01	1.327	10.05	0.753	99.54	186.63	392.58	205.95	0.9505	1.7331
–5	2.43	1.311	12.08	0.763	82.76	193.27	395.56	202.29	0.9754	1.7297
0	2.93	1.295	14.43	0.772	69.28	200.00	398.49	198.49	1.0000	1.7267
5	3.50	1.278	17.14	0.782	58.35	206.79	401.37	194.58	1.0243	1.7241
10	4.15	1.261	20.23	0.793	49.43	213.65	404.19	190.54	1.0484	1.7217
15	4.88	1.243	23.76	0.804	42.08	220.58	406.94	186.35	1.0723	1.7196
20	5.72	1.225	27.78	0.816	35.99	227.59	409.61	182.02	1.0960	1.7176
25	6.65	1.206	32.35	0.829	30.91	234.67	412.20	177.53	1.1195	1.7158
30	7.70	1.187	37.53	0.842	26.65	241.83	414.69	172.86	1.1429	1.7141
35	8.87	1.167	43.40	0.857	23.04	249.08	417.07	168.00	1.1663	1.7124
40	10.17	1.146	50.06	0.872	19.98	256.43	419.33	162.90	1.1897	1.7107
45	11.60	1.125	57.62	0.889	17.36	263.90	421.44	157.54	1.2132	1.7090
50	13.18	1.102	66.21	0.908	15.10	271.52	423.38	151.86	1.2367	1.7071
55	14.92	1.078	76.03	0.928	13.15	279.32	425.12	145.80	1.2605	1.7049
60	16.82	1.053	87.28	0.950	11.46	287.33	426.63	139.30	1.2845	1.7024
65	18.90	1.026	100.27	0.975	9.97	295.60	427.84	132.24	1.3089	1.6994
70	21.17	0.996	115.42	1.004	8.66	304.18	428.70	124.52	1.3337	1.6957

Vapour Pressure in bar

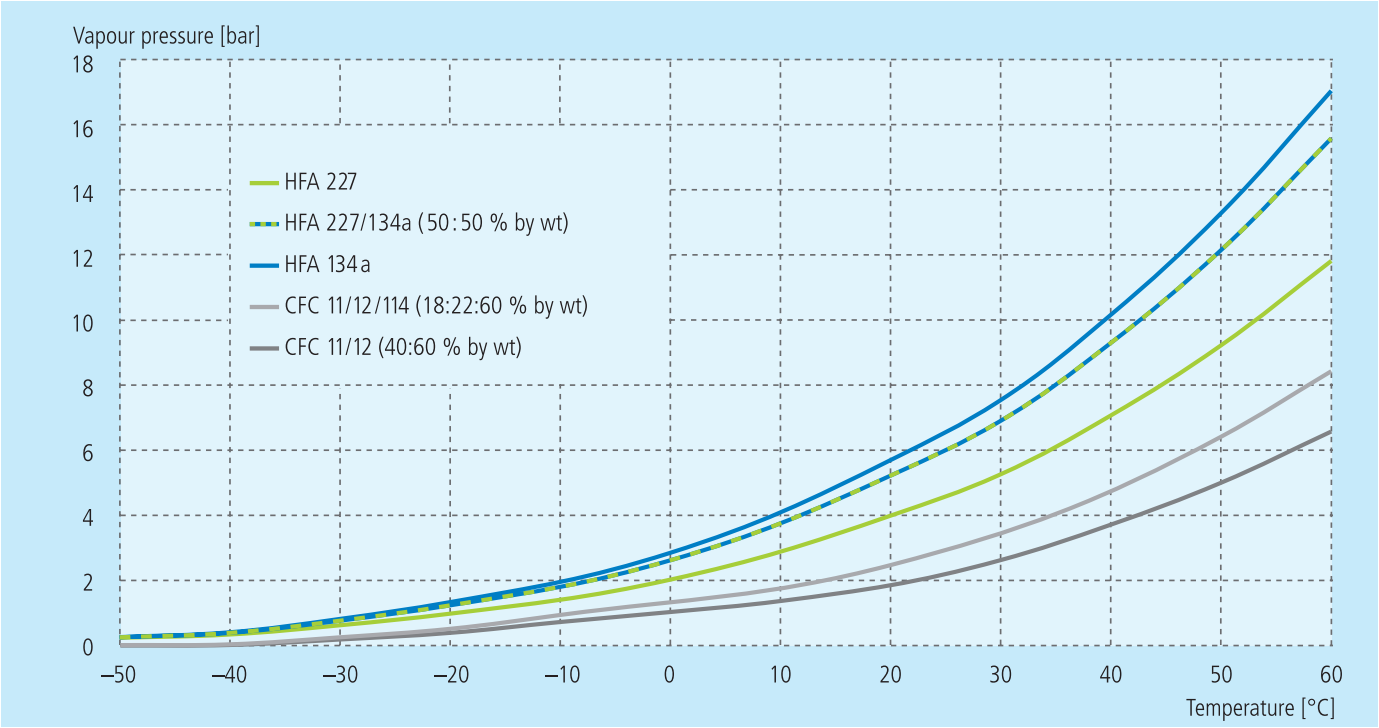


Fig. 11: Vapour pressure of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma [19] including a 50:50 blend depending on temperature in comparison to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60) [20]

Vapour Table Wet Vapour Range SOLKANE™ 227 pharma [19] [US/UK Units]

t [°F]	P [psia]	rho´ [lb/ft³]	rho´´ [lb/ft³]	v´ [ft³/lb]	v´´ [ft³/lb]	h´ [Btu/lb]	h´´ [Btu/lb]	r [Btu/lb]	s´ [Btu/R·lb]	s´´ [Btu/R·lb]
–76	1.45	103.13	0.06	0.0097	17.041	59.28	122.85	63.57	0.1778	0.3435
–67	1.89	102.44	0.08	0.0098	12.613	61.34	124.19	62.85	0.1831	0.3432
–58	2.61	101.63	0.11	0.0098	9.423	63.42	125.54	62.12	0.1884	0.3431
–49	3.63	100.88	0.14	0.0099	7.151	65.54	126.90	61.36	0.1936	0.3430
–40	4.64	100.07	0.18	0.0100	5.524	67.69	128.28	60.59	0.1988	0.3431
–31	6.09	99.20	0.23	0.0101	4.306	69.87	129.66	59.79	0.2039	0.3434
–22	7.83	98.32	0.29	0.0102	3.401	72.08	131.04	58.96	0.2090	0.3437
–13	10.01	97.45	0.37	0.0103	2.715	74.32	132.44	58.11	0.2141	0.3442
–4	12.62	96.51	0.46	0.0104	2.188	76.59	133.83	57.24	0.2191	0.3447
5	15.66	95.58	0.56	0.0105	1.780	78.90	135.23	56.33	0.2241	0.3453
14	19.29	94.58	0.68	0.0106	1.462	81.23	136.62	55.39	0.2291	0.3460
23	23.50	93.58	0.83	0.0107	1.209	83.59	138.02	54.42	0.2340	0.3467
32	28.43	92.52	0.99	0.0108	1.007	85.98	139.41	53.43	0.2388	0.3475
41	34.08	91.46	1.18	0.0109	0.845	88.41	140.80	52.39	0.2437	0.3484
50	40.61	90.27	1.40	0.0111	0.713	90.86	142.18	51.32	0.2485	0.3492
59	48.15	89.15	1.65	0.0112	0.605	93.34	143.55	50.22	0.2533	0.3501
68	56.56	87.90	1.94	0.0114	0.516	95.84	144.92	49.07	0.2581	0.3511
77	66.14	86.65	2.26	0.0115	0.442	98.38	146.27	47.88	0.2628	0.3521
86	76.73	85.34	2.63	0.0117	0.380	100.95	147.60	46.65	0.2675	0.3530
95	88.62	83.97	3.05	0.0119	0.328	103.55	148.91	45.36	0.2722	0.3540
104	101.96	82.53	3.52	0.0121	0.284	106.19	150.20	44.01	0.2769	0.3549
113	116.61	81.03	4.06	0.0123	0.246	108.87	151.46	42.59	0.2816	0.3559
122	132.85	79.41	4.67	0.0126	0.214	111.60	152.69	41.09	0.2862	0.3568
131	150.84	77.79	5.37	0.0129	0.186	114.37	153.87	39.50	0.2908	0.3577
140	170.42	75.97	6.17	0.0132	0.162	117.20	154.99	37.80	0.2955	0.3586
149	192.03	74.10	7.09	0.0135	0.141	120.09	156.06	35.96	0.3002	0.3593
158	215.67	72.04	8.17	0.0139	0.122	123.07	157.03	33.96	0.3050	0.3600

Density in lb/ft³

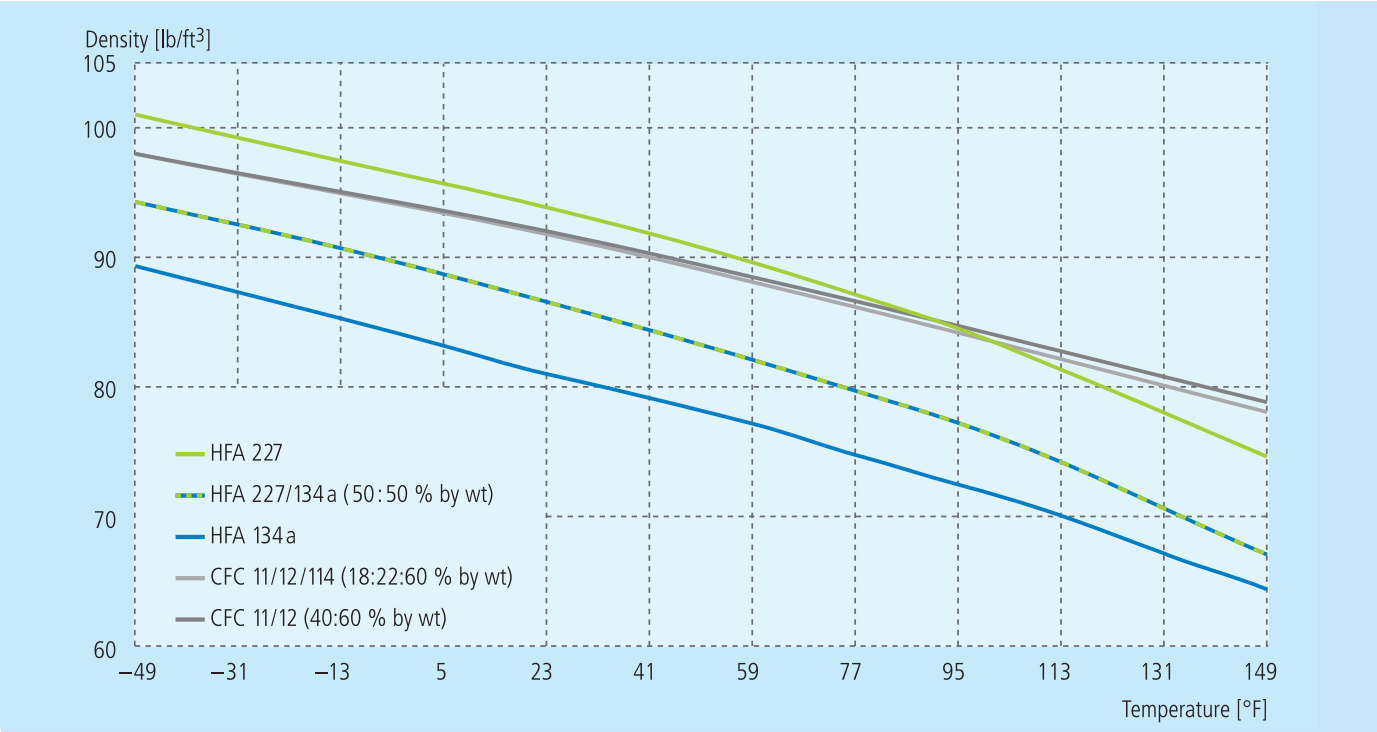


Fig. 12: Density of liquid SOLKANE™ 227 pharma and SOLKANE™ 134a pharma [19] including a 50:50 blend depending on temperature in comparison to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60) [20]

Vapour Table Wet Vapour Range SOLKANE™ 134a pharma [19] [US/UK Units]

t [°F]	p [psia]	rho´ [lb/ft³]	rho´´ [lb/ft³]	v´ [ft³/lb]	v´´ [ft³/lb]	h´ [Btu/lb]	h´´ [Btu/lb]	r [Btu/lb]	s´ [Btu/R·lb]	s´´ [Btu/R·lb]
–76	2.32	92.08	0.06	0.0109	17.224	52.96	155.39	102.43	0.1639	0.4305
–67	3.19	91.21	0.08	0.0110	12.814	55.68	156.75	101.07	0.1705	0.4279
–58	4.21	90.34	0.10	0.0111	9.708	58.37	158.11	99.74	0.1771	0.4256
–49	5.66	89.46	0.13	0.0112	7.450	61.05	159.47	98.42	0.1836	0.4236
–40	7.40	88.53	0.17	0.0113	5.783	63.73	160.83	97.10	0.1900	0.4217
–31	9.57	87.65	0.22	0.0114	4.551	66.42	162.18	95.76	0.1964	0.4201
–22	12.18	86.72	0.28	0.0115	3.616	69.13	163.53	94.40	0.2027	0.4186
–13	15.37	85.78	0.34	0.0117	2.907	71.87	164.87	93.00	0.2089	0.4173
–4	19.29	84.84	0.42	0.0118	2.359	74.63	166.20	91.57	0.2151	0.4161
5	23.79	83.84	0.52	0.0119	1.932	77.43	167.51	90.09	0.2212	0.4151
14	29.15	82.84	0.63	0.0121	1.594	80.25	168.81	88.56	0.2272	0.4142
23	35.24	81.85	0.75	0.0122	1.326	83.11	170.09	86.98	0.2331	0.4134
32	42.50	80.85	0.90	0.0124	1.110	86.00	171.35	85.35	0.2390	0.4127
41	50.76	79.79	1.07	0.0125	0.935	88.92	172.59	83.67	0.2448	0.4121
50	60.19	78.72	1.26	0.0127	0.792	91.87	173.80	81.93	0.2506	0.4115
59	70.78	77.60	1.48	0.0129	0.674	94.85	174.98	80.13	0.2563	0.4110
68	82.96	76.48	1.73	0.0131	0.577	97.86	176.13	78.27	0.2619	0.4105
77	96.45	75.29	2.02	0.0133	0.495	100.91	177.25	76.34	0.2676	0.4101
86	111.68	74.10	2.34	0.0135	0.427	103.99	178.32	74.33	0.2732	0.4097
95	128.65	72.86	2.71	0.0137	0.369	107.10	179.34	72.24	0.2787	0.4093
104	147.51	71.54	3.13	0.0140	0.320	110.26	180.31	70.05	0.2843	0.4089
113	168.25	70.23	3.60	0.0142	0.278	113.48	181.22	67.74	0.2900	0.4085
122	191.16	68.80	4.13	0.0145	0.242	116.75	182.05	65.30	0.2956	0.4080
131	216.40	67.30	4.75	0.0149	0.211	120.11	182.80	62.69	0.3013	0.4075
140	243.96	65.74	5.45	0.0152	0.184	123.55	183.45	59.90	0.3070	0.4069
149	274.13	64.05	6.26	0.0156	0.160	127.11	183.97	56.86	0.3128	0.4062
158	307.05	62.18	7.21	0.0161	0.139	130.80	184.34	53.54	0.3188	0.4053

Vapour Pressure in psia

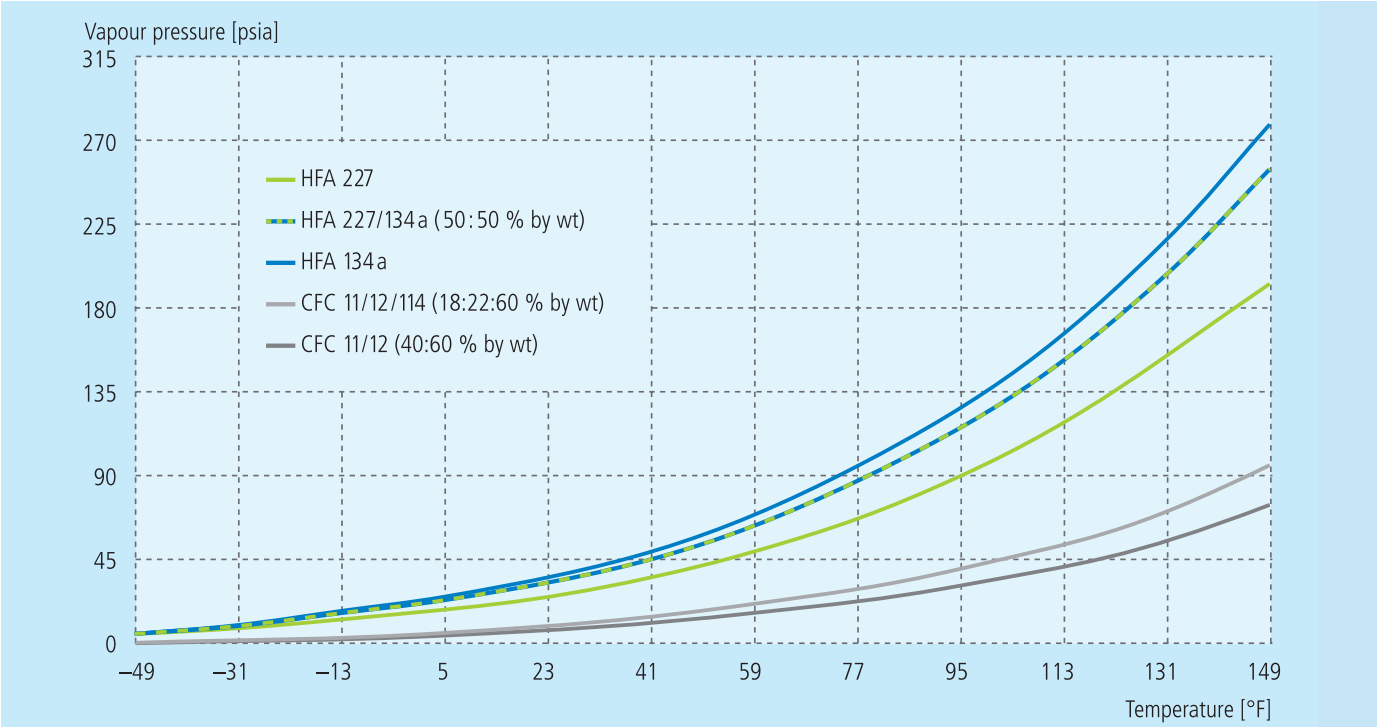


Fig. 13: Vapour pressure of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma [19] including a 50:50 blend depending on temperature in comparson to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60) [20]

Viscosity in mPa·s

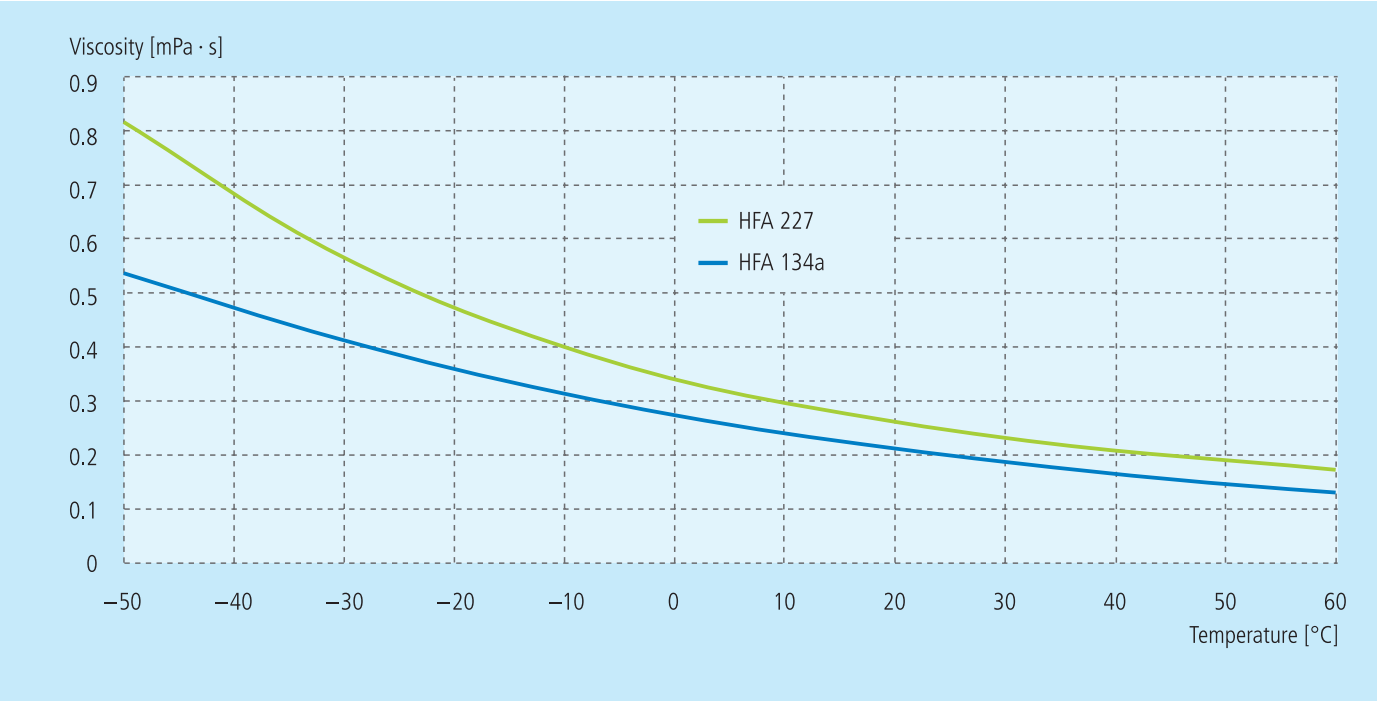


Fig. 14: Dynamic viscosity of liquid SOLKANE™ 227 pharma and SOLKANE™ 134a pharma depending on temperature[19]

Surface Tension in mN/m²

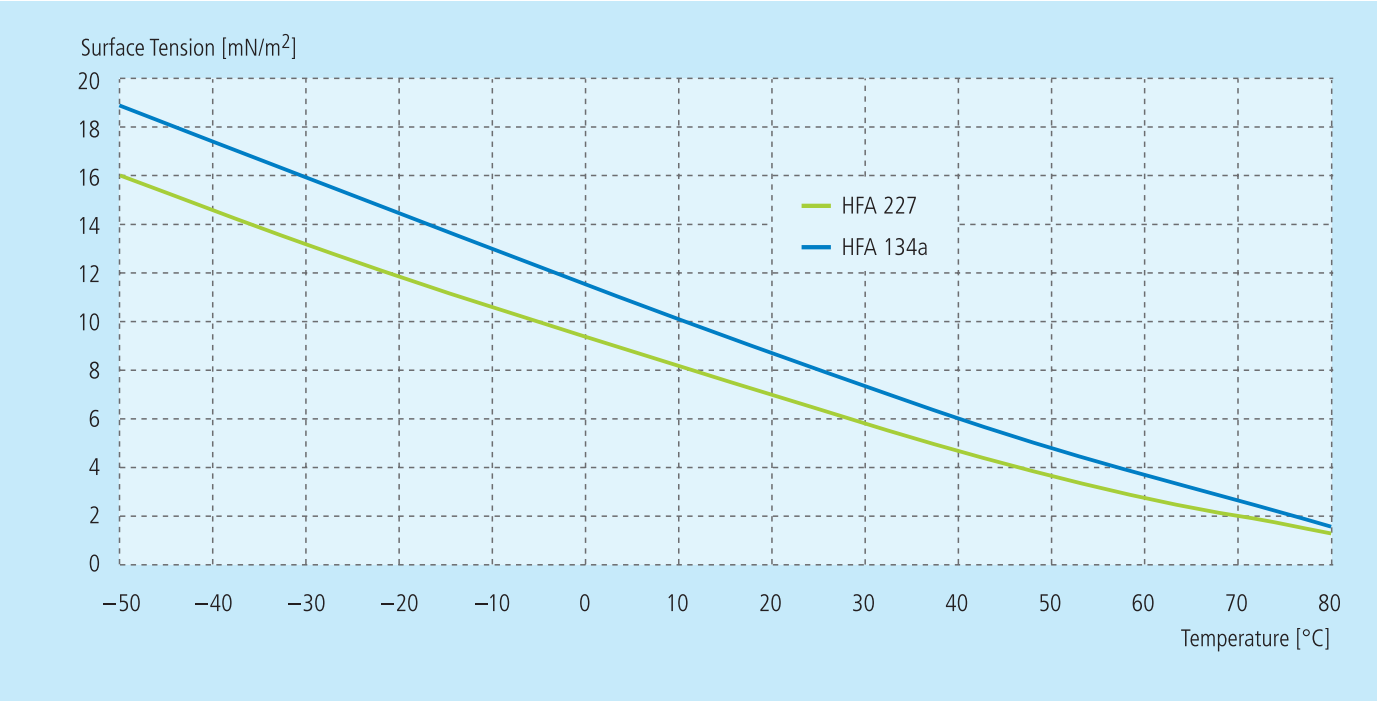


Fig. 15: Surface tension of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma depending on temperature[19]

Solubility Parameters / Characteristics

Solubility Values

Solubility in			SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Water [21]	at 20 °C, 68 °F	ppm	58	193
Octanol [21]	at 20 °C, 68 °F	ppm	5.070	2.140

Solubility in HFA 227 and HFA 134a of				
Oxygen [22]	at atmospheric conditions: at 25 °C (77 °F), in liquid phase	g/kg	approx. 0.08	approx. 0.10
Nitrogen [23]	at atmospheric conditions: at 25 °C (77 °F), in liquid phase	g/kg	0.55	0.15
Water [21]	**Measured values at 25 °C in liquid phase**	g/kg	0.61	2.20
	Experimental results in liquid phase at 25 °C [24]	g/kg	n.d.	1.21
Ethanol [21]			Miscible	Miscible
Silicone Oil [25]	high viscosity oil (V1000)	ppm (wt.)	149	317
Silicone Oil [25]	low viscosity oil (V300)	ppm (wt.)	585	505

Solubility Characteristics

Dipole Moment measured value liquid phase	debye	0.93 [14]	2.058 [26]
Dipole Moment calculated value gas phase [14]	debye	1.46	n.d.
Octanol-Water-Coefficient [20]	log P_{ow}	2.05	1.06
Kauri-Butanol-Index		13 [21]	9.2 [27]
Solubility Parameter calculated value [19]		5.4	6.8

Solubility of Water

There is a notable difference in water solubility between HFA 227 and HFA 134a. As shown in Fig. 17, the moisture uptake of HFA 134a is six times higher compared to HFA 227 (measured values) due to its higher polarity. Therefore HFA 227 is preferred for formulations which might change due to water uptake during the MDI shelf life, e.g. for drugs such as sodium cromoglycate, cromoglycic acid, nedocromil sodium, nedocromil, ipratropium bromide, salbutamol sulfate, terbutaline hemisulfate or formoterol. In general, the HFAs are more polar than CFCs and thus more hygroscopic.

Dipole Moments [20]

HFA 134a	**2.06**
H_2O	1.85
Ethanol	1.68
HFA 227	**1.46**; (0,93) [14]
CFC 114	0.66
CFC 12	0.51
CFC 11	0.45

Water Solubility in HFA 134a

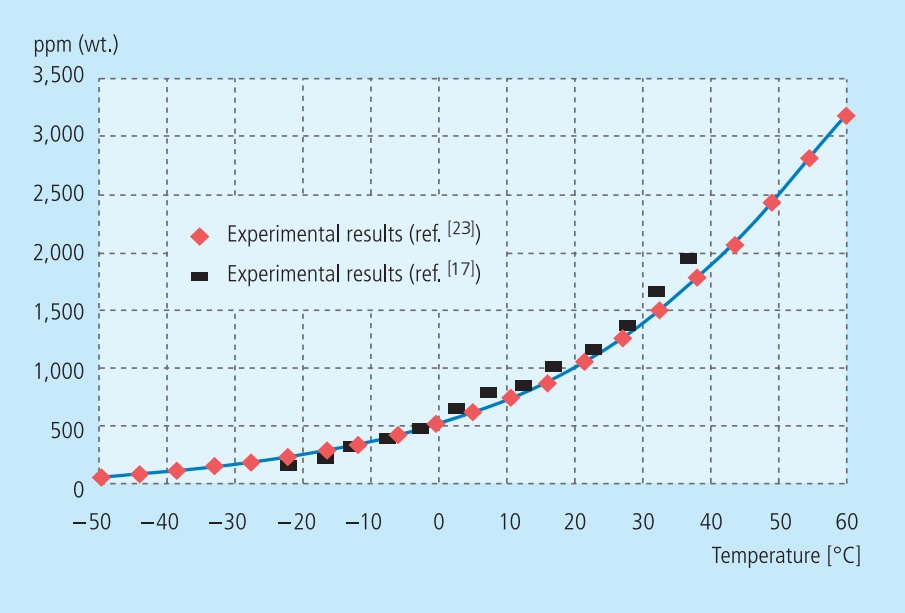


Fig. 16: Illustration of the experimental results for water solubility in HFA 134a in liquid phase [23, 17]

Moisture Uptake

Sources of Moisture Uptake in MDIs:

Due to partial pressure differences inside and outside of the MDI, moisture uptake takes place by diffusion.

Possible Effects of Moisture Uptake:

- Improves solubility of polar substances in the propellants
- Reduces the solubility of lipophile, hydrophobic substances
- Increases probability that sensitive substances become oxidised during shelf live
- Increases the corrosion risk of aluminium cans over the shelf life
- Agglomeration of suspended drug substances
- Influences the discharge behaviour of the active substances

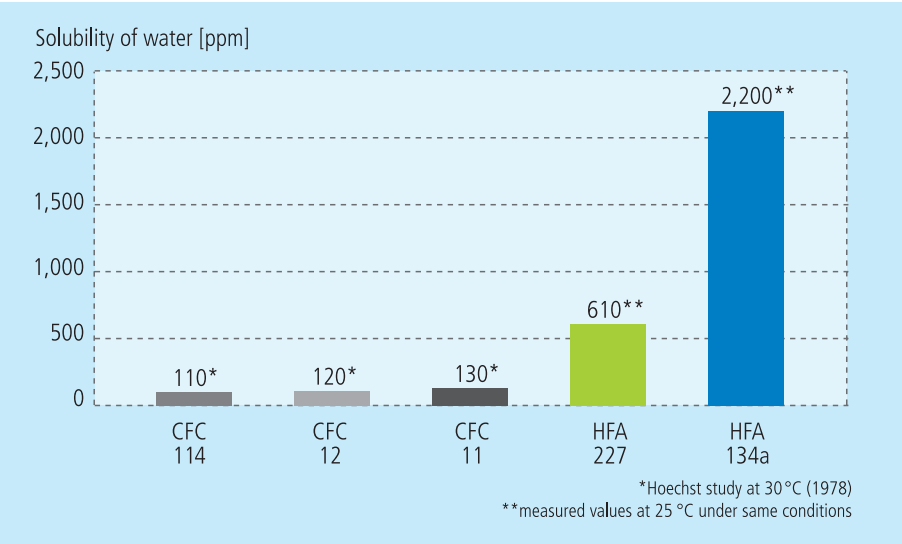


Fig. 17: Solubility of water in HFAs compared to CFCs

Solubility of Oxygen and Nitrogen

		SOLKANE™ 227 pharma Adsorption Number Q	SOLKANE™ 134a pharma Adsorption Number Q
Oxygen** Experimental results converted to atmospheric conditions* in the liquid phase [22]	g/kg	approx. 0.08	approx. 0.10
Experimental results converted to the conditions: partial pressure of O_2 = 1.0 bar, temperature 25 °C in the liquid phase	g/kg g/kg	approx. 0.36 [22] 0.21 [20]	approx. 0.70 [22] 0.34 [20]
Nitrogen** Experimental results converted by linear fitting to the atmospheric conditions* (see illustration below)	g/kg g/kg	n.d. 0.55 [20]	0.51 [23] 0.15 [20]
Experimental results at the conditions: partial pressure of N_2 = 1.0 bar, temperature 25 °C	g/kg g/kg	n.d. 0.69 [20]	0.63 [23] 0.19 [20]

* Atmospheric conditions: 25 °C, 1 bar, partial pressure of O_2 = 0.2 bar, partial pressure of N_2 = 0.8 bar
** All values are indicative values due to dependence on the filling factor (different distribution and equilibrium in gaseous and liquid phase)

Solubility of Nitrogen in HFA 134a

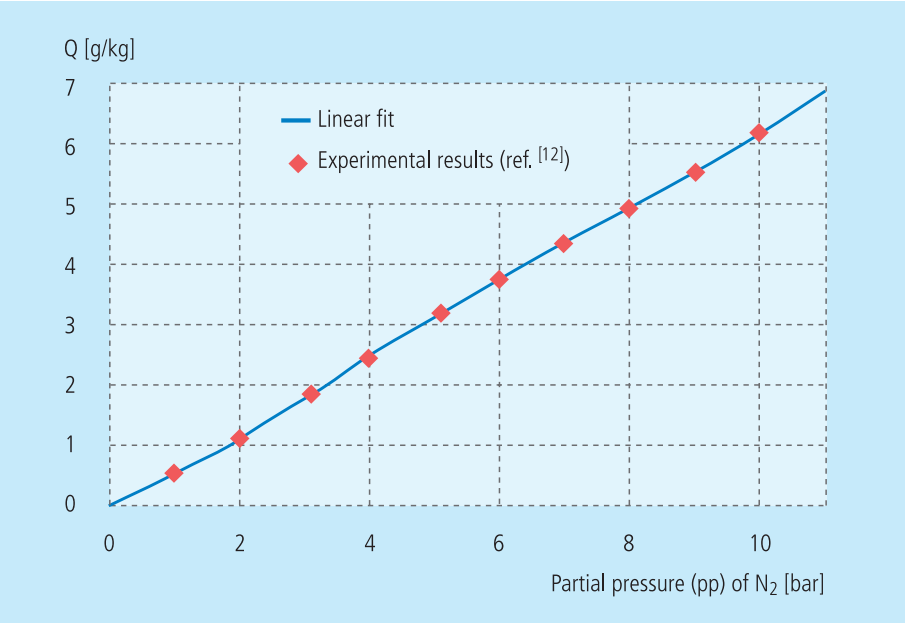
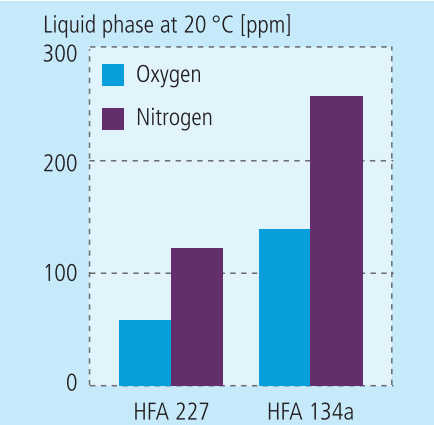


Fig. 18: Illustration of experimental results for solubility of N_2 in SOLKANE™ 134a pharma at 25 °C as a function of the partial pressure of nitrogen [23]

Solubility of Oxygen

During the manufacture of MDIs (metered dose inhalers), organic molecules (for example active substances e.g. sodium cromoglycate), tensides (e.g. oleic acid) and solubilisers (e.g. ethanol) are suspended or solubilised in HFA 227 and/or HFA 134a. Because organic molecules can be oxidised by oxygen, it is important for the manufacture of MDIs to know the solubility of oxygen in the propellant being used (such as SOLKANE™ 227 pharma and SOLKANE™ 134a pharma).

Gases like oxygen and nitrogen always form equilibria with pressurised liquefied gases in the gas phase and the liquid phase. These equilibria depend on temperature, filling factor and total pressure. Therefore, the figures show precisely determined values but only for one temperature, one filling factor and a specific amount of gas. The most important result is that there is a big difference between the oxygen and nitrogen content in the gas phase compared to the liquid phase.



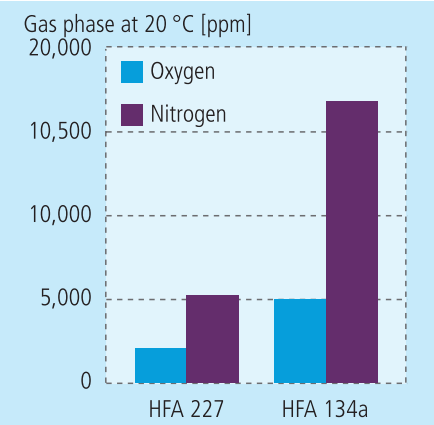


Fig. 19/20: Typical content of oxygen and nitrogen in SOLKANE™ 227 pharma and SOLKANE™ 134a pharma

Influence of Ethanol on HFA 227 and HFA 134a

Ethanol is widely used as an exipient in pharmaceutical formulations for MDIs because of its miscibility with the HFA propellant and the positive influence on the solubility of organic molecules due to the higher polarity. The addition of ethanol increases the polar/hydrophobic characteristics of a formulation. However, the addition of ethanol also increases the moisture uptake capacity of the MDI formulation which might have an impact on the shelf life. Furthermore, in the case of HFA 134a the addition of ethanol slightly reduces the pressure of the propellant.

Adding ethanol to a formulation also reduces the density of the mixture. The pressure versus mixture curves (Fig. 21) were derived from measured data (Hoechst 90/91).

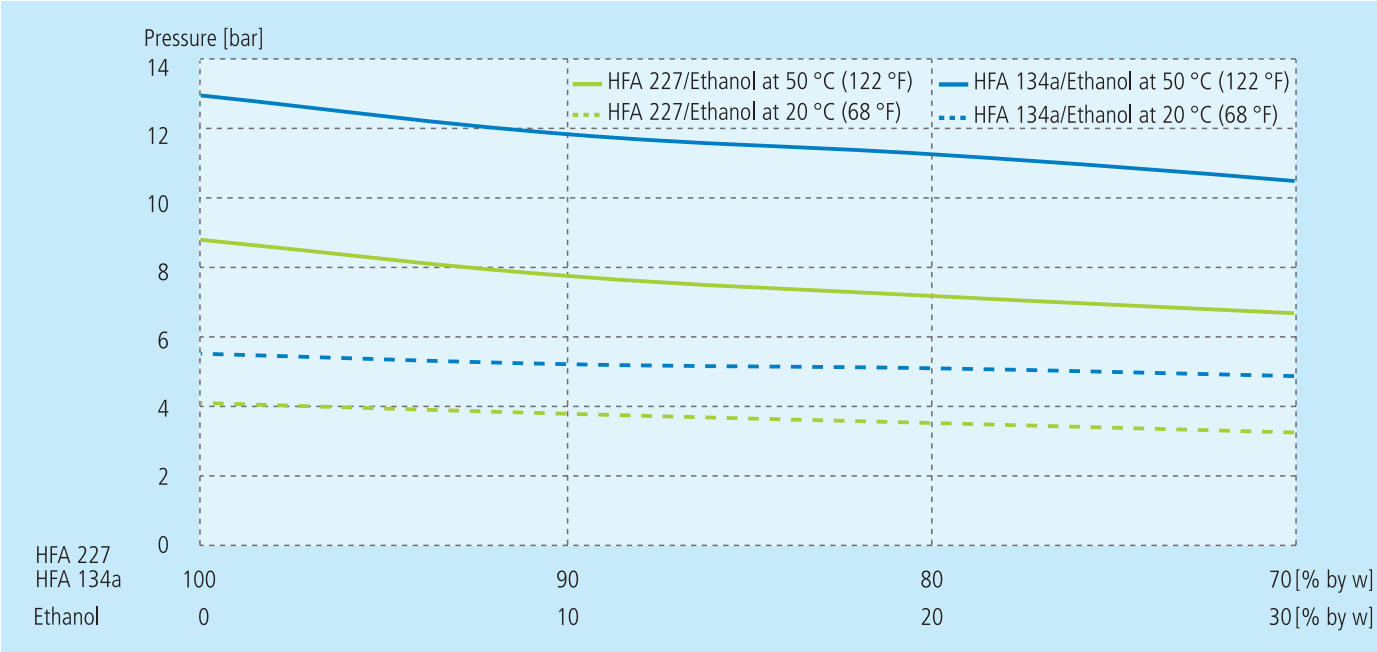


Fig. 21: Illustration of experimental results: pressure versus mixture curve of HFA 227 and HFA 134a with ethanol 99.8 % [wt.]

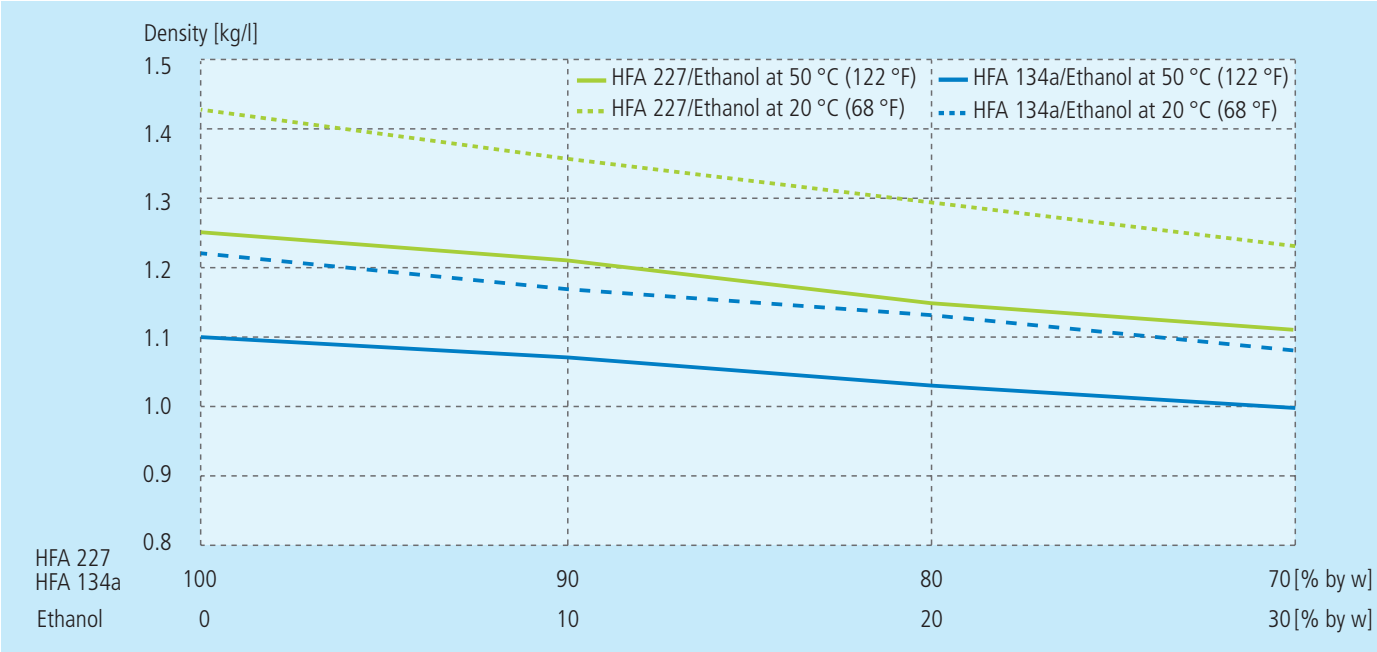


Fig. 22: Density of HFA 227 and HFA 134a in mixtures with ethanol 99.8 % at 20 °C and 50 °C

Chemical Behaviour

Material Compatibility

The material compatibility is tested to determine the specifications for materials suitable for the manufacture of pharmaceutical aerosols (e.g. composition of seals, metering chambers, gaskets, seats or stems).

Aspects analysed include changes in weight, volume, length, width, shore hardness, appearance (e.g. bubble formation), permeability of water and amount of extractables.

Classification of Materials for Use in MDIs

	HFA 227	HFA 227 and HFA 134a	HFA 134a
Sealing Material	CR, NBR, NR, EPDM (5), PVC (6), PCTFE (6), PA (6), PBT (6), PP (6)	PTFE (6), IRR	HNBR, POM, PET
General Use	NBR, IRR, POM	PTFE, PCTFE, PBT, PA, CR, NR	HNBR
Partly Use	HNBR (4)	FPM (1), PE (3)	NBR (2), EPDM (2)

(1) Strong swelling behaviour and presence of bubbles
(2) Permeability of water
(3) Bubble formation on material surface
(4) Strong swelling
(5) Recommended in the absence of mineral oil or alkyl benzene
(6) If technical specification designs allow, e.g. PTFE used in connection with metal joints

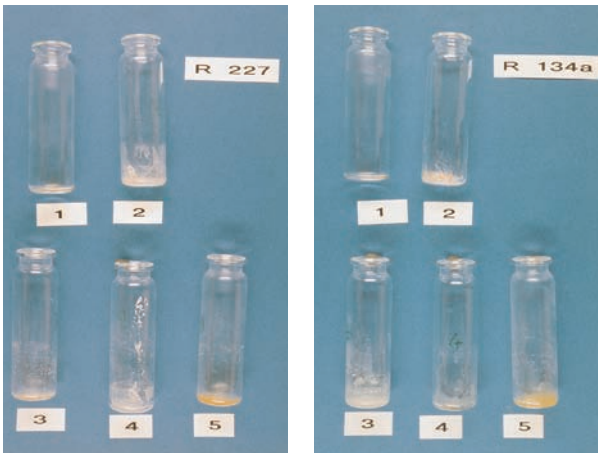


Fig. 23: Extractables from plastics:
1.) Polyethylene (PE),
2.) Polyamide 6.6 (PA),
3.) Polyacetal (POM),
4.) Poly(butylene terephthalate) (PBT), and
5.) Polypropylene (PP) after immersion in HFA 227/5 wt % EtOH and HFA 134a/5 wt % EtOH for 500 h at 80 °C;
Polytetrafluoroethylene (PTFE) produced zero extractables

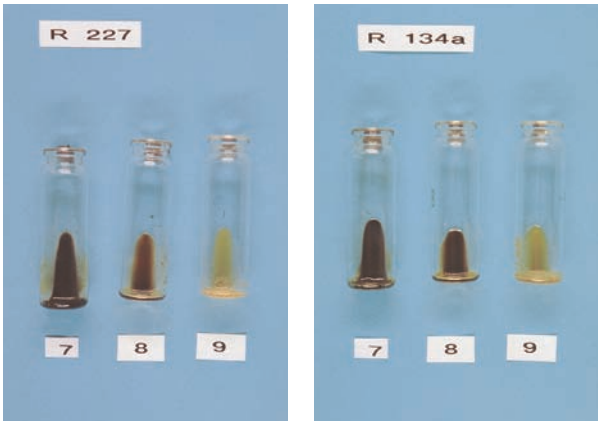


Fig. 24: Extractables from elastomers
7.) Acrylonitrile-butadiene rubber (NBR),
8.) Ethylene-propylene-diene rubber (EPDM) and
9.) Chloroprene rubber (CR)
after immersion in HFA 227/5 wt % EtOH and HFA 134a/5 wt % EtOH for 500 h at 80 °C

Evaluation Criteria for Material Compatibility

There is a large range of elastomers and plastics on the market with different trade names which are made of similar raw materials and which are only distinguished by certain additives. These additives may affect the thermal and mechanical stability, the swelling properties, as well as the resistance to aging of elastomers and plastics.

When assessing complete systems, it is necessary to include the compability characteristics of the drug formulation.

			SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
1. Metals/Valves/Fittings/Vessels/Cans			HFA 227 and HFA 134a are compatible with mild steel, stainless steel, $CuBe_2$ membranes, brass and aluminium, black sheet iron, copper and galvanised sheet metal when the presence of water can be excluded. Water content might lead to an increase in corrosion, with the exception of 1.4551 V2A–steel.	
Material ISO 1629	Chemical Abbr.	Trade name	Compatibility	Compatibility
2. Elastomers [1]				
Chlorobutadiene rubber	CR	Neoprene®	+	+
Hydrated acrylonitrilene-butadiene rubber	HNBR	Perbunan® Bayprene® Tomac®	+	+
Natural rubber	NR	Dynaprene®	+	+
Butyl rubber	IIR	Europrene®	+	+
Fluorinated rubber	FPM	DAI-EL, Viton®, Fluorel® , Tecnoflon®	–	–
Acrylonitrile-butadiene rubber	NBR	Perbunan® N, Krynal®, Hycar®, Chemigum®	+	+
Ethylene-propylenediene rubber	EPDM	Nordel®	+	+
3. Plastics				
Polytetrafluoroethylene	PTFE	Polyflon, Hostaflon® TFM, Algoflon®	+	+
High density polyethylene	HDPE	Alathon®, Eltex®	o	o
Polyacetal	POM	Hostaform® C9021	+	+
Polyphenylene sulfide	PPS	Fortron®, Rylon®	*	+
Liquid crystal polymers	LCP	Vectra®	*	+
Polyester fibre	PET	Trevira®, Hostaplast®, Hostaphan®	*	+
Polyvinylchloride	PVC	Hostalit®, Solvin®	+	+
Polychlorotrifluoro ethylene	PCTFE	Neoflon	+	+
Polyamide	PA	Isonamid®	+	+
Polybutylene-terephtalate	PBT	Celanex® X5002, Valox®, Arnite®	+	+
Polypropylene	PP	Adell®, A-Fax®, Eltex P®, Hostalen®	+	+
Polystyrene	PS	Styron®	*	o

[1]According to ASTM D 1418-01

+ compatible / o borderline / – incompatible / *no information, tests required

Toxicological Profiles

Toxicological Profile of HFA 227

HFA 227 is a colourless gas with an ethereal odor at ambient temperature. It has a very low acute toxicity. No deaths occurred when rats and mice were exposed by inhalation once to 300,000 and 500,000 ppm respectively. Signs of narcosis were observed from 100,000 ppm.

HFA 227 released into the eyes of rabbits did not induce any sign of irritation. Long term exposure of the airways of different test species (rats, dogs) at experimentally high concentrations of HFA 227 caused no irritation nor any untoward effect on the integrity of the respiratory tract function.

HFA 227 can induce cardiac sensitisation in dogs at concentrations from 100,000 ppm (10% v/v) and higher after an exogenous epinephrine challenge.

In long term studies in which rats and dogs were exposed via inhalation to HFA 227 at concentrations up to 240,000 ppm (1 hour per day for 6 months), no treatment related effects of toxicological significance were observed.

Toxicity Test	HFA 227
Recommended workplace guide value [10]	1,000 ml/m³
Acute inhalation toxicity LC_{50}*	800,000 ppm [28]
Cardiac sensitisation LOAEL**	100,000 ppm [28]
Effects on: pulse, blood pressure, ECG, lung function [29] in human volunteers	No adverse effects after exposure levels up to 8,000 ppm
Reverse mutation assay	Non-mutagenic
Carcinogenicity	Non-carcinogenic
Teratogenicity	Non-teratogenic
Irritation of eyes, rabbit [10]	Non irritant
Degradation	Bio-transformed at very low rates to hexafluoroacetone trihydrate [30]

* LC_{50}, lethal concentration for 50 % of the population of rats, 4h exposure
** LOAEL: Lowest Observable Adverse Effect Level

In several fertility studies in male and female rats in which animals were exposed for 1 to 6 hours per day to HFA 227 concentrations up to 150,000 ppm, no effects of toxicological significance were observed when measured on the fertility and pregnancy index. Concentrations of up to 150,000 ppm HFA 227 had no embryotoxic nor fetotoxic effects in rats or rabbits. Similar concentrations had no significant effect on the development and behaviour of the offspring of exposed rats.

Different in vitro and in vivo mutagenicity tests were performed with HFA 227. No genotoxic potential was observed. The in vitro chromosomal aberration test performed on human lymphocytes showed effects that were considered to be related to oxygen deprivation in the test system.

When rats and mice were exposed by inhalation to concentrations of 0, 60,000, 120,000 and 240,000 ppm for 2 years at a regimen of 1 hour per day, no increased incidence of benign or malign neoplasms were observed when compared to controls.

Some alveolar histiocytosis was observed in the lungs of rats exposed to high doses of HFA 227. In view of its normal incidence in this strain of animals and its only very slightly increased severity compared to controls, this effect was considered of no biological significance.

In human volunteers exposed to concentrations up to 8,000 ppm for one hour, no treatment related effects on cardiac performance, pulse rate, blood pressure and lung function were observed when compared to air control and CFC-12 reference conditions.

Pharmacokinetic parameters indicated that blood levels of HFA 227 increased in an exposure related pattern. In males, blood levels were higher than in females.

HFA 227 showed a biphasic elimination from the body after exposure. (mean T1/2: approx. 6.5 minutes and 44.5 minutes). These values appeared to be independent of the exposure concentration.

Acute toxicity to aquatic organisms is very low (LC_0 (lethal concentration to 0% of test organisms) fish = or > 30 mg/l; EC_0 (effective concentration to 0% of test organisms) bacterial activity ≥ 173 mg/l). Although no significant biodegradation has been observed, the high volatility and low bio-accumulation potency makes any impact of heptafluoropropane on the aquatic environment highly unlikely.

Toxicological Profile of HFA 134a

HFA 134a is a non-flammable, colourless gas with a faint ethereal odor.

HFA 134a has a very low order of acute toxicity. Concentrations over 700,000 ppm in inhaled air are required to produce lethal effects. The symptoms of acute intoxication are characterised by central nervous system effects due to narcotic properties seen only at extremely high exposure concentrations.

When HFA 134a is in contact with cutaneous or ocular mucosal membranes it causes slight irritation possibly due to evaporation. It does not sensitise the skin.

HFA 134a can induce cardiac sensitisation in dogs at levels of 80,000 ppm (8% v/v) and higher following exogenous epinephrine challenge.

The chronic toxicity of HFA 134a was studied in rats at inhalation exposure levels up to 50,000 ppm. No significant toxicological effects were observed in these studies.

Toxicity Test	HFA 134a
Recommended workplace guide value [8]	1,000 ml/m³
Acute inhalation toxicity LC_{50}*	500,000 ppm [31]
Cardiac sensitisation LOAEL**	80,000 ppm [32]
Effects on: pulse, blood pressure, ECG, lung function [29] in human volunteers	No adverse effects after exposure levels up to 8,000 ppm
Reverse mutation assay	Non-mutagenic
Carcinogenicity	Non-carcinogenic
Teratogenicity	Non-teratogenic
Irritation of eyes, rabbit [10]	Slightly irritant
Degradation	Degradation in troposphere to trifluoroacetic, formic and hydrofluoric acid and carbon dioxide [29]

* LC_{50}, lethal concentration for 50 % of the population of rats, 4h exposure
** LOAEL: Lowest Observable Adverse Effect Level

HFA 134a showed no adverse effects on fertility in mice. It was not teratogenic in rats or rabbits. Only non-specific effects on fetal maturation, in the form of delayed fetal ossification in rats were observed at 50,000 ppm and above.

HFA 134a was not genotoxic in vitro or in vivo as shown in a large variety of studies, including all important end points.

In a limited study in rats involving daily oral administration of 300 mg/kg body weight HFA 134a dissolved in corn oil over a period of 1 year, and a 16 month post-treatment observation phase, no tumorigenic effects were seen.

In a two year inhalation study with exposures up to 50,000 ppm, HFA 134a only produced some benign changes in the testes of rats exposed to the highest concentrations. These changes are considered of limited relevance to humans.

In human volunteers exposed to concentrations up to 8,000 ppm for one hour, no treatment related effects on cardiac performance, pulse rate, blood pressure and lung function were observed when compared to air control and CFC-12 reference conditions.

Pharmacokinetic parameters indicated that blood levels of HFA 134a increased in an exposure related pattern. In males, blood levels were higher than in females. HFA 134a showed biphasic elimination from the body after the end of exposure. (T1/2: approx. 10 minutes and 43 minutes). These values appeared to be independent of the exposure concentration.

Acute toxicity to aquatic organisms is very low. Although no significant biodegradation has been observed, the high volatility and low bio-accumulation potency makes any impact on the aquatic environment highly unlikely.

Instructions

Safety Instructions

SOLKANE™ 227 pharma and SOLKANE™ 134a pharma are liquefied compressed gases.

According to pressure vessel regulations, compressed gases are substances whose vapour pressure at 50 °C is above 3 bar. In line with the regulations governing pressure vessels, these may only be transferred to approved and labelled gas-tight gas cylinders or containers.

Recommended Safety Procedure

HFA 227 and HFA 134a are non-flammable gases. But, wherever they are handled, there must be no open flames or heat sources (e.g. hot metallic surfaces) or reactive products. The propellants can decompose and the decomposition products are corrosive, irritate the mucous membranes and are poisonous when inhaled.

The decomposition compound, hydrogen fluoride, is highly toxic. However, it is easily recognised by its odor. Even small amounts, below the danger limit for humans, are noticeable in the ambient air. Also, the decomposition product vapours should be prevented from contacting hot spots and electric arcs (welding). Containers that have been exposed to fire should not be approached until sufficiently cooled (e.g. by large quantities of water).

HFA 227 and HFA 134a should only be used with the equipment and materials which are compatible with the products. Contact with alkaline and alkaline-earth metals may provoke violent reactions or explosions.

Storage and work areas must be well ventilated. In particular, ventilation must be effective at ground level because the propellant vapour is heavier than air and displaces available oxygen.

Recommended Working Conditions

When inhaled at high concentrations (for inhalation limits see page 28), there is a danger of narcosis, cardiac arrhythmia or asphyxia through lack of oxygen. Therefore, all products should be handled in a ventilated, cool area. An important precondition is strict adherence to the threshold limit value (TLV).

Respiratory Protection:

- Minimal need if the local exhaust ventilation is adequate
- Self-contained breathing apparatus should be used when insufficient oxygen is present (large uncontrolled emissions) and in all circumstances when the mask and cartridge do not give adequate protection
- Use only respiratory protection that conforms to international and/or national standards

HFA 227 and HFA 134a as vapours have little or no effect on the skin or eyes. To avoid the cold irritation and frostbite from exposure to the liquid propellants, certain precautions have to be followed during handling. Skin frequently exposed to the propellant can become dry and chapped and there is a risk of developing chronic dermatitis.

Severe eye irritation, watering, redness and swelling of the eyelids, burns (frostbite) can occur as a result of contact with liquefied propellant.

Flammability

HFA 227 and HFA 134a are non-flammable gases and do not form explosive mixtures with air at any mixing ratio under ambient temperature and atmospheric pressure. However, all propellants containing hydrogen may form explosive mixtures with air under certain conditions.

HFA 134a vapour may form explosive mixtures with air under increased pressure. At atmospheric pressure, an HFA 134a pharma vapour/air mixture is not explosive at temperatures below 280 °C [33]. The pressure limit for the formation of explosive mixtures in air is dependent on the temperature.

During leak detection or pressure testing, compressed gas must never be used with propellants which contain hydrogen.

SOLKANE™ 227 pharma and SOLKANE™ 134a pharma

- **Hazardous Decomposition Products:**
  Hydrogen fluoride, fluorophosgene (HFA 227), carbon monoxide (HFA 134a)
- **Packaging Material:**
  Ordinary steel, aluminium
- **Flammability Limits in Air at Normal Conditions:**
  None

Skin Protection:

- Handle only with impervious apron/boots if there is a risk of splashing
- Gloves, overalls and boots should be double layered (protection against cold)

Hand Protection:

- Protective gloves (recommended material for HFA 227 and HFA 134a is polyvinylalcohol)

Eye Protection:

- Wear protective goggles for all industrial operations
- If risk of splashing: chemical-proof goggles/face shield are required

Handling and Storage Instructions

SOLKANE™ 227 pharma (HFA 227) and SOLKANE™ 134a pharma (HFA 134a) are liquefied compressed gases.

According to pressure vessel regulations, compressed gases are substances whose vapour pressure at 50 °C is above 3 bar. In line with the regulations governing pressure vessels these may only be transferred to approved and labelled gas-tight gas cylinders or containers. HFA 227 and HFA 134a are non-flammable gases. But, wherever they are handled, there must be no open flames or heat sources (e.g. hot metallic surfaces) or reactive products.

An important precondition is strict adherence to the threshold limit value (TLV).

Handling

Be sure to close all cylinder valves when not in use. The valves of empty cylinders should also be closed.

Ensure that gas cylinders are transported so that they do not tip, fall or roll. Gas cylinders should be secured to the cylinder trucks or carts. Regulators should be removed and valve protection caps should be secured in place before moving cylinders.

Also, cylinder valves should be closed before moving cylinders.

Appropriate lifting devices, such as cradles or nets, must be used when using a crane, hoist or derrick to transport gas cylinders. Do not use magnets or slings to lift gas cylinders. Do not use the valve protection cap to lift a gas cylinder.

It is necessary to take precautions to prevent gas cylinders being dropped or striking each other or other objects. Dropping or striking may damage the cylinder valve, which could turn the cylinder into a dangerous torpedo with the potential to destroy property and/or injure personnel.

Storage

Gas cylinders should be properly secured at all times to prevent tipping, falling or rolling. They can be secured with straps or chains connected to a wall bracket or other fixed surface, or by using a cylinder stand. **Store cylinders in a cool, dry, well-ventilated, fire-resistant area in accordance with local regulations.**

A cylinder storage area should be located in an area where the cylinders will not be knocked over or damaged by falling objects. When a cylinder is not being used, the valve should be closed and the valve protector secured in place.

Inspection

Gas cylinders should be visually inspected to ensure that they are in a safe condition. If necessary, a cylinder can be tested ultrasonically for hidden defects. Leaking regulators, cylinder valves or other equipment should be taken out of service. A cylinder's contents should be identified at all times. Cylinder status should also be identified; for example, whether the cylinder is full, empty or in service.

Emptying

The safest and best way to empty larger amounts of HFAs from a container, e.g. one tonne cylinder, is to use an oil-free pump.

MSDS

Consult the appropriate MSDS for detailed information on the chemical contained in the gas cylinder. Specific chemical handling and storage precautions will be outlined in the MSDS. The MSDS will also have specifications for appropriate personal protective equipment for worker protection. [31]

Container Closure System

Packaging

Supply of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma

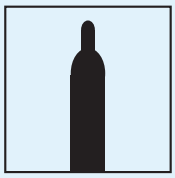
Global deliveries of SOLKANE™ 227 pharma grades and SOLKANE™ 134a pharma grades take place using dedicated ISO tank containers in quantities of 15,000 to 19,000 kg. Both SOLKANE™ pharma qualities are also available in 10 l, 60 l or 900 l steel cylinders. All our cylinders have an additional safety device, which prevents the cylinders from accidental backflow of the material.

Applied Tests

All Daikin Refrigerants Europe GmbH pressure containers (steel cylinders, ISO containers) are tested by the local authority before they are released for use. Steel cylinders have to be re-certified every ten years.

Fig. 25: ISO Tank Container for supply of Solkane propellants

Returnable Cylinders

	Unit			
SOLKANE™ 227 pharma	**kg/lb**	**12/26**	**70/154**	**1,050/2,314**
SOLKANE™ 134a pharma	**kg/lb**	**10/22**	**60/132**	**900/1,984**
Capacity approx.	l	10	61	910
Height incl. protection cap approx.	cm	100	106	–
Height excl. protection cap approx.	cm	81	92.5	–
Length approx.	cm	–	–	223
Diameter across beads approx.	cm	14	32	86
Tare weight approx.	kg	13	30	500 – 550
Test pressure	bar (abs)	300	43	44

ISO Tank Containers

ISO Tank Container

SOLKANE™ 227 pharma: approx. 17,000 kg/37,478 lb

SOLKANE™ 134a pharma: approx. 16,500 kg/36,333 lb

Classification and Transport Information

	SOLKANE™ 227 pharma	**SOLKANE™ 134a pharma**
Chemical Name	1,1,1,2,3,3,3,-Heptafluoropropane	1,1,1,2-Tetrafluoroethane
Chemical Formula	$CF_3–CFH–CF_3$	$CF_3–CH_2F$
CAS-No.	431-89-0	811-97-2
EG-No. (EINSEC)	207-079-2	212-377-0
UN No.	3296	3159
Hazardous good Label	Compressed gas, non-flammable, Class 2, Figure 2	Compressed gas, non-flammable Class 2, Figure 2
GHS-Label	Gas cylinder, GHS04	Gas cylinder, GHS04

International Standards for Valves, Connectors and Adapters

Cylinders for SOLKANE™ 227 pharma or SOLKANE™ 134a pharma are equipped with a Y-valve including a dip tube for product withdrawal as vapour or liquid depending on the side adapter used (Connector No. 6, according to DIN 477).

The valves, connectors and fittings used with HFA 227 or HFA 134a should be manufactured in brass or stainless steel. Seals and gaskets are tested as described on pages 20/27.

The adapters listed below are suitable for both SOLKANE™ 227 pharma and SOLKANE™ 134a pharma

Possible Side Adapters depending on the Standards:

Cylinder Valves

- meeting the DIN (Deutsches Institut für Normen) Standard DIN 477 Part 1; connector No. 6, thread size W 21.8 x 1/14", side adapter A, valve screw in hole 28.8 or 19.8
- meeting the CGA (Compressed Gas Association) Standard; connector CGA No. 660, thread size 1.030", 14 threads per inch, right handed external thread
- meeting the BS (British Standard) BS 341 No. 6 (BS6); thread size G 5/8", right handed external thread

900 l Cylinder Cylinder Valves

- meeting the DIN Standard DIN 4676; thread size W 1¼", 31.8 ° 7

Adapter for ISO Container:

- Leakage-free dry Arta® coupling system, sterile connection elements are used, male and female, material 1.4435 electropolished, available in the following nominal diameters: DN 25, DN 40, DN 50, DN 80, DN 100, DN 150

Fig. 26: Y-Valve adapter (red) liquid phase

Fig. 27: Y-Valve adapter (blue) vapour phase

Fig. 28: Arta® coupling for bulk off-loading

Product Stewardship

Chemical manufacturers have a duty to minimise any health, safety and environmental risks related to their products. At the same time, they must meet the needs of their customers and the public for safely usable and environmentally compatible products. In the framework of the Responsible Care initiative, the concept of Product Stewardship has become an important building block in the attainment of sustainable development. [34]

Environmental Protection

The commitments of Daikin Refrigerants Europe GmbH to protect people and the environment are demonstrated in many practical ways by SOLKANE™ 227 pharma and SOLKANE™ 134a pharma.

Environmental consulting includes responding to questions from customers and the public directed to Daikin Refrigerants Europe GmbH as the producer of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma.

Recovery/Reclamation

Recovery is performed when a system requires maintenance. There are several recovery devices on the market. These devices contain a compressor and a condenser, and may be used for liquid and vapour recovery.

The pharmaceutical propellants are included in a reclamation programme, however, reclaimed propellants can never be reused in pharmaceutical products or manufacture.

Recycling

The producer guarantees to take back and reutilize used single component propellants, commercial blends and mixtures of different propellants. The procedure is called secondary recycling and enables valuable raw materials for the chemical industry (hydrofluoric acid and hydrochloric acid) to be reprocessed from either CFC, HCFC or HFC propellants by thermal decomposition. These substances are reused as raw materials in chemical production or other applications.

Propellants containing active pharmaceutical ingredients undergo secondary recycling.

The decomposition products are reused in other processes. Solid wastes for landfill disposal and toxic waste gases are avoided. At the heart of the process, an H_2/O_2 flame with a temperature of 2,000 °C thermally decomposes CFCs, HCFCs and HFCs. The degree of separation under the given conditions was found to be greater than 99.99 %. Using O_2 instead of air to feed the flame avoids forming additional nitrous oxides. [35]

Fig. 31: Reprocessing of HF and HCl from CFCs, HCFCs and HFCs by thermal decomposition

Daikin – Your Specialists for Fluorochemicals

Daikin

For more than 80 years, Daikin has been involved in the research and production of fluorochemicals, and is one of the world's foremost manufacturers of fluorochemical products today. Daikin's unique expertise is essential to a variety of industrial fields: With world-class technology, Daikin offers a wide range of high quality products featuring advanced properties such as heat resistance, chemical resistance, water and oil repellency, and lubricity, with applications in automobiles, consumer cookware, wire and cable, textile and fabric treatment, paper and packaging, optics and displays, coatings and more. Daikin has a global presence with more than 210 sites and almost 60,000 employees worldwide.

Professional Fluorochemistry

We're in it for the long haul. Being the only company in the world dedicated to manufacturing both air conditioning systems and refrigerants, Daikin's deep-rooted commitment to fluorine chemistry is essential to sustain our global #1 market position in air conditioning. We remain fully invested in the research and development required to meet the ever changing needs of your markets. Our professional team of experienced chemists, sales and customer service staff is committed to taking on any challenge and to solving problems in close co-operation with our customers.

Fig. 32 Plant Frankfurt, Germany

Product Range

Hydrofluorocarbons

- SOLKANE™ 227 pharma
  SOLKANE™ 134 a pharma
- SOLKANE™ 134 a
  SOLKANE™ 404A
  SOLKANE™ 407C
  SOLKANE™ 410A
  SOLKANE™ 507
  R32
  R407A
  R407H
  R417A
  R417B

Fluoroplastics

- POLYFLON PTFE
- NEOFLON PFA
  NEOFLON FEP
  NEOFLON ETFE
  NEOFLON PCTFE
  NEOFLON EFEP
  NEOFLON CPT
- POLYFLON MPA
  POLYFLON PTFE Low Polymer

Fluoroelastomers

- DAI-EL
  DAI-EL F-TPV

Additives

- PPA

Surface Modification Technologies

- UNIDYNE
- OPTOOL
- ZEFFLE
- ZEFFLE infrared reflective coating
- FTONE
- DAIFREE
- DEMNUM
- DAIFLOIL

Etching agents for semiconductors

- Hydrofluoric acid

Materials for Lithium Ion Batteries

- Electrolytes

Organic Intermediates

- Fluorinated alcohols
- Fluorinated methacrylate monomers
- Fluorination technology
- Synthesis of aliphatic fluorine intermediates

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Formula Key

t	= Temperature
p	= Pressure
v'	= Specific volume, liquid
v''	= Specific volume, vapour
rho'	= Density, liquid
rho''	= Density, vapour
h'	= Enthalpy, liquid
h''	= Enthalpy, vapour
r	= Enthalpy of the evaporation
s'	= Entropy, liquid
s''	= Entropy, vapour

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Final Report
ASHRAE RP-923

WATER SOLUBILITY AND CLATHRATE HYDRATES IN HFC REFRIGERANTS AND REFRIGERANT BLENDS

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ABSTRACT

This research project determined the solubility of water in HFC refrigerants R-134a, R-32, R-143a, R-125, and R-152a and HFC refrigerant blends R410A, R407C, R507A, and R404A from -100°F (-73°C) to 160°F (71°C) (or within 15°F (8.3°C) of critical temperature) in liquid refrigerant and in the presence of refrigerant clathrate hydrate below 60°F (16°C). Water solubility curves were constructed for each refrigerant and blend by measuring water content at 20°F (11°C) increments over the entire temperature range. In this study, all refrigerants in the presence of 1% w/w water were confirmed to form stable solid clathrate hydrates between 50°F (10°C) and 60°F (16°C), with R-32 and blends containing R-32 demonstrating stable clathrate hydrates up to 80°F (27°C).

Evaluation of water solubility in HFC refrigerants and blends was performed using a small, bench-top unit constructed of type 316 stainless steel that was temperature controlled, inexpensive to build, and easy to operate. The test cell/unit controlled the temperature of both the liquid and vapor refrigerant phases. This instrument and a Karl Fischer coulometer were used to measure the water equilibrium in solution of the aforementioned HFC refrigerants and blends at the specified temperatures, as well as water equilibrium between clathrate hydrate and liquid refrigerant. This project determined the maximum amount of water permissible for operating systems down to -40°F (-40°C).

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INTRODUCTION

One of the universal contaminants in hermetic systems is water, which can enter the system through manufacturing and other means. HVAC sealed systems are manufactured, evacuated, and nitrogen purged with heat to remove moisture before refrigerant is added. The solubility of water in refrigerant is important nonetheless. Knowing the solubility properties of water in refrigerant is necessary to help manufacturers in the production of sealed systems, the calculation of desiccant quantity, the determination of water distribution ratios, and the prevention of freeze-up conditions. Normally, a properly desiccated system has a water content below 50 ppm, which generally does not pose a problem.

Desiccants play the vital role of maintaining refrigerant systems in an acceptably dry state and free of circulating inorganic acid contaminants (Cavestri and Schooley 1998). Historically, refrigerant systems were CFC and HCFC chemicals with mineral or alkylbenzene lubricants. However, the latest systems are quite different; HFC refrigerants generally use polyolesters, which are more polar oxygen bearing lubricants. The equilibrium water solubility in HFCs may be different and requires measurement. Since the circulating water equilibrium conditions are desiccant/temperature dependent, knowledge of water equilibrium with desiccant at various temperatures is a necessity (Cavestri and Schafer 1999a and 1999b).

Unlike CFC refrigerants, HFC and HCFC refrigerants carry hydrogen atoms that create a polarized portion of the molecule, increasing the solubility of water. Refrigerants that are fully substituted, such as R-12, carry the least amount of water in solution (ASHRAE 1994 and DuPont 1982a). One or two hydrogen-substituted carbon refrigerants such as R-22 and R-134a provide the best solubility for water.

Regardless of which refrigerant or lubricant is used, moisture can cause problems in refrigerating and air-conditioning systems. These problems are avoidable when loose and solid filter driers are used with new and/or field-serviced equipment, or with refrigerant reclaim and recycle equipment. For maximum life and reliability, it is essential for a system to be maintained at a minimum circulating water content.

BACKGROUND

No measured data is available regarding the solubility of water in HFC refrigerants R-32, R-143a, R-125, and R-152a and blends of these refrigerants, R410A, R407C, R507A, and R404A. While data for R-123, R-134a, and R-22 is available (ASHRAE 1994), literature on simple, cost-effective test methods that provide unequivocal analytical data is not. Thrasher *et al*. (1993), using an NMR to measure dissolved water, reported measurement difficulties at low temperatures.

The temperature range of this research study was -100°F (-73°C) to 160°F (71°C), or within 15°F (8.3°C) of critical temperature. The formation of clathrate hydrates was a serious point of concern, since their constraints on this project were unknown. However, an abundance of information on clathrate hydrates has been published by such researchers as Chinworth and Katz (1947), Akiya *et al*. (1997), Holder *et al*. (1988), Walker *et al*. (1960), and Sloan (1990). The main objective of this research was to determine the solubility of water in liquid refrigerants; this is simple in theory, but difficult in practice. Logic dictated the development of a test device and method that was insensitive to temperature, refrigerant changes, and solid suspensions. The method was actualized with a device custom-built from readily available components.

ANALYTICAL PROTOCOL

The initial protocol was to load an apparatus that circulated a quantity of degassed refrigerant and dissolved water. Dissolved air was reported to reduce water solubility at the specified temperature and pressure in an excess of 2.7% deionized, degassed water (w/w) (Thrasher *et al*. 1993).

Test Unit 1

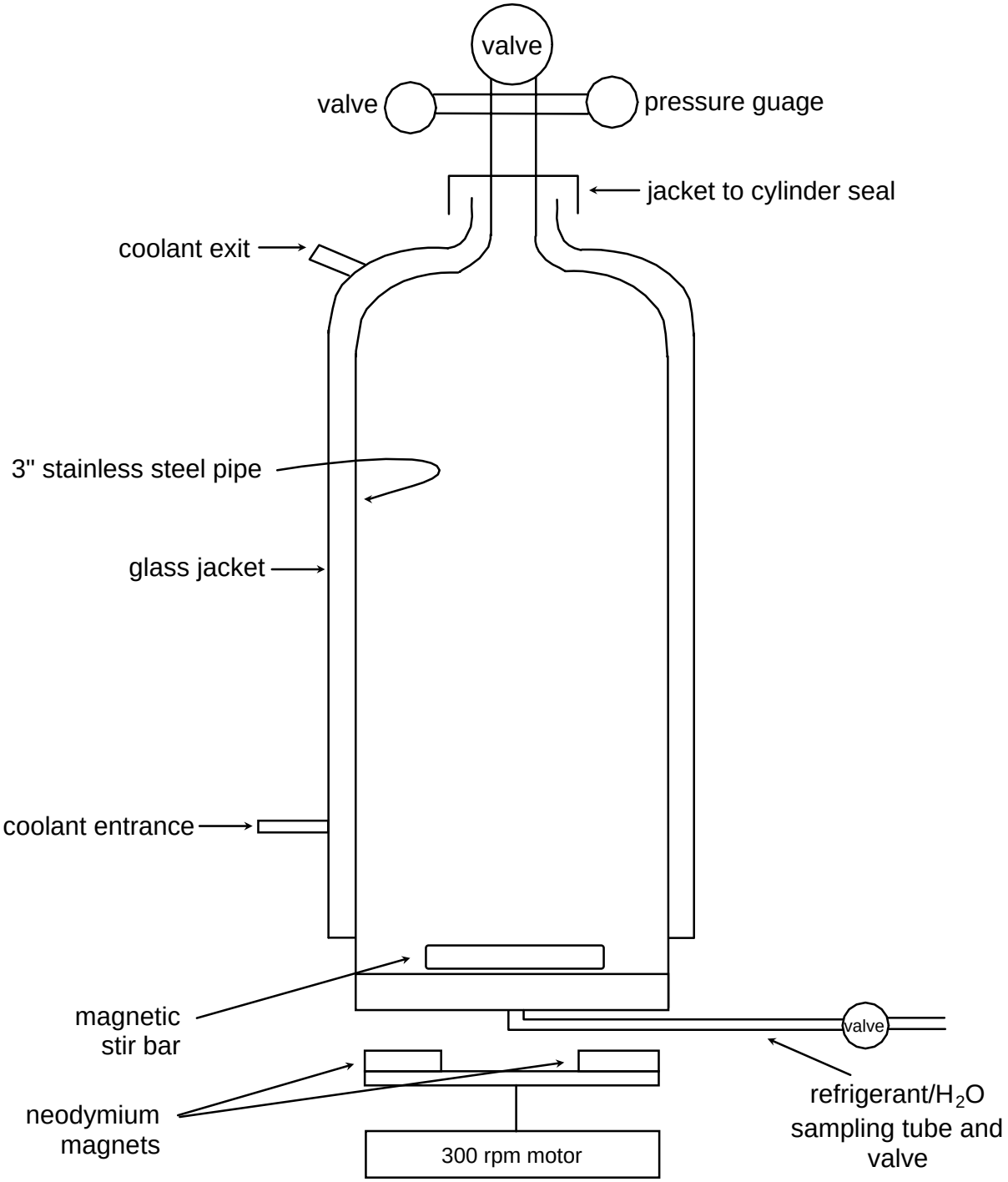
The first test device (Figure 1), designed for safety and high pressure, was intended to promote slow agitation of the water and liquid refrigerant and to incorporate the vapor space in a temperature controlled environment. This was similar in concept and design to a device used by

DuPont (Sturgis 1996). Test Unit 1 consisted of an inverted 3.5” OD x 14” stainless steel tube fitted at the top with a weld cap and pipe fitting assembly. The bottom was configured with a type C flange, drilled, and tapped to accept 5/16 x 18 studs. The bottom plate was stainless steel configured with a sampling tube and tap. The test cylinder was enclosed in an insulated glass jacket for temperature control. Temperature was regulated by circulating refrigerated methanol, with the aid of solid dry ice for temperatures below -40°F (-40°C), from a microprocessor-controlled cryostat between the test cylinder and the glass jacket. For temperatures of 80°F (27°C) and above, a microprocessor-controlled heating bath was used to circulate a water/ethylene glycol mixture. This system was used to test R-134a, R-143a, R-125, R410A, R407C, and R507A. Temperature test points were taken from 80°F (27°C) to 160°F (71°C) (or within 15°F (8.3°C) of critical temperature) and then from 60°F (16°C) to -100°F (-73°C).

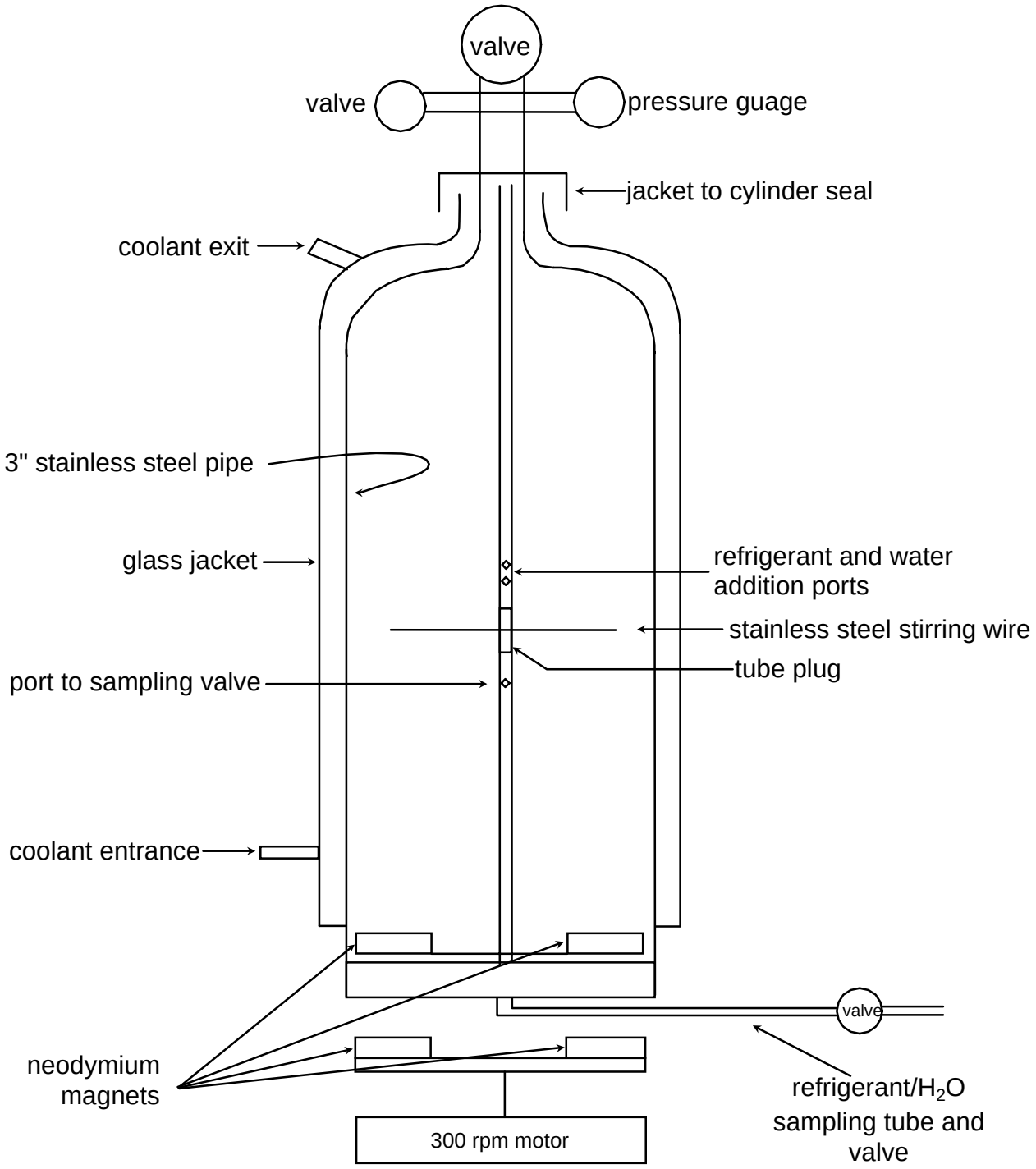
Test Unit 2

The second test system (Figure 2), simply a modification of Test Unit 1, was designed and built to provide additional slow stirring of the entire mixture and to minimize clathrate hydrate formation near the sampling port. In the second test unit, the magnetic stirring bar was replaced with a ¼” diameter, stainless steel tube equipped with two stirring arms, two opposing neodymium magnets, and three holes to permit sample flow to the sampling port. The mixing device, which sat on the base of the enclosed cylinder, was rotated by a 300 rpm stirring motor. Water and refrigerant were introduced in the usual manner, but the principal difference was that the sampling orifice was placed 2½” up from the bottom. The sample was stirred by both a 1/16” diameter pin that held the internal tube plug and the bottom magnet armature. This system was used to test R-32, R-152a, and R404A. It was also used in the attempt to collect R-22 and R-23 data. The temperature test points were taken in order from lowest to highest (-40°F (-40°C) through 160°F (71°C)) (or within 15°F (8.3°C) of critical temperature) per the committee’s suggestion. The lowest temperature at which data points were collected changed from -100°F (-73°C) to -40°F (-40°C) because data collected below -40°F (-40°C) was not reproducible.

Test Unit 1
Figure 1



Test Unit 2
Figure 2



The redesign of Test Unit 1 resulted from examining the water equilibrium test points plotted as log refrigerant water content (ppm) vs. temperature (1000/°K). In particular, R-143a clearly demonstrated two distinct slopes (see *Discussion*). At this point in the project, clathrate hydrates were assumed less dense than the refrigerant; therefore, it was presumed, they would float. Additional experimentation became necessary to learn more about the characteristics of clathrate hydrates.

Unlike previous investigations (Akiya *et al*. 1997 and Lederhos *et al*. 1992), this study showed clathrate hydrate formation in excess refrigerant. In order to characterize the physical properties of the clathrate hydrates formed, sealed tubes were made with 1% and 5% water (w/w) (Appendix C), which was outside the scope of the work statement, but necessary for this investigation. Observation of the sealed tubes containing water and refrigerant confirmed clathrate hydrate formation and disappearance as temperatures increased and decreased between 0°F (-18°C) and 80°F (27°C) (Appendix C). The amount of clathrate hydrates formed and the temperature at which they appeared depended on the amount of water in the system, the refrigerant being tested, and whether measurements were taken as the temperature was decreasing or increasing (Figures 3 and 4).

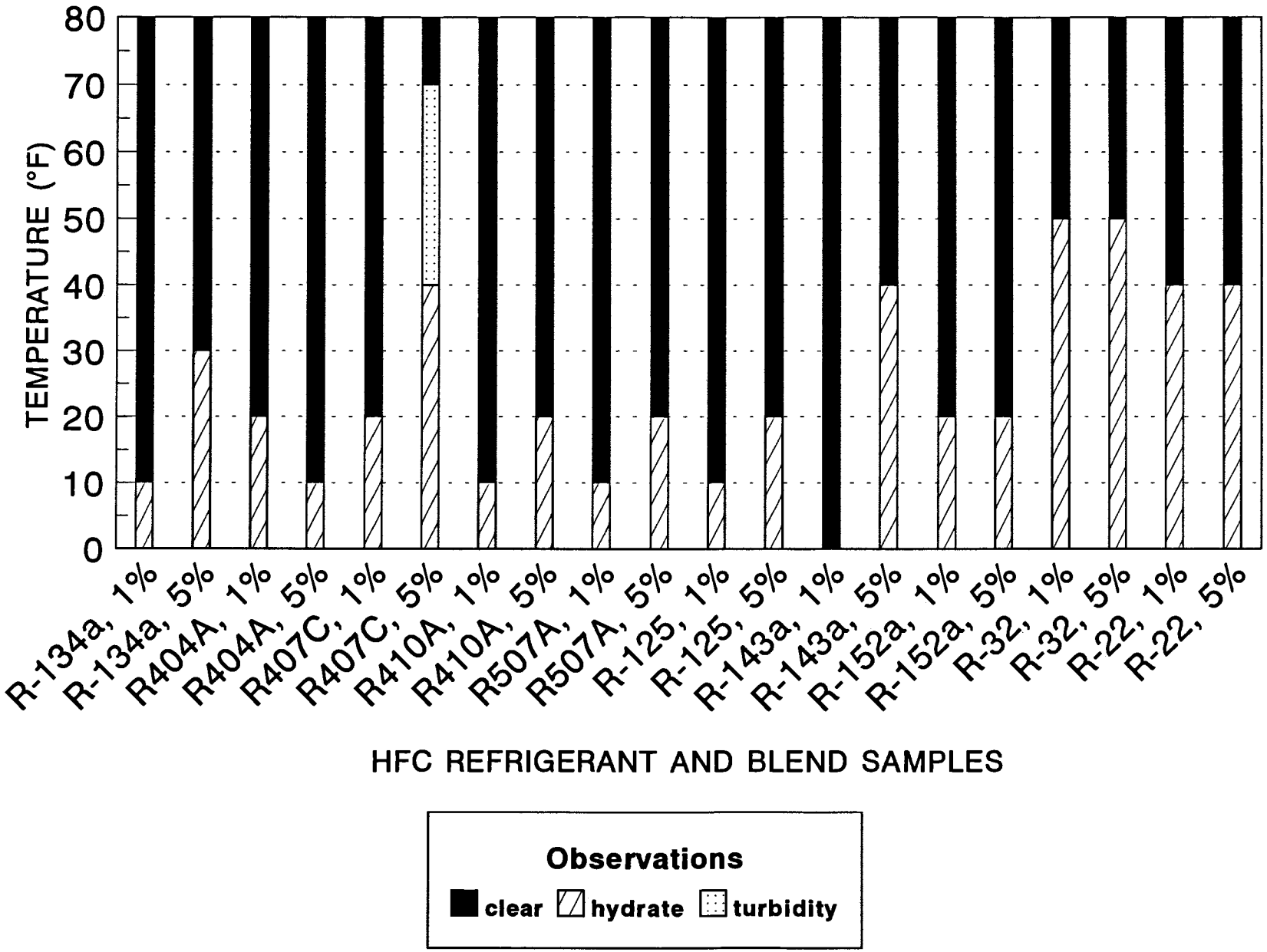
Test Unit 3

Test Unit 3 (Figure 5) is a modification of Test Unit 2. It was suggested that free water should not be used in water solubility equilibrium studies with liquid refrigerant and that the available water be retained in a saturated desiccant in an effort to minimize clathrate hydrate crystal formation (Parrish *et al.* 1982 and Walker *et al.* 1960). A small can was fabricated that could hold up to 75g of desiccant by using 30 gauge stainless steel sheet metal and 80 mesh screens. The top was removable, but spring loaded in compression to retain the desiccant. The top, sides, and bottom of the can had slots allowing free flow of the liquid refrigerant. The set up of the system was otherwise the same as Test Unit 2. This system was used only with R-32 (see *Discussion*).

Observations of HFC Refrigerants and Blends with 1 % and 5% Water (w/w) Added

Observations made at ten degree intervals starting at 80°F(27°C) down through 0°F(-18°C)

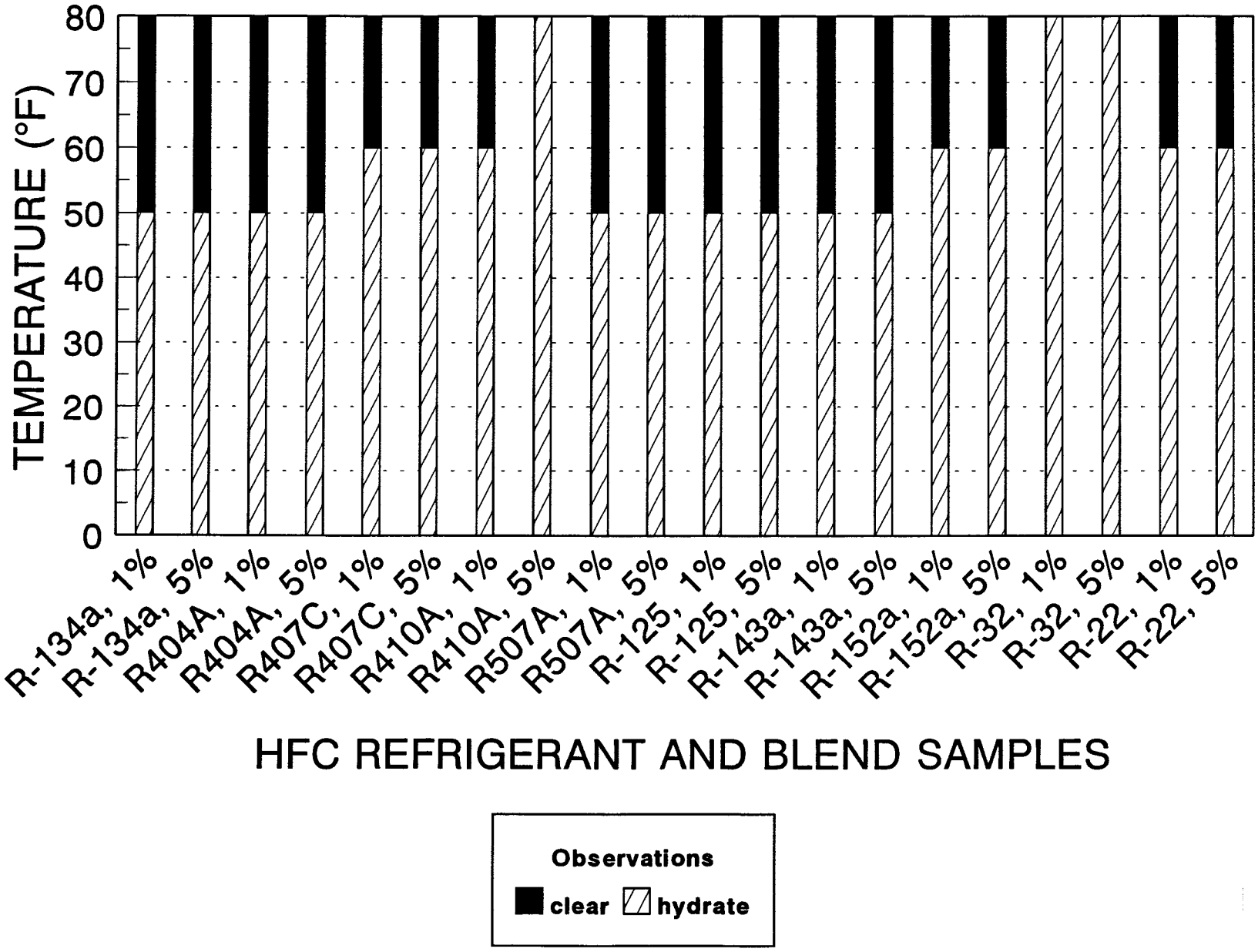
Figure 3



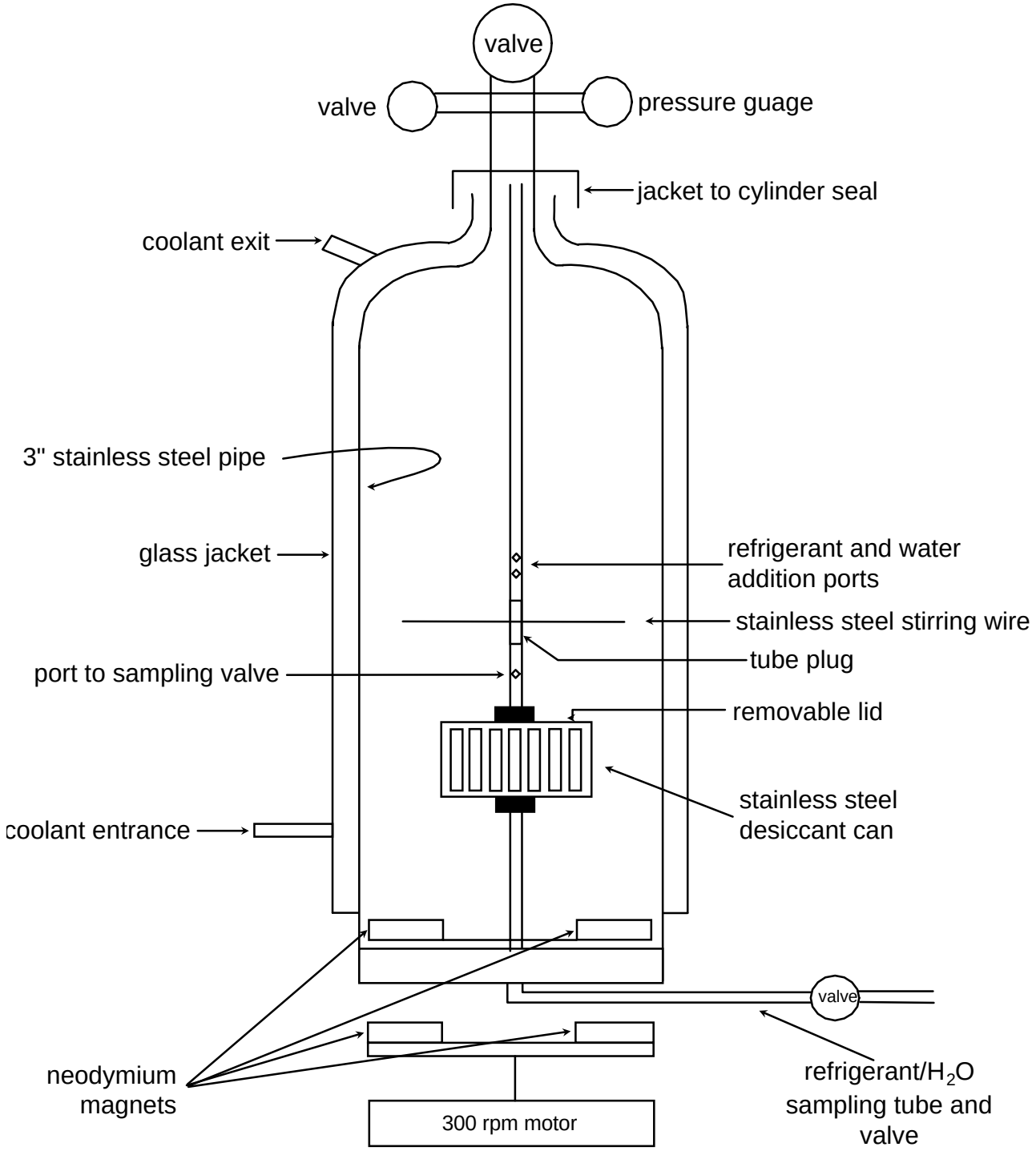
Observations of HFC Refrigerants and Blends with 1 % and 5% Water (w/w) Added

Observations made at ten degree intervals starting at 0°F(-18°C) up through 80°F(27°C)

Figure 4



Test Unit 3
Figure 5



Clathrate Hydrates

A brief discussion of clathrate hydrates, commonly referred to as gas hydrates, is necessary given the impact these crystalline molecular complexes have on the findings of this study. A hydrate is a complex containing water that belongs to the class of compounds known as clathrates. Clathrate refers to an open crystalline structure of one compound, in this case water, which encloses molecules of another compound, which are usually gas molecules typically referred to as the guest molecule. The guest molecule or gas molecule (refrigerant) is referred to as such even when it is not in the gas phase. There is no chemical tie between the gas and water molecules; instead, they interact through van der Waals type dispersion forces (Holder *et al*. 1988). These forces between molecules reflect the momentary and induced dipoles from electrons normally moving about; the net result is attraction between the two molecules. van der Waals forces are short range and act between portions of different molecules that are in close contact (Morrison and Boyd 1973). The crystalline lattice entrapping the gas molecules is formed by strong hydrogen bonds between water molecules. Examination of clathrate hydrates reveals that they may have two different structural forms, referred to as Structures I and II. Formation of either structure is dependent on their stability and both can coexist under certain conditions. Structure I is comprised of 46 water molecules configured to provide two small and six large cavities for gas molecules to occupy. Structure II's arrangement of 136 water molecules hosts 16 small and eight large cavities in which gas molecules can reside (Holder *et al*. 1988).

A discussion of clathrate hydrates centers around three concepts: solubility, metastability, and the establishment of critical nuclei as they relate to water clustering (Sloan 1990). The water in refrigerant, as temperature decreases, becomes a short-lived liquid cluster of irregular and broken hydrogen-bonded water molecules (metastability) surrounding a dissolved hydrocarbon. This metastability develops into well-formed hydrogen bonds fixed in position to form a solid clathrate cage around a guest molecule (refrigerant) defining the critical nuclei or nucleation phase (Sloan 1990). Therefore, water measurements above the metastable temperature represent water solubility/equilibrium in liquid refrigerant. Water measured at metastability or nucleation temperatures is likely decomposed clathrate hydrate in liquid refrigerant.

While the subject of gas hydrates is well documented, most of the research has focused on the plugging of natural gas lines and naturally formed hydrates found beneath the earth's surface that are an attractive source of natural gasses (Holder *et al*. 1988). Clathrate hydrates are formed in a variety of conditions with a variety of gasses and their existence must be acknowledged when interpreting the results of this study.

The presence of clathrate hydrates in liquid refrigerant poses problems in interpreting water solubility measurements in HFC refrigerants and blends below 80°F (27°C). For instance, it is known that clathrate hydrates separate from refrigerant at temperatures above the freezing point of water (ASHRAE 1994, Chinworth and Katz 1947, and Downing 1988). Other investigators show clathrate hydrate formation by several refrigerants, but do not report water solubility measurements in those refrigerants or in HFCs (Chinworth and Katz 1947). Studies focused primarily on clathrate hydrate formation were conducted by Lederhos *et al*. (1992), Akiya *et al*. (1997), Sugaya *et al*. (1996), and Mori *et al*. (1989), all of whom used a water rich phase, as opposed to the refrigerant rich phase used in this study. The *Fluorocarbon Refrigerants Handbook* (Downing 1988) briefly discusses clathrate hydrates, but discusses the solubility of water in liquid refrigerant separately. With regard to clathrate hydrates, the handbook states that there is not a sufficiently large amount of water present in refrigeration systems to present a clathrate hydrate formation problem. The information on solubility of water in liquid refrigerant does not address clathrate hydrates, nor does it provide a test method (ASHRAE 1994). Like many of the other references, it provides an abundance of information, discussion, and graphs on the solubility of refrigerant in water.

In summary, there is a short supply of documented research addressing the impact of clathrate hydrates on measuring water solubility in refrigerants. The test procedures used to compile the data for the small number of published solubility charts and graphs are equally difficult to find.

All of the refrigerants examined clearly form clathrate hydrates. Once formed at lower temperatures, clathrate hydrates with R-32 and blends containing R-32 are stable up to 80°F (27°C). More importantly, in this study, some clathrate hydrates were denser than the refrigerant under test, which necessitated a redesign of Test Unit 1.

Method

Hydrofluorocarbon refrigerants are known to form clathrate hydrates at substantially lower temperatures (Chinworth and Katz 1947) than their decomposition temperatures (Akiya *et al*. 1997). Therefore, the following method was devised. This method was based on the concept that the metastable period of water solubility exists and then ends just before the onset of the secondary nucleation of the clathrate hydrate crystals (Sloan 1990). The temperature profile protocol was designed based on these reported observations and on those that described the decomposition temperature of HFC refrigerant gas hydrates in water rich systems. Akiya *et al*. (1997) reports the critical decomposition temperature for R-134a (70°F/21°C), R-125 (52°F/11°C), R-32 (50°F/10°C), R407C (68°F/20°C), and R410A (57°F/14°C); these correlate well with our sealed tube observations of a refrigerant rich system. In order to prolong the metastable period of liquid water equilibrium solubility, the temperature was lowered in 20°F increments starting from 80°F (27°C).

The water solubility data for R-134a, R-143a, R-125, R410A, R407C, and R507A was measured by thermostatting the test cell at 80°F (27°C) and then proceeding upward to 160°F (71°C) (or within 15°F (8.3°C) of critical temperature) in 20°F (11°C) increments, as previously mentioned. This provided the liquid water solubility equilibria with liquid refrigerant in the absence of any solid clathrate. After the upper temperature scan was complete, the cell was cooled to the lower temperatures. The starting point was 60°F (16°C). The temperature was then lowered to -100°F (-73°C) in 20°F (11°C) increments. Based on data in the progress reports submitted during this study, the project monitoring committee decided that water solubility determinations be accomplished by starting at -40°F (-40°C) and proceeding upwards in 20°F (11°C) increments to 160°F (71°C) (or within 15°F (8.3°C) of critical temperature). Refrigerants R-32, R-152a, and R404A were processed in this manner.

Refrigerant and Water Introduction

To guarantee that a sufficient amount of water was present to ensure saturation of liquid refrigerant, the initial target was approximately 10,000 ppm or 1% water (w/w). To introduce

refrigerant and water into any of the test systems, the apparatus was first placed under vacuum by the top sampling port valve for approximately 15-30 minutes. After isolating the system with the top valve, the appropriate amount of water was aspirated into the apparatus through the bottom sampling port valve (Test Units 1 and 2) and then the system was cooled to 0°F (-18°C). Test Unit 3 required disassembly for wetted silica gel addition for each refrigerant test. Then, a second vacuum was pulled from the top cell valve for approximately one minute and the appropriate amount of refrigerant was added through the bottom port.

The amount of water in the test system was also critical to data collection at lower temperatures (<80°F (27°C)). Ideally, water should be present in slight excess of saturation at each temperature measurement to insure maximum water saturation (Daniels *et al*. 1962). Clathrate hydrate formation is compounded by the addition of too much water (see Appendix C).

Data Collection

To obtain a measurement of water solubility in wet refrigerant, the test system was allowed to stir for a minimum of four hours at the desired temperature to attain equilibrium. Stirring was discontinued 15-30 minutes prior to sampling. A 5-10g sample was introduced into a pre-weighed sampling device under vacuum and cooled with either ice water or liquid nitrogen if necessary. After the sampling device was weighed, it was placed in a 220°F (104°C) sand bath and the sample was slowly discharged into a coulometer for moisture determination. Finally, a dry nitrogen gas purge of the sampling device insured that all sample moisture was extracted. Each data point is the average of multiple raw data determinations (see Appendices A and B). Error, represented by error bars on the graphs, was calculated as standard deviation of the measurements (see Figures 6-15). This sampling method was utilized with all test units.

DISCUSSION OF RESULTS

Water solubility in liquid refrigerant data was graphed as temperature (1000/°K) vs. log refrigerant water content (ppm), with most refrigerants clearly showing two distinct water solubility slopes (see Figures 6-15). Figure 16 shows water solubility comparisons of all pure

refrigerants used in this study and figures 17-20 show water solubility data for the blends, azeotropes, and their components. Some refrigerants tested have data points at -60°F (-51°C), -80°F (-62°C), and -100°F (-73°C), but these low temperature data points were excluded from the water solubility graphs because the percent error calculations called their validity into question.

R-134a

The water (w/w) content of 0.8% produced curves that began to closely resemble the data presented previously by ASHRAE (1994) (see Figure 6). R-134a measurements, taken with Test Unit 1, followed the initial sampling protocol of raising the temperature from 80°F (27°C) to 160°F (71°C) and then lowering it from 60°F (16°C) to -100°F (-73°C). Figure 6 illustrates a small change in solubility in the temperature region where clathrate hydrates are known to form (see Figure 3). This suggests a maximum allowable water content of 70 ppm or less in liquid refrigerant for the low-pressure region of a system that operates below -20°F (-29°C) to prevent clathrate hydrate formation. (See also Appendix D, Picture 1)

R-32

R-32 measurements used Test Unit 2. The cell was loaded with 1% water (w/w) and data recorded from 20°F (-6.7°C) to 100°F (38°C). No samples were attempted above 140°F (60°C) because of safety concerns due to high pressure; attempts below 20°F (-6.7°C) resulted in clogging of the sampling valve. Figure 7 shows a dramatic change in the water solubility at 60°F (16°C). Referring to Gibbs Phase Rule,

$$F = 2 + C - P$$

where F = number of degrees of freedom (system variance),

C = number of components, and

P = number of phases,

and allowing one degree of freedom to set the system temperature, it is possible to have three phases using a pure refrigerant. At 60°F (16°C), there was a phase change from clathrate hydrate

to liquid water, thereby affecting water solubility. The other two phases are liquid and vapor refrigerant. Figure 7 shows that a water level below 125 ppm at 20°F (-6.7°C) will reduce clathrate hydrate formation in the evaporator region of an operating system.

R-32 was also tested using Test Unit 3 (Figure 5) with wetted 14-20 mesh silica gel as the source of water (25 g H_2O/50 g silica gel) (see Figure 8). No data was taken between -40°F (-40°C) and 60°F (16°C) due to clogging of the sampling valve. In this work, solubility results obtained using a solid adsorbent (silica gel) as the water source differed from results using straight water addition. The adsorbent method of water reported by Walker *et al*. (1960) was limited to one data point for R-22 at 86°F (30°C) in their study of the stability of fluorocarbon refrigerants and refrigerating oil mixtures. Here, the adsorbent-generated data form a straight line while the water-addition data form two intersecting lines (see Figures 7 and 8). Since both data sets are limited, it is difficult to draw a conclusion about which method of water addition is better. (See also Appendix D, Picture 2)

R-143a

R-143a measurements used the same temperature, sampling protocol, amount of water, and test unit used with R-134a. Figure 9 clearly demonstrates the difference of solubility between liquid water in refrigerant and clathrate hydrate in refrigerant when plotted using the log profile. Again, a marked change in the slope is apparent at 60°F (16°C), signifying a phase change from liquid water to clathrate hydrate, adhering to Gibbs Phase Rule. Water levels below 15 ppm at -40°F (-40°C) are advisable to avoid clathrate hydrate formation in the evaporating low-pressure region of an operational system. (See also Appendix D, Picture 3)

R-125

R-125 measurements used the same temperature, sampling protocol, and test unit (loaded with 1% water (w/w)) used with R-134a. This data is graphed in Figure 10. Water solubility in R-125 is affected by a phase change from liquid water in R-125 to the solubility of clathrate hydrate in R-125 at 40°F (4.4°C). In order to minimize clathrate hydrate formation on the low-

pressure side of a system, water levels should be below 125 ppm at -20°F (-29°C). (See also Appendix D, Picture 4)

R-152a

Based on occurrences within the test cell during R-143a experimentation and sealed tube observations, R-152a measurements used Test Unit 2. The cell was loaded with 1% water (w/w) and the temperature scanned from 0°F (-18°C) to 140°F (60°C). This data is shown in Figure 11. The log plot clearly shows that two water solubility slopes could be plotted, indicating the phase change of liquid water to clathrate hydrate at 60°F (16°C) and the results of liquid water and clathrate hydrate solubility in R-152a. The phase change temperature of 60°F (16°C) was predicted with the sealed tube observations (see Figure 4). The sampling valve was clogged at lower temperatures. The maximum allowable water content of an operating system should be less than or equal to 350 ppm at 0°F (-18°C) to prevent clathrate hydrate formation in the low-pressure region of the system. (See also Appendix D, Picture 5)

R410A

R410A measurements used the same temperature, sampling protocol, and test unit as R-134a with 1% water (w/w). This data is shown by itself in Figure 12 and with components R-32 and R-125 in Figure 17. The R410A results are a good example of complications caused by clathrate hydrates. It appears as if two lines intersect at 0°F (-18°C). The solubility is less below 0°F (-18°C) because of clathrate hydrate formation. Figure 12 indicates that a water level less than 15 ppm at -40°F (-40°C) will prevent clathrate hydrate formation in the low-pressure region of an operational system. Sealed tube observations confirm clathrate hydrate formation at 10°F (-12°C) (see Figure 3). Figure 12 illustrates a change in water solubility at 0°F (-18°C). Considering Gibbs Rule ($F = 2 + C – P$) and the fact that this azeotrope has two components, the number of components is three (R-32, R-125, and water), thereby permitting the existence of four phases so that one degree of freedom remains in tact for setting the temperature of the system.

Therefore, the phase changes affecting water solubility in R410A at 0°F (-18°C) through 10°F (-12°C) might be from the presence of V, L_1, and L_2 to one of the following combinations:

1) V, L_1, L_2, and H_I *or* H_{II},
2) V, L_2, I, and H_I *or* H_{II}, or
3) V, L_2, H_I, *and* H_{II},

where: V = refrigerant vapor,

L_1 = liquid water,

L_2 = liquid refrigerant,

I = solid water (ice),

H_I = clathrate hydrate structure I, and

H_{II} = clathrate hydrate structure II.

The sealed tube observations show clathrate hydrate appearance at 10°F (-12°C) for R410A and R-125 and at 50°F (10°C) for R-32 (see Figure 3). This is interesting because the existence of a hydrate azeotrope has been reported with a lower dissociation pressure than that of either of the components of the mixture (Holder *et al*. 1988). (See also Appendix D, Picture 6)

R407C

R407C measurements used the same temperature, sampling protocol, and test unit as R-134a with 1% water (w/w). This data is shown in Figures 13 and 18. The R407C figures illustrate a more subtle change in water equilibrium below 20°F (-6.7°C) with respect to temperature points taken at 20°F (-6.7°C) and above. This can be explained by the temperature at which clathrate hydrate is formed and dissolved (see Figure 3, R407C with 1% water (w/w)). This is not surprising since clathrate hydrate observance for R407C and its components, except R-32, is below 20°F (-6.7°C). A change in water solubility is noted below 20°F (-6.7°C), reflecting a change in water equilibrium in R407C to clathrate hydrate equilibrium in R407C. Operating levels of 15 ppm water at -40°F (-40°C) prevent clathrate hydrate formation in the evaporator. (See also Appendix D, Picture 7)

R507A

R507A measurements used the same temperature, sampling protocol, and test unit as R-134a. 1% water (w/w) was added. This data is displayed in Figures 14 and 19. R507A is a blend of R-125 and R-143a and below 40°F (4.4°C) the water/clathrate hydrate solubility in R507A falls between that of its two component refrigerants. All three refrigerants' water/clathrate hydrate solubility lines on Figure 19 show two changes in the slope, one at either 40°F (4.4°C), 60°F (16°C), or 80°F (27°C) and one at 20°F (-6.7°C). The slope changes for R507A and its components correspond with a phase change from liquid water to liquid water and hydrate, liquid water to ice and hydrate, or liquid water to hydrate. This data confirms the sealed tube observations in Figure 3. In addition, examination of Figure 14 predicts that water levels should be lower than 30 ppm at -40°F (-40°C) to prevent clathrate hydrates from forming in the evaporator. (See also Appendix D, Picture 8)

R404A

R404A measurements used Test Unit 2. The cell was loaded with 1% water (w/w) and data acquired successfully from -40°F (-40°C) to 100°F (38°C). This data is shown in Figures 15 and 20. Clearly, two slopes exist, one for data above 40°F (4.4°C) and another for data below 40°F (4.4°C). Keeping water levels below 30 ppm at -40°F (-40°C) will reduce clathrate hydrates in an operating systems' evaporator region. Comparing R404A with its components (see Figure 20), each refrigerant goes through a phase change near 20°F (-6.7°C). (See also Appendix D, Picture 9)

R-22

Although published R-22 water solubility data was intended to be an analytical control along with R-134a in this study, at the time the proposal was written it was unknown that R-22 formed significant amounts of clathrate hydrates. The results of this project predict clathrate hydrate formation at or below 60°F (16°C); Chinworth and Katz (1947) reported that wet R-22

formed a solid hydrate at 64°F (18°C). Nevertheless, R-22 water solubility measurements were attempted for comparison with published ASHRAE data (1994). The water solubility of R-22 was comparable to the reported ASHRAE value, 950 ppm vs. 970 ppm respectively, at 60°F (16°C), but was vastly different at 80°F (27°C). Because R-22 forms flocculant clathrate hydrates as readily as R-32 (see Appendix D, Pictures 2 and 10) and based on the difficulty experienced during R-32 testing at lower temperatures, further R-22 testing was terminated.

R-23

Although liquid R-23 was to be tested in this project, no data points were attempted. Raising the test unit to 80°F (27°C) and above with R-23 would have resulted in pressures greater than 600psig, which exceeded safe limitations of the test apparatus. In addition, based on previous testing, water solubility information obtained at temperatures of 60°F (16°C) or below would have been misleading because of clathrate hydrate existence/interference. Because no meaningful data could have been obtained without extensive reconstruction of the test cell, R-23 was eliminated from the project.

CONCLUSION

At lower temperatures, the amount of water in the test assembly is related to the amount of clathrate hydrates formed, which interferes with the measurement of water and/or clathrate hydrate solubility. The straight addition of water to the test system gives the analyst the most precise method of controlling how much water is introduced. It is not advisable to exceed 2% water (w/w) or to use less than 1% water (w/w). These amounts of water are in slight excess of saturation so that maximum solubility is achieved at each temperature while the amount of clathrate hydrate production is minimized at the lower temperatures (see Appendix D, 1% v. 5% water (w/w) added).

The water solubility data reported by ASHRAE (1994) in Table 1, *Solubility of Water in the Liquid Phase of Certain Refrigerants*, matches the data (excluding R-134a and R-123) reported by DuPont in Bulletins B-43 (1982a) and M-5 (1982b) up to 100°F (38°C). More

importantly, Chinworth and Katz (1947) reported the formation of refrigerant clathrate hydrates for R-11 (47°F/8.3°C), R-12 (52°F/11°C), and R-22 (62°F/17°C). This is further confirmed by Briggs and Barduhn (1962). Some data supplied to the industry was correlated to experimental data and may represent water solubility measured in the presence of clathrate hydrates. It is questionable to conclude that straight-line water solubility exists based on the results of this research. The more recent data for R-134a seems to have been partially obtained from an ASHRAE research project (RP-602) using an NMR technique. The data reported in the ASHRAE handbook was taken from a temperature range of -9.7°F (-23°C) to 98°F (37°C), which is within the range of clathrate hydrate formation. Examining the water solubility range below 0°F (-18°C) is pointless due to NMR crystal broad banding. Downing (1988) reports the solubility of R-152a and R-23 at temperatures where both clathrate hydrates and liquid conditions exist. However, he reports straight-line solubility curves in regions where clathrate hydrates may exist.

The solubility of water is the concentration of water in solution in the immiscible refrigerant-rich liquid phase in equilibrium with 1) a water rich liquid phase or 2) at or below metastable temperatures, the solid clathrate hydrate phase. The solubility of water plotted as log refrigerant water content (ppm) vs. temperature (1000/°K) may show a different slope in the clathrate hydrate temperature region than in the non-clathrate hydrate temperature region because of a phase change affecting water solubility. The solubility of liquid water in liquid refrigerant above the clathrate hydrate formation temperature is independent of the overall water concentration in the test cell. However, water content does indeed have a noticeable effect at the lower temperatures when clathrate hydrates are formed. This is due to the varying amounts of liquid water and/or clathrate hydrate formation. It is difficult to determine the impact blends and azeotropes have on clathrate hydrate formation. By itself, one component of a blend may form clathrate hydrates at an observed temperature. However, the presence of other components in a blend or azeotrope may change the clathrate hydrate formation temperature.

When interpreting the results of this study on water and/or clathrate hydrate equilibrium/solubility in a liquid refrigerant rich environment under isothermal conditions, the impact of clathrate hydrates cannot be ignored. Although clathrate hydrates were not the focal point of this research, their presence affected the level of equilibrium water solubility. The fact

that water was measured in temperature regions where clathrate hydrates exist is significant. The water level measured can be attributed to clathrate hydrates since, recalling Gibbs Phase Rule (F=2+C-P) for a pure refrigerant rich environment at a temperature supporting metastability and nucleation, only three phases can exist: liquid and vapor refrigerant and clathrate hydrate. This means that some clathrate hydrate was expelled with refrigerant during the sampling procedure, representing the solubility of clathrate in refrigerant at that sampling temperature and theoretically accounting for all the water in that sample's result.

This research provides ASHRAE with data and relevant information regarding liquid refrigerant properties in the presence of water. It also contributes a firm foundation for further research to understand water solubility in refrigerants. The use of liquid water in a water equilibrium isothermal situation with liquid refrigerant is a sound approach at a temperature above clathrate hydrate formation. The water solubility data generated in this research compares favorably with R-134a data taken by an NMR method (Thrasher *et al*. 1993) and data taken using near infrared spectroscopy (Jackson *et al*. 1995).

Finally, based on this research the authors recommend the maximum tolerable amount of water in liquid refrigerant for system operation below -40°F (-40°C). Typically, in mineral oil and R-22 systems, desiccants routinely maintain water concentration below 30 ppm. It is unknown, however, the effect typical amounts of synthetic lubricant may have on solubility and clathrate formation at these lower temperatures. In conclusion, for each refrigerant tested, the maximum amount (ppm) of water that should be tolerated for operations at -40°F (-40°C) is:

Maximum Amount of Water Tolerable in Systems at -40°F (-40°C)
Based on Clathrate Formation
Table 1

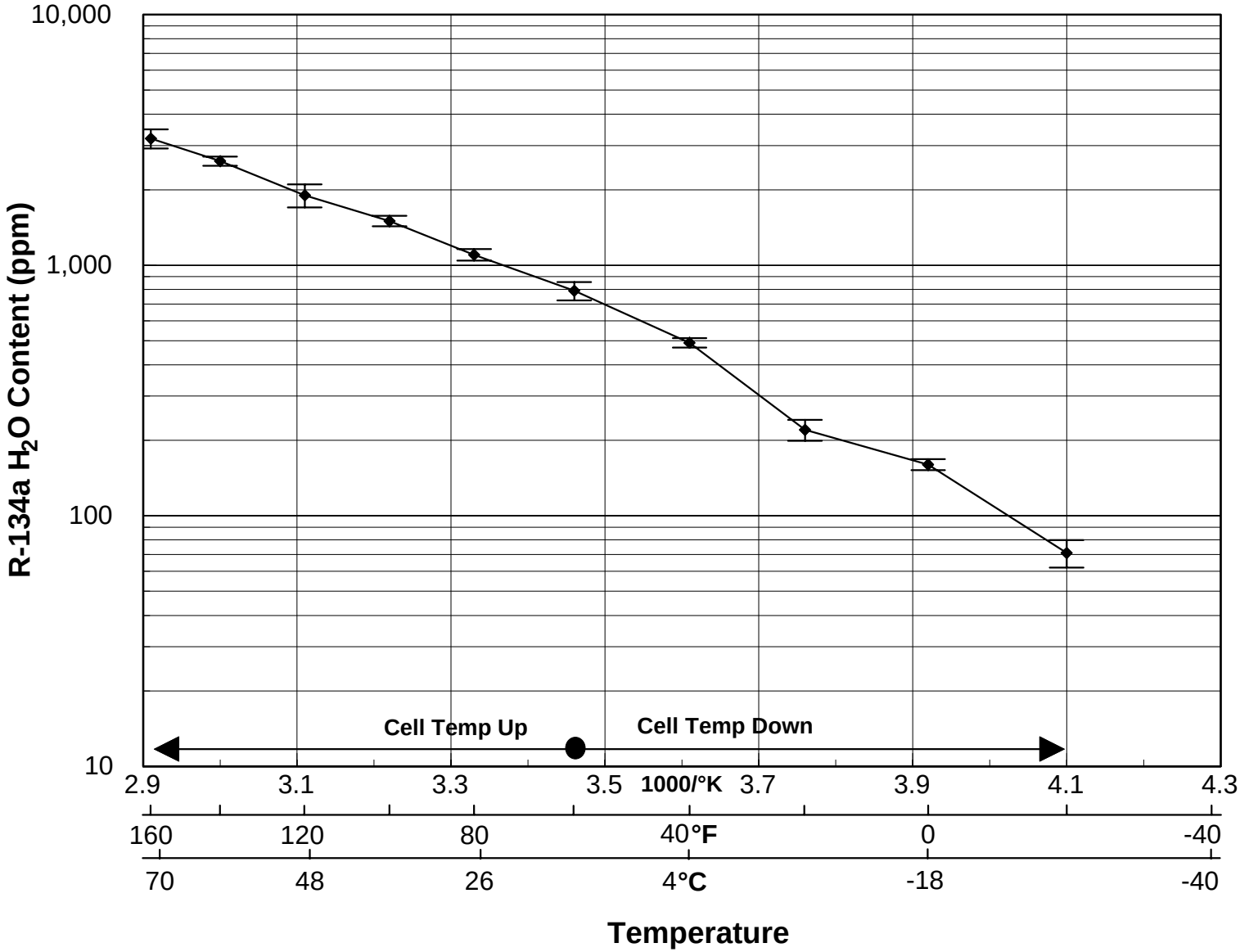
Refrigerant	Water (ppm)
R-134a	30*
R-32	<10*
R-143a	15
R-125	200*
R-152a	150*
R410A	15
R407C	15
R507A	40
R404A	40

*extrapolated

Water Solubility in R-134a

8.0g H_2O and 1.0Kg R-134a

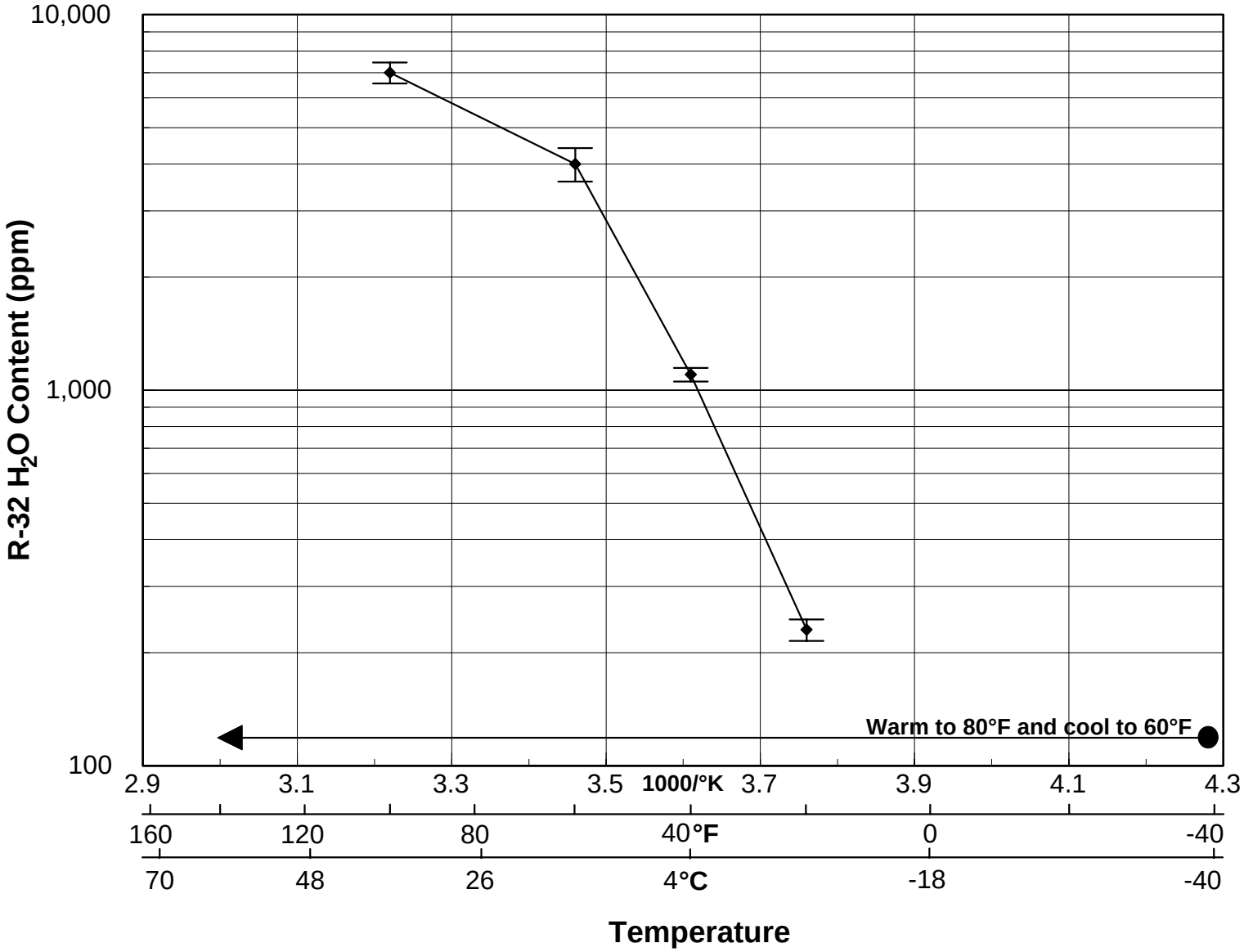
Figure 6



Water Solubility in R-32

15g H_2O and 1.5Kg R-32

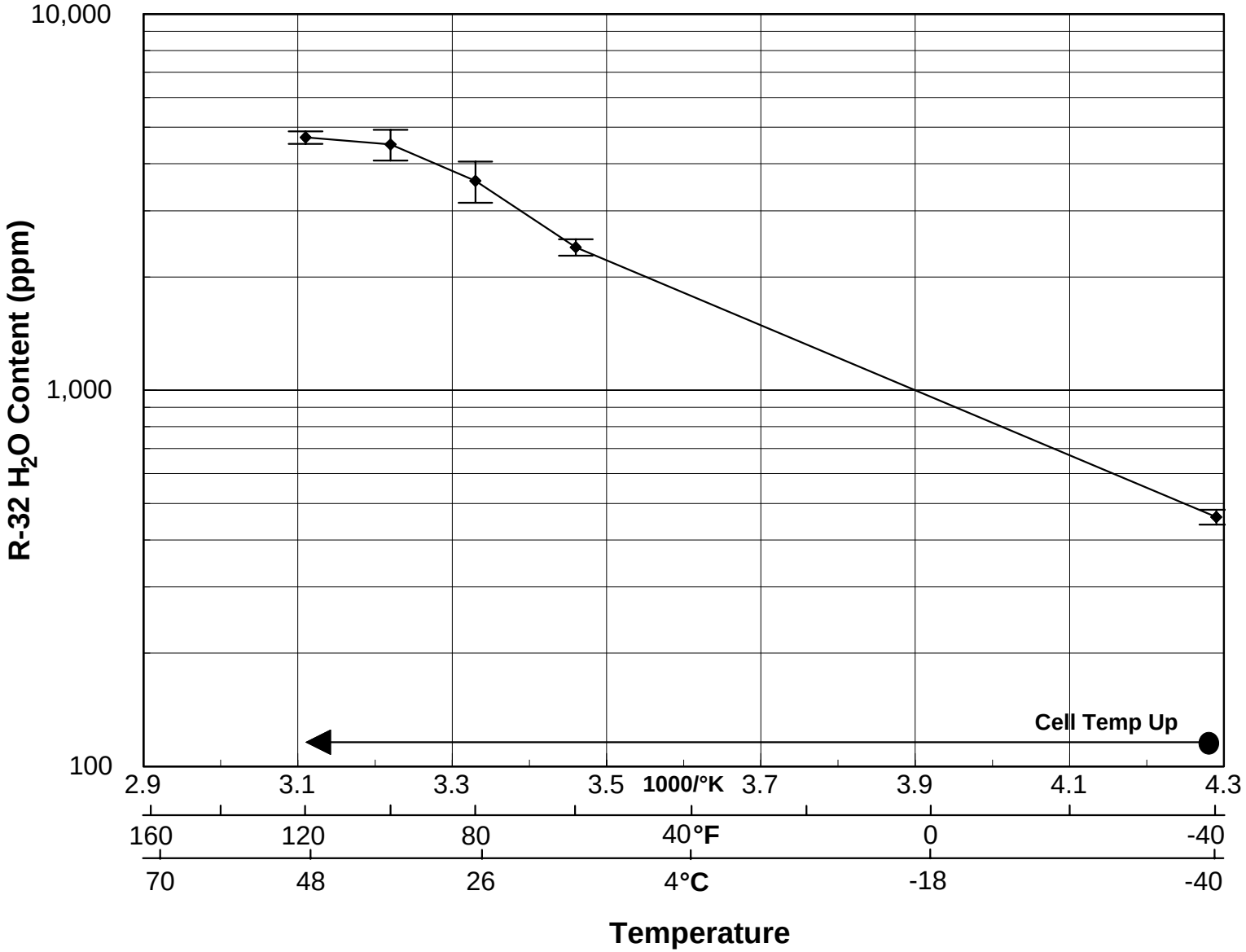
Figure 7



Water Solubility in R-32

25g H_2O in 50g 14-20 mesh Silica Gel and 1.5Kg R-32

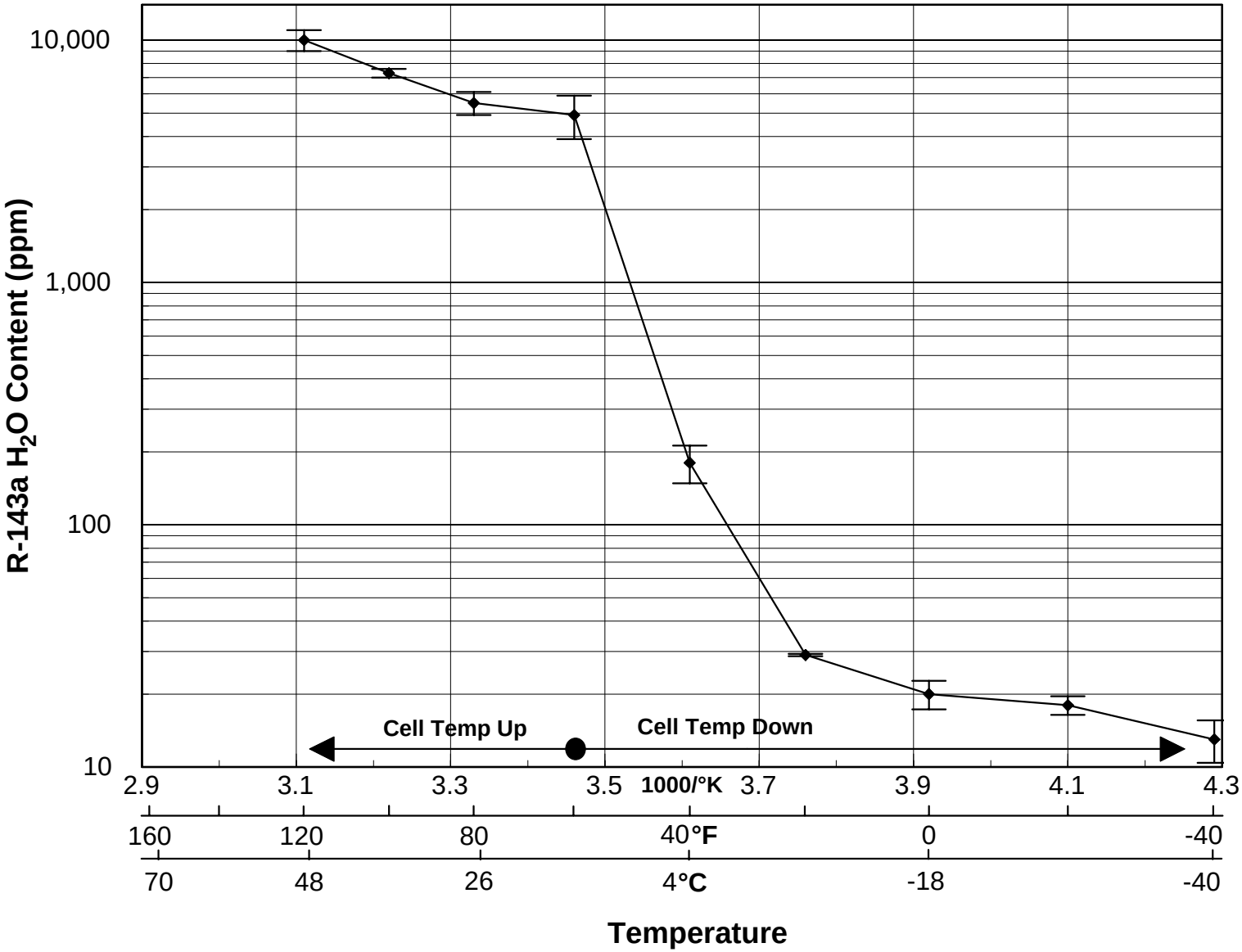
Figure 8



Water Solubility in R-143a

15g H_2O and 1.5Kg R-143a

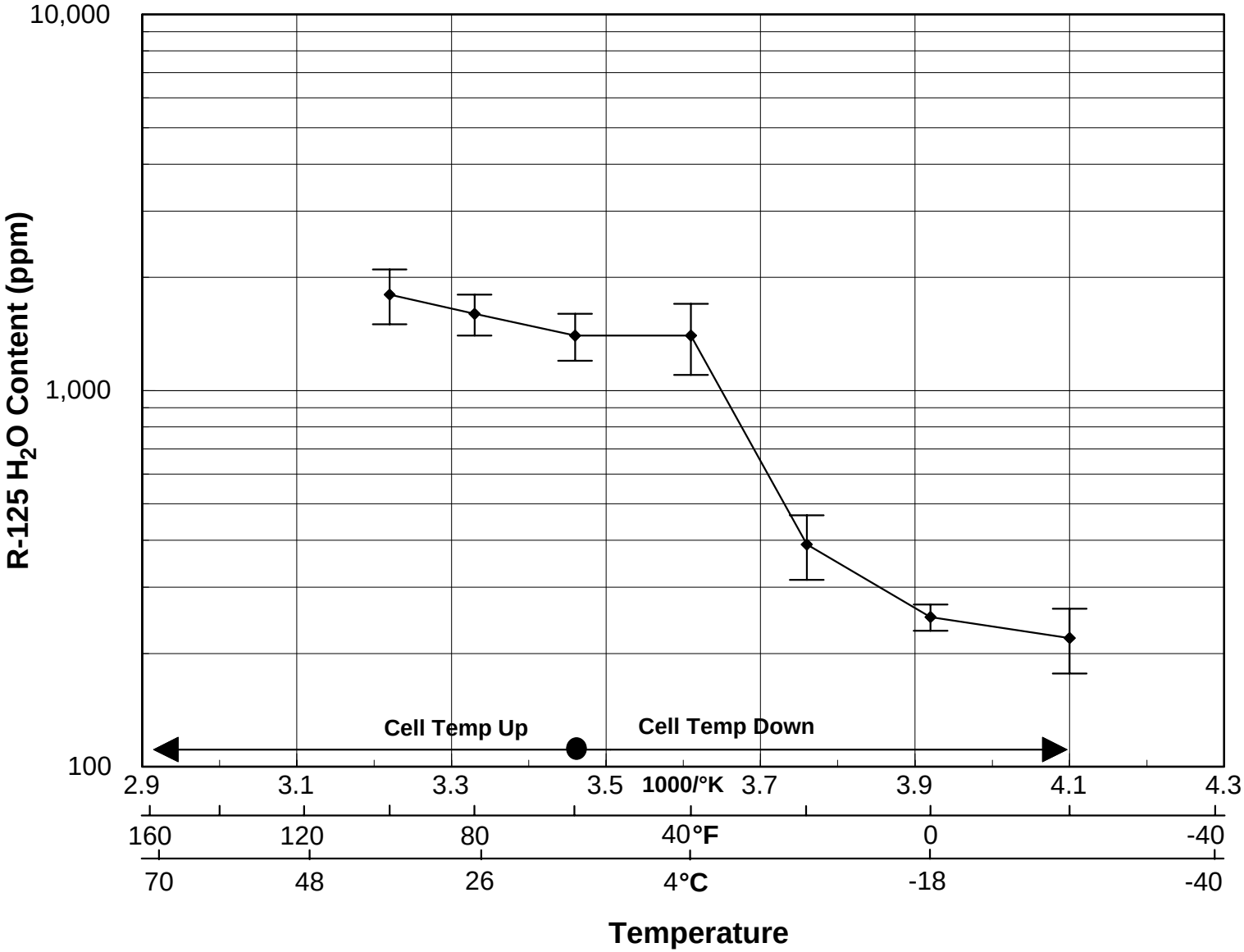
Figure 9



Water Solubility in R-125

10g H_2O and 1.0Kg R-125

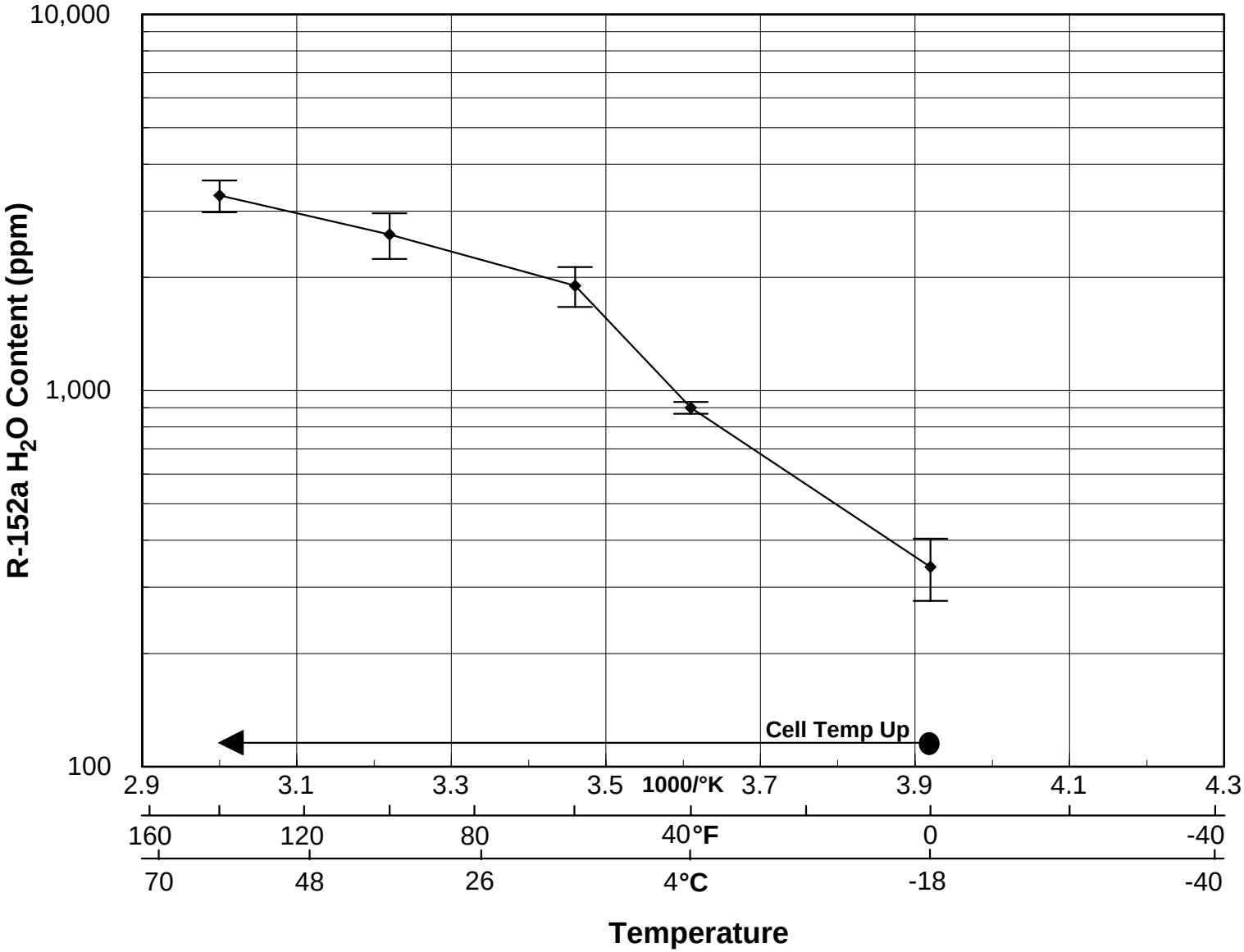
Figure 10



Water Solubility in R-152a

15g H_2O and 1.5Kg R-152a

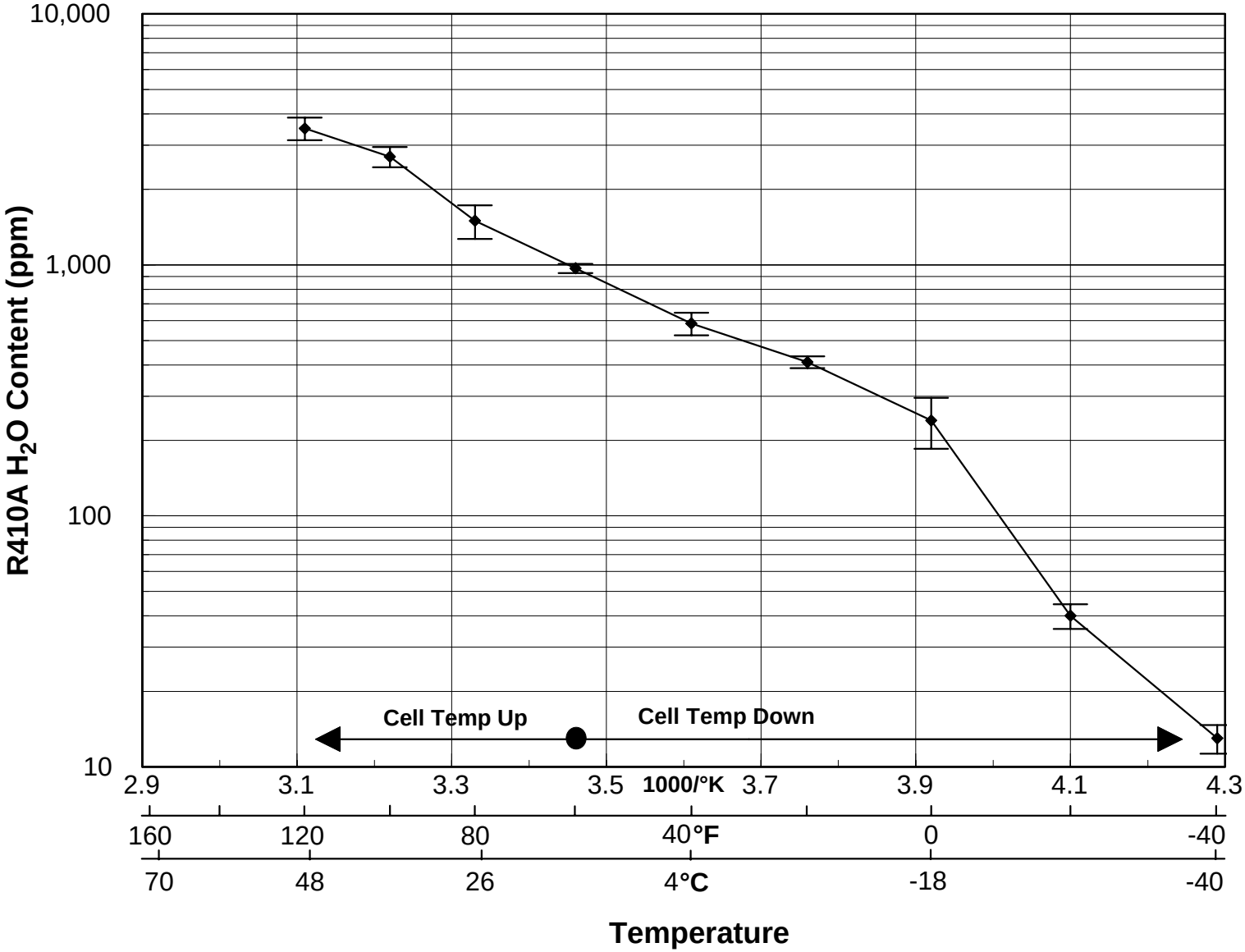
Figure 11



Water Solubility in R410A

10g H_2O and 1.0Kg R410A

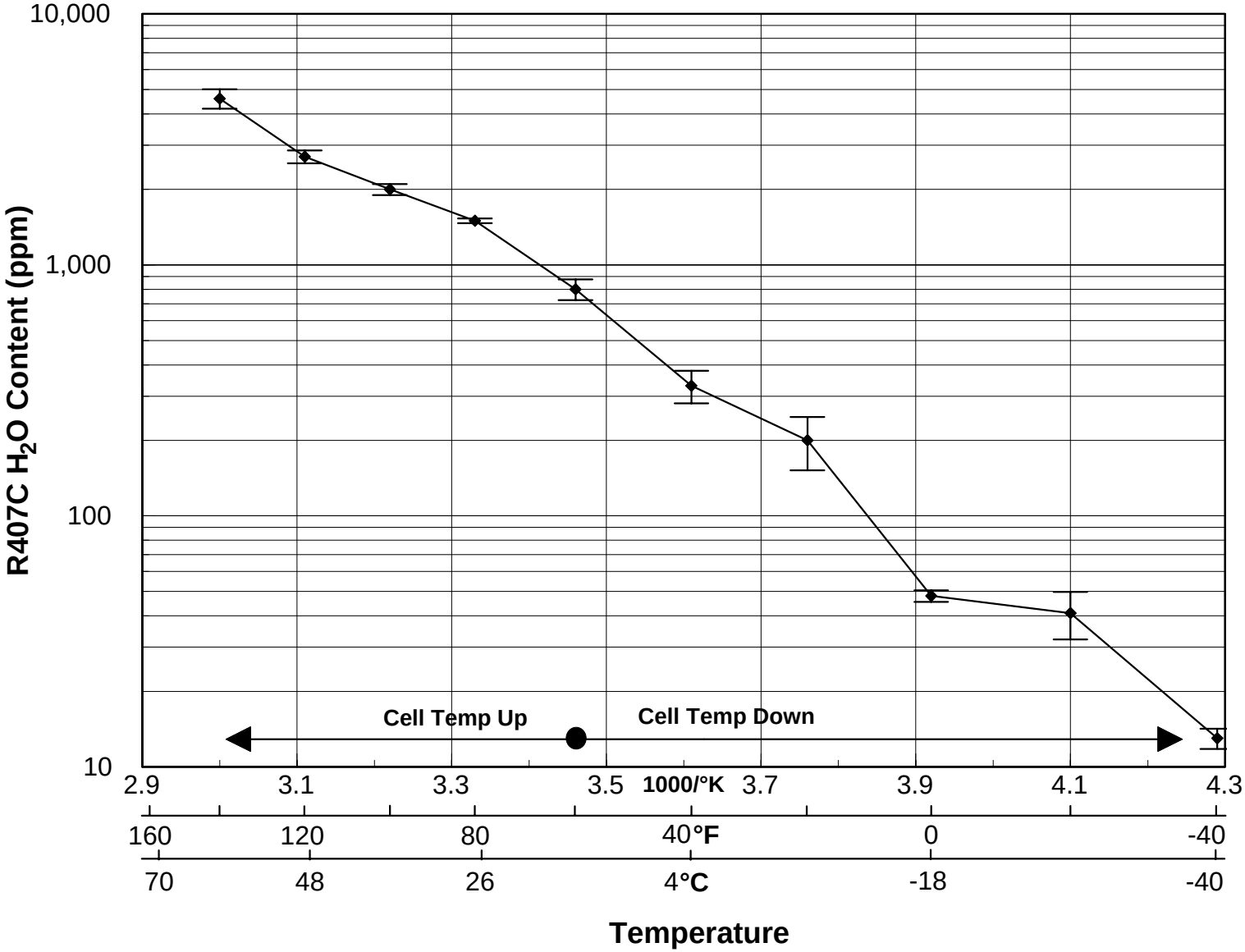
Figure 12



Water Solubility in R407C

10g H_2O and 1.0Kg R407C

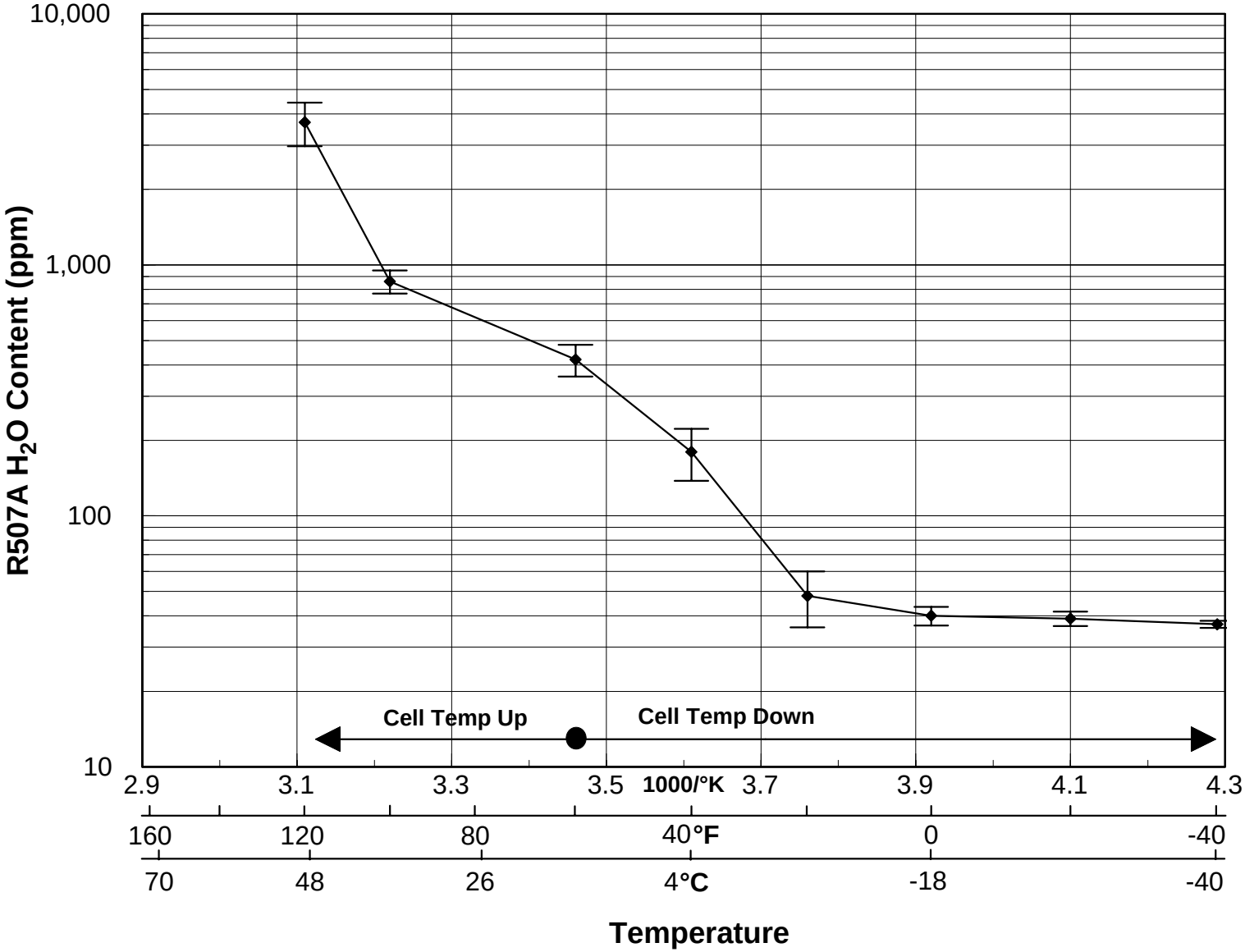
Figure 13



Water Solubility in R507A

10g H_2O and 1.0Kg R507A

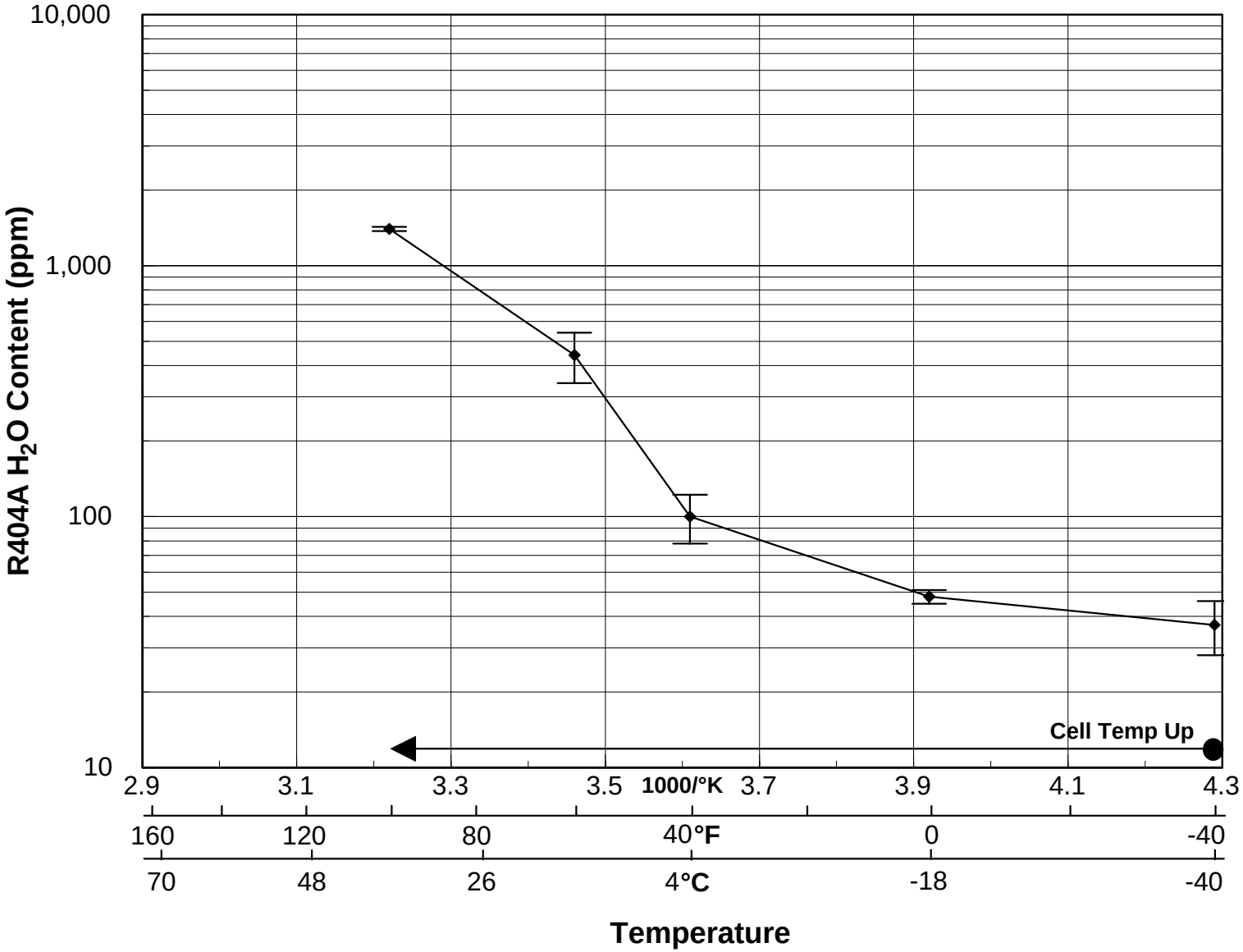
Figure 14



Water Solubility in R404A

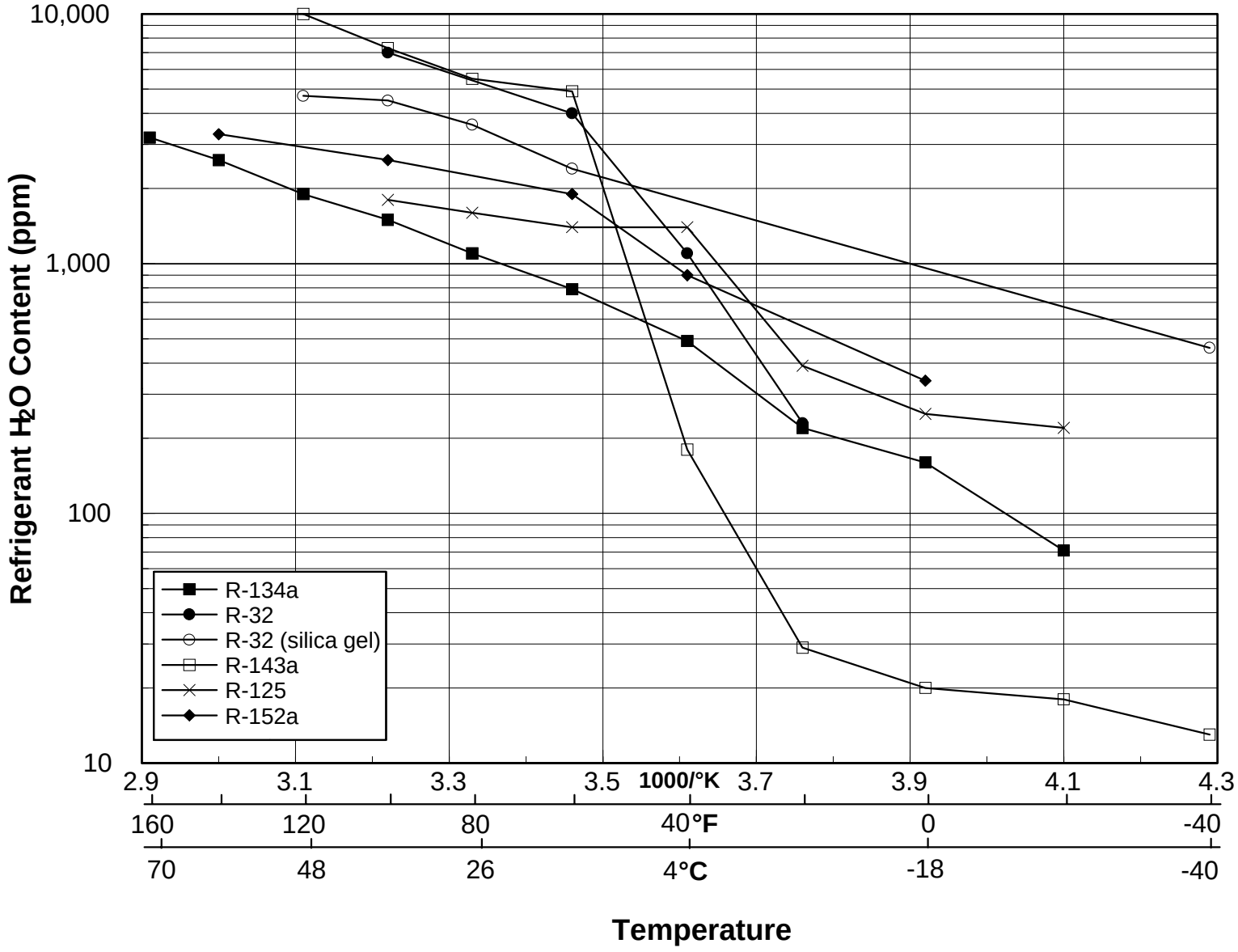
15g H_2O and 1.5Kg R404A

Figure 15



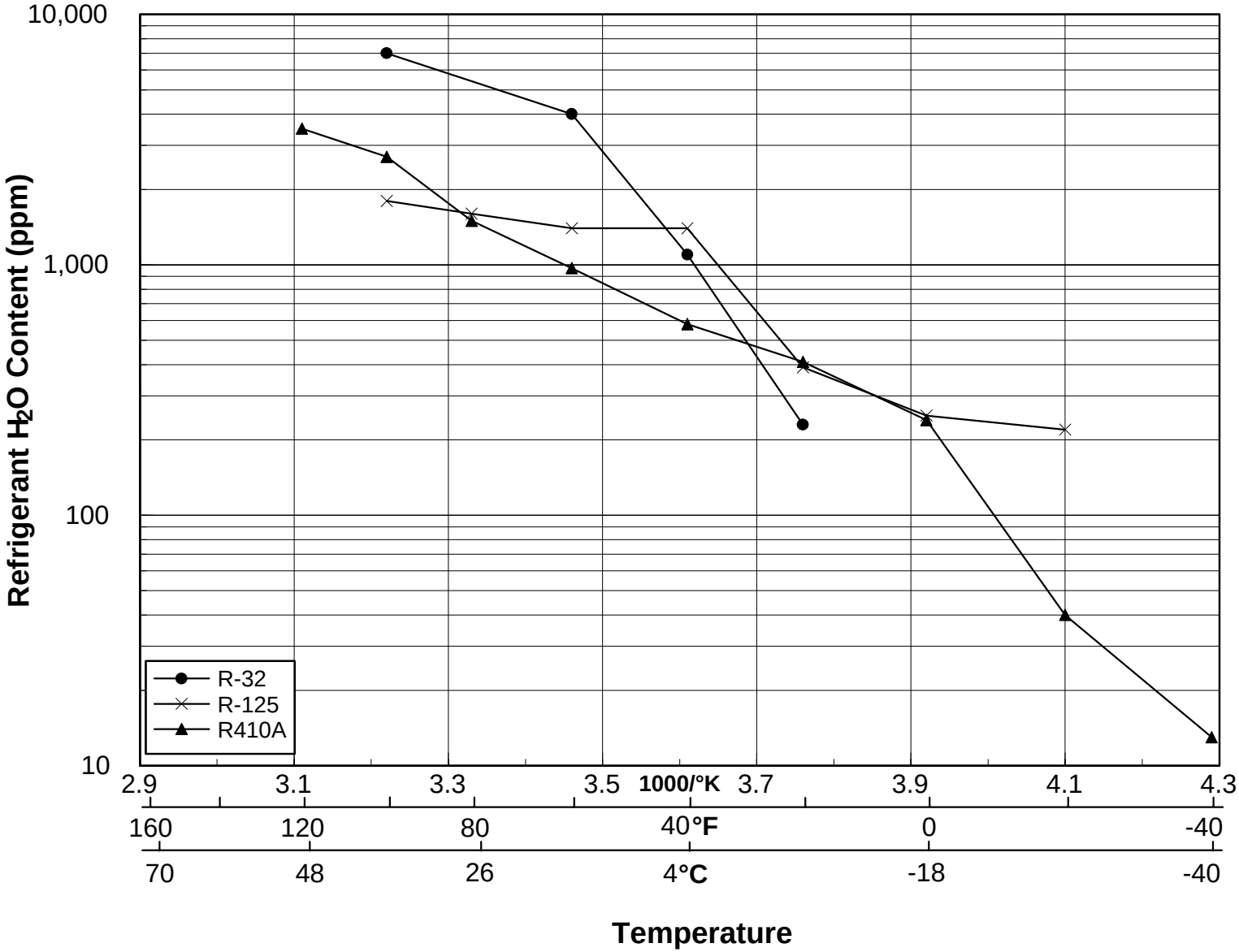
Water Solubility Comparison of R-134a, R-32, R-143a, R-125, and R-152a

Figure 16



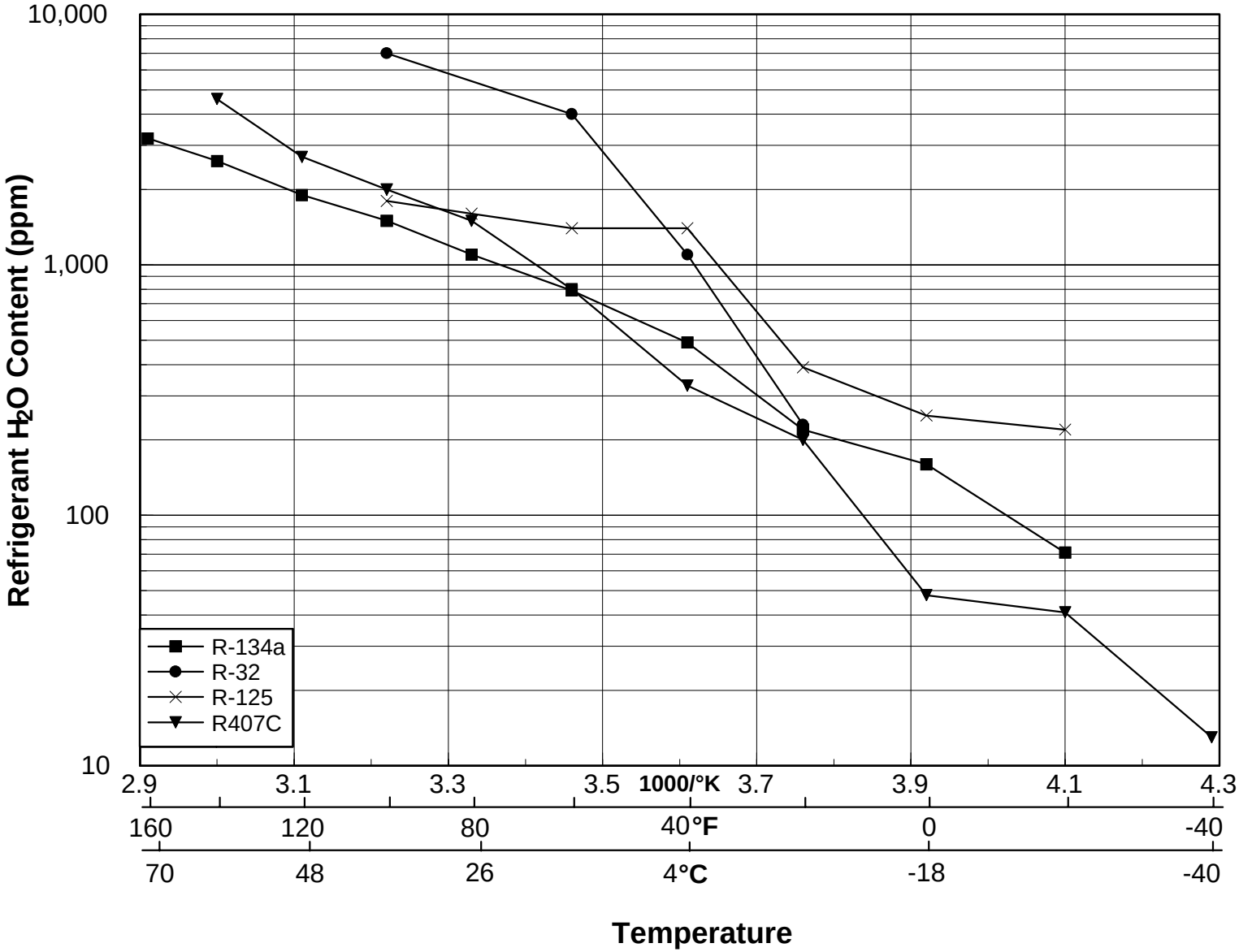
Water Solubility Comparison of R-32, R-125, and R410A

Figure 17



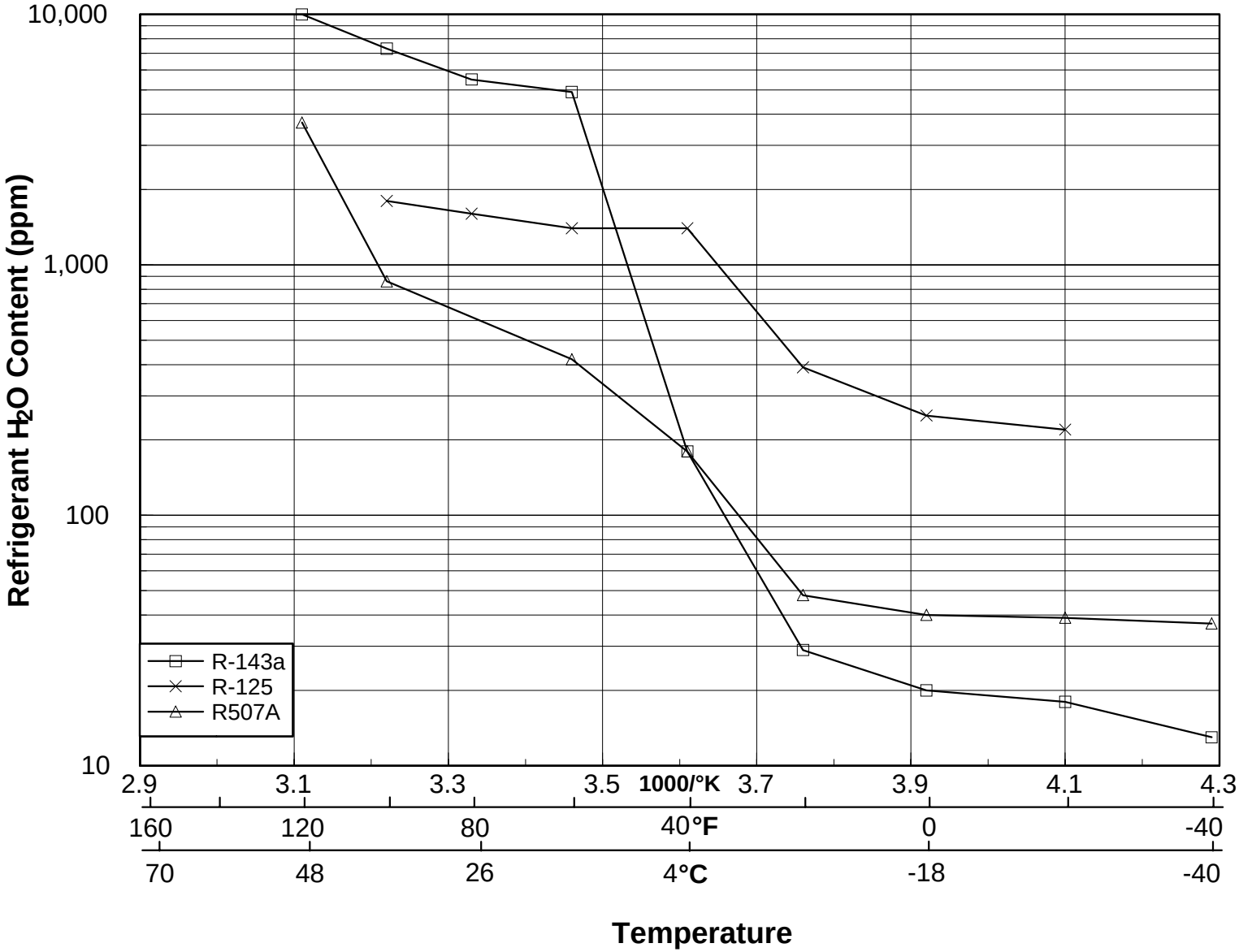
Water Solubility Comparison of R-134a, R-32, R-125, and R407C

Figure 18



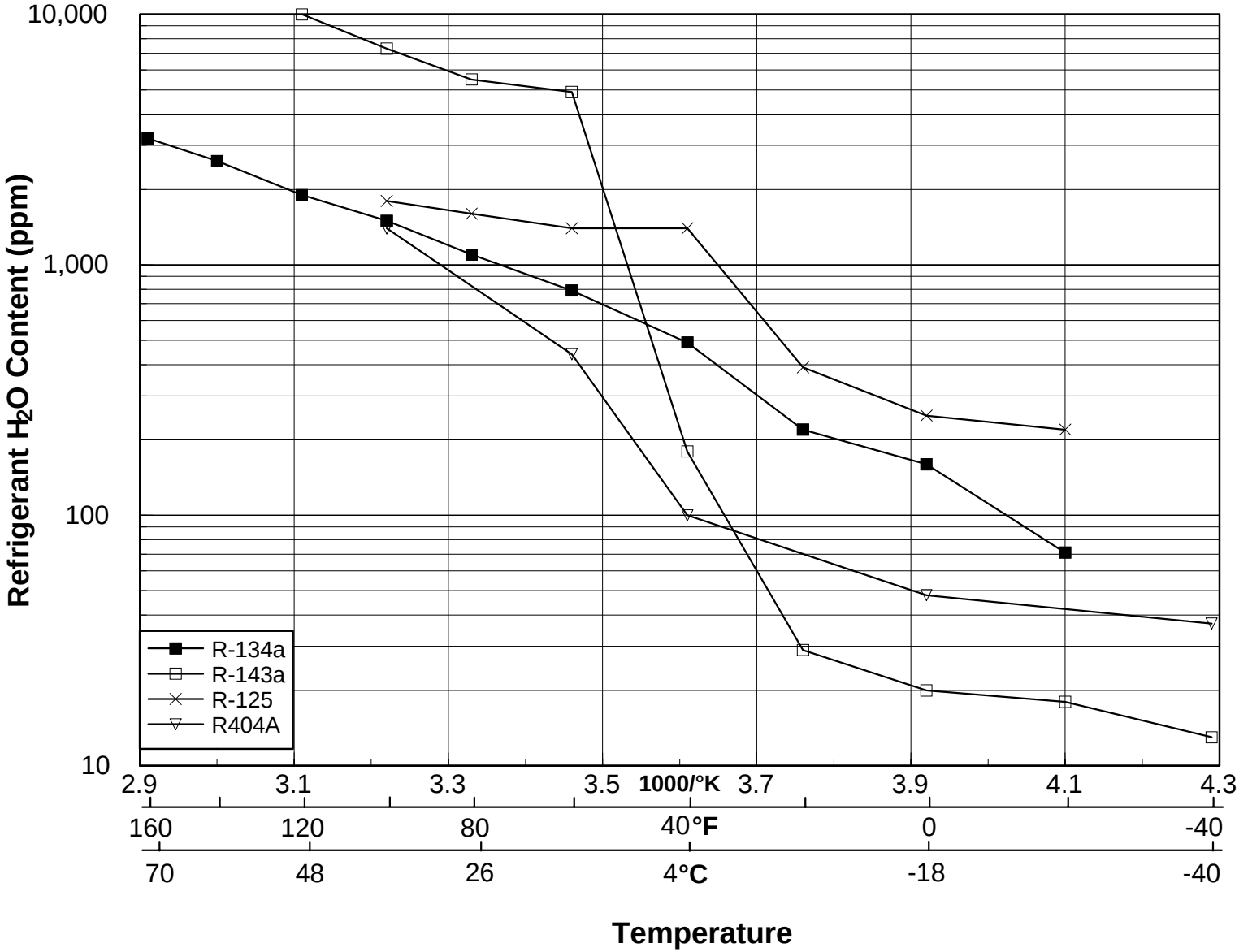
Water Solubility Comparison of R-143a, R-125, and R507A

Figure 19



Water Solubility Comparison of R-134a, R-143a, R-125, and R404A

Figure 20



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Appendix A
Raw Data

Raw Data Points: Solubility of H_2O in R-134a with 8.0g H_2O and 1.0Kg R-134a
Table A.1

Temperature		H_2O (ppm)	
(°F/°C)	(1000/°K)	Raw Data Points	Average
-100/-73	5.00	0	5.7
		0	
		0	
		22.8	
-80/-62	4.74	32.3	12
		0	
		0	
		15.7	
-60/-51	4.50	16.1	23
		0	
		52.3	
		23.6	
-20/-29	4.10	64.7	71
		79.9	
		63.5	
		76.9	
0/-18	3.92	168	160
		162	
		158	
20/-6.7	3.76	225	220
		199	
		227	
		237	
40/4.4	3.61	478	490
		469	
		511	
		509	
		483	
60/16	3.46	763	790
		730	
		810	
		856	
80/27	3.33	1,067	1,100
		1,094	
		1,088	
		1,092	
		1,042	
100/38	3.22	1,546	1,500
		1,552	
		1,428	
		1,488	
		1,529	

Temperature		H_2O (ppm)	
(°F/°C)	(1000/°K)	Raw Data Points	Average
120/49	3.11	2,057	1,900
		1,929	
		1,823	
		1,754	
		2,097	
		1,837	
140/60	3.00	2,488	2,600
		2,667	
		2,687	
		2,511	
160/71	2.91	3,040	3,200
		3,018	
		3,482	
		3,481	
		2,936	
		3,008	

Raw Data Points: Solubility of H_2O in R-32 with 15g H_2O and 1.5Kg R-32
Table A.2

Temperature		H_2O (ppm)	
(°F/°C)	**(1000/°K)**	**Raw Data Points**	**Average**
20/-6.7	3.76	243	230
		215	
40/4.4	3.61	1,054	1,100
		1,108	
60/16	3.46	4,411	4,000
		3,601	
100/38	3.22	7,108	7,000
		7,367	
		6,548	

Raw Data Points: Solubility of H_2O in R-32 with 25g H_2O in 50g 14-20 mesh Silica Gel and 1.5Kg R-32
Table A.3

Temperature		H_2O (ppm)	
(°F/°C)	**(1000/°K)**	**Raw Data Points**	**Average**
-40/-40	4.29	479	460
		439	
		462	
60/16	3.46	2,520	2,400
		2,393	
		2,303	
80/27	3.33	3,883	3,600
		3,152	
		3,870	
100/38	3.22	4,271	4,500
		4,289	
		4,919	
120/49	3.11	4,519	4,700
		4,567	
		4,645	
		4,720	
		4,804	

Raw Data Points: Solubility of H_2O in R-143a with 15g H_2O and 1.5Kg R-143a
Table A.4

Temperature		H_2O (ppm)	
(°F/°C)	**(1000/°K)**	**Raw Data Points**	**Average**
-100/-73	5.00	1.20	2.5
		3.80	
-80/-62	4.74	0	4.1
		0	
		12.2	
-60/-51	4.50	3.51	6.9
		0	
		17.2	
-40/-40	4.29	15.6	13
		10.9	
		11.8	
-20/-29	4.10	17.6	18
		16.9	
		19.6	
0/-18	3.92	21.9	20
		17.3	
20/-6.7	3.76	29.3	29
		29.3	
40/4.4	3.61	148	180
		194	
		189	
60/16	3.46	5,170	4,900
		3,899	
		5,563	
80/27	3.33	5,800	5,500
		4,900	
		5,800	
100/38	3.22	7,600	7,300
		7,000	
120/49	3.11	11,100	10,000
		9,000	

Raw Data Points: Solubility of H_2O in R-125 with 10g H_2O and 1.0Kg R-125
Table A.5

Temperature		H_2O (ppm)	
(°F/°C)	**(1000/°K)**	**Raw Data Points**	**Average**
-100/-73	5.00	71.1	52
		32.9	
-80/-62	4.74	0	72
		144	
-60/-51	4.50	28.0	100
		172	
-20/-29	4.10	249	220
		177	
		214	
		225	
0/-18	3.92	267	250
		230	
20/-6.7	3.76	350	390
		404	
		466	
		336	
40/4.4	3.61	1,500	1,400
		1,500	
		1,100	
60/16	3.46	1,400	1,400
		1,200	
		1,600	
80/27	3.33	1,700	1,600
		1,400	
100/38	3.22	2,000	1,800
		1,900	
		1,500	

Raw Data Points: Solubility of H_2O in R-152a with 15g H_2O and 1.5Kg R-152a
Table A.6

Temperature		H_2O (ppm)	
(°F/°C)	**(1000/°K)**	**Raw Data Points**	**Average**
0/-18	3.92	375	340
		357	
		276	
40/4.4	3.61	868	900
		922	
60/16	3.46	2,062	1,900
		1,674	
100/38	3.22	2,816	2,600
		2,240	
		2,669	
140/60	3.00	3,622	3,300
		3,202	
		3,058	

Raw Data Points: Solubility of H_2O in R410A with 10g H_2O and 1.0Kg R410A
Table A.7

Temperature		H_2O (ppm)	
(°F/°C)	**(1000/°K)**	**Raw Data Points**	**Average**
-100/-73	5.00	0.114	0.06
		0	
-80/-62	4.74	0.200	0.31
		0.630	
		0	
		0.410	
-60/-51	4.50	0	1.7
		5.07	
		0	
		1.67	
-40/-40	4.29	11.6	13
		14.7	
		12.7	
		11.7	
-20/-29	4.10	39.2	40
		44.5	
		39.5	
		36.0	
0/-18	3.92	253	240
		295	
		222	
		193	
20/-6.7	3.76	407	410
		395	
		432	
40/4.4	3.61	645	580
		550	
		545	
		585	
60/16	3.46	953	970
		937	
		1,011	
		983	
80/27	3.33	1,420	1,500
		1,293	
		1,731	
100/38	3.22	2,759	2,700
		2,466	
		2,952	
120/49	3.11	3,252	3,500
		3,356	
		3,862	

Raw Data Points: Solubility of H_2O in R407C with 10g H_2O and 1.0Kg R407C
Table A.8

Temperature		H_2O (ppm)	
(°F/°C)	(1000/°K)	Raw Data Points	Average
-100/-73	5.00	0	1.2
		2.36	
-80/-62	4.74	5.10	2.6
		0	
-60/-51	4.50	0	5.5
		16.5	
		0	
-40/-40	4.29	14.2	13
		12.3	
-20/-29	4.10	48.8	41
		41.4	
		32.2	
0/-18	3.92	48.3	48
		50.5	
		46.3	
20/-6.7	3.76	162	200
		227	
		213	
		237	
		152	
40/4.4	3.61	320	330
		379	
		297	
60/16	3.46	777	800
		876	
		729	
		804	
		792	
80/27	3.33	1,513	1,500
		1,533	
		1,511	
		1,532	
100/38	3.22	1,908	2,000
		2,078	
		2,055	
		1,897	
120/49	3.11	2,861	2,700
		2,643	
		2,745	
		2,569	
140/60	3.00	4,188	4,600
		4,935	

Raw Data Points: Solubility of H_2O in R507A with 10g H_2O and 1.0Kg R507A
Table A.9

Temperature		H_2O (ppm)	
(°F/°C)	**(1000/°K)**	**Raw Data Points**	**Average**
-100/-73	5.00	0	3.8
		7.50	
-80/-62	4.74	3.20	7.3
		11.4	
-60/-51	4.50	6.90	14
		20.6	
-40/-40	4.29	37.8	37
		35.8	
-20/-29	4.10	40.9	39
		36.4	
0/-18	3.92	37.5	40
		43.4	
		37.6	
		38.1	
20/-6.7	3.76	41.5	48
		59.6	
		42.3	
40/4.4	3.61	154	180
		148	
		210	
		154	
		222	
60/16	3.46	481	420
		409	
		406	
		375	
100/38	3.22	934	860
		897	
		773	
		769	
		946	
120/49	3.11	3,711	3,700
		4,355	
		2,974	

Raw Data Points: Solubility of H_2O in R404A with 15g H_2O and 1.5Kg R404A
Table A.10

Temperature		H_2O (ppm)	
(°F/°C)	**(1000/°K)**	**Raw Data Points**	**Average**
-40/-40	4.29	45	37
		28	
0/-18	3.92	50	48
		45	
40/4.4	3.61	122	100
		82	
60/16	3.46	338	440
		535	
		453	
100/38	3.22	1,426	1,400
		1,384	
		1,421	

Appendix B
Data Points (averaged)

Data Points (averaged): Solubility of H_2O in R-134a with 8.0g H_2O and 1.0Kg R-134a
Table B.1

Temperature		H_2O	Error	Error (ppm)/H_2O (ppm)
(°F/°C)	(1000/°K)	(ppm)	(ppm)	(%)
-100/-73	5.00	5.7	±17	300
-80/-62	4.74	12	±20	170
-60/-51	4.50	23	±29	130
-20/-29	4.10	71	±8.9	13
0/-18	3.92	160	±8.0	5.0
20/-6.7	3.76	220	±21	10
40/4.4	3.61	490	±21	4.3
60/16	3.46	790	±66	8.4
80/27	3.33	1,100	±58	5.3
100/38	3.22	1,500	±72	4.8
120/49	3.11	1,900	±200	11
140/60	3.00	2,600	±110	4.2
160/71	2.91	3,200	±280	8.8

Data Points (averaged): Solubility of H_2O in R-32 with 15g H_2O and 1.5Kg R-32
Table B.2

Temperature		H_2O	Error	Error (ppm)/H_2O (ppm)
(°F/°C)	(1000/°K)	(ppm)	(ppm)	(%)
20/-6.7	3.76	230	±15	6.5
40/4.4	3.61	1,100	±46	4.2
60/16	3.46	4,000	±410	9.8
100/38	3.22	7,000	±450	6.4

Data Points (averaged): Solubility of H_2O in R-32 with 25g H_2O in 50g 14-20 mesh Silica Gel and 1.5Kg R-32
Table B.3

Temperature		H_2O	Error	Error (ppm)/H_2O (ppm)
(°F/°C)	(1000/°K)	(ppm)	(ppm)	(%)
-40/-40	4.29	460	±21	4.6
60/16	3.46	2,400	±120	5.0
80/27	3.33	3,600	±450	13
100/38	3.22	4,500	±420	9.3
120/49	3.11	4,700	±180	3.8

Data Points (averaged): Solubility of H_2O in R-143a with 15g H_2O and 1.5Kg R-143a
Table B.4

Temperature		H_2O	Error	Error (ppm)/H_2O (ppm)
(°F/°C)	(1000/°K)	(ppm)	(ppm)	(%)
-100/-73	5.00	2.5	±1.3	52
-80/-62	4.74	4.1	±8.1	200
-60/-51	4.50	6.9	±10	140
-40/-40	4.29	13	±2.6	20
-20/-29	4.10	18	±1.6	8.9
0/-18	3.92	20	±2.7	14
20/-6.7	3.76	29	±0.3	1.0
40/4.4	3.61	180	±32	18
60/16	3.46	4,900	±1,000	20
80/27	3.33	5,500	±600	11
100/38	3.22	7,300	±300	4.1
120/49	3.11	10,000	±1,000	10

Data Points (averaged): Solubility of H_2O in R-125 with 10g H_2O and 1.0Kg R-125
Table B.5

Temperature		H_2O	Error	Error (ppm)/H_2O (ppm)
(°F/°C)	(1000/°K)	(ppm)	(ppm)	(%)
-100/-73	5.00	52	±19	37
-80/-62	4.74	72	±72	100
-60/-51	4.50	100	±72	72
-20/-29	4.10	220	±43	20
0/-18	3.92	250	±20	8.0
20/-6.7	3.76	390	±76	19
40/4.4	3.61	1,400	±300	21
60/16	3.46	1,400	±200	14
80/27	3.33	1,600	±200	13
100/38	3.22	1,800	±300	17

Data Points (averaged): Solubility of H_2O in R-152a with 15g H_2O and 1.5Kg R-152a
Table B.6

Temperature		H_2O	Error	Error (ppm)/H_2O (ppm)
(°F/°C)	(1000/°K)	(ppm)	(ppm)	(%)
0/-18	3.92	340	±64	19
40/4.4	3.61	900	±32	3.6
60/16	3.46	1,900	±230	12
100/38	3.22	2,600	±360	14
140/60	3.00	3,300	±320	9.7

Data Points (averaged): Solubility of H_2O in R410A with 10g H_2O and 1.0Kg R410A
Table B.7

Temperature		H_2O	Error	Error (ppm)/H_2O (ppm)
(°F/°C)	(1000/°K)	(ppm)	(ppm)	(%)
-100/-73	5.00	0.06	±0.06	100
-80/-62	4.74	0.31	±0.32	97
-60/-51	4.50	1.7	±3.4	170
-40/-40	4.29	13	±1.7	13
-20/-29	4.10	40	±4.5	11
0/-18	3.92	240	±55	23
20/-6.7	3.76	410	±22	5.4
40/4.4	3.61	580	±65	11
60/16	3.46	970	±41	4.2
80/27	3.33	1,500	±230	15
100/38	3.22	2,700	±250	9.3
120/49	3.11	3,500	±360	10

Data Points (averaged): Solubility of H_2O in R407C with 10g H_2O and 1.0Kg R407C
Table B.8

Temperature		H_2O	Error	Error (ppm)/H_2O (ppm)
(°F/°C)	(1000/°K)	(ppm)	(ppm)	(%)
-100/-73	5.00	1.2	±1.2	100
-80/-62	4.74	2.6	±2.6	100
-60/-51	4.50	5.5	±11	200
-40/-40	4.29	13	±1.2	9.2
-20/-29	4.10	41	±8.8	21
0/-18	3.92	48	±2.5	5.2
20/-6.7	3.76	200	±48	24
40/4.4	3.61	330	±49	15
60/16	3.46	800	±76	9.5
80/27	3.33	1,500	±33	2.2
100/38	3.22	2,000	±100	5.0
120/49	3.11	2,700	±160	5.9
140/60	3.00	4,600	±410	8.9

Data Points (averaged): Solubility of H_2O in R507A with 10g H_2O and 1.0Kg R507A
Table B.9

Temperature		H_2O	Error	Error (ppm)/H_2O (ppm)
(°F/°C)	(1000/°K)	(ppm)	(ppm)	(%)
-100/-73	5.00	3.8	±3.8	100
-80/-62	4.74	7.3	±4.1	56
-60/-51	4.50	14	±7.1	51
-40/-40	4.29	37	±1.2	3.2
-20/-29	4.10	39	±2.6	6.7
0/-18	3.92	40	±3.4	8.5
20/-6.7	3.76	48	±12	25
40/4.4	3.61	180	±42	23
60/16	3.46	420	±61	15
100/38	3.22	860	±91	11
120/49	3.11	3,700	±730	20

Data Points (averaged): Solubility of H_2O in R404A with 15g H_2O and 1.5Kg R404A
Table B.10

Temperature		H_2O	Error	Error (ppm)/H_2O (ppm)
(°F/°C)	(1000/°K)	(ppm)	(ppm)	(%)
-40/-40	4.29	37	±9	24
0/-18	3.92	48	±3	6.3
40/4.4	3.61	100	±22	22
60/16	3.46	440	±100	23
100/38	3.22	1,400	±26	1.9

Appendix C
Sealed Tube Analysis Method

Sealed tubes were prepared to observe the formation and disappearance of clathrate hydrates in water and refrigerant as temperatures decreased from 80°F (27°C) to 0°F (-18°C) and increased from 0°F (-18°C) to 80°F (27°C). Specific ratios of water and refrigerant were sealed in heavy walled glass tubes labeled with ceramic marking ink on both ends. When labeling tubes, the ink turns red as it is burned into the glass with a propane torch, then a cooler flame is used to smooth the stress lines in the glass around the burned area.

The total weight of water and refrigerant in the specified ratio in the macro tubes should be approximately 10g. The amount of water needed in each tube is calculated and added to the tube using a 10µl syringe or a long Pasteur pipette. A four-place electronic balance is used for weighing and the weights are recorded before and after water addition.

Oxygen and a MAPP gas torch form a thick-walled capillary in the glass above the water in each tube, about 2½" from the top. A uniform glass wall thickness should be maintained while constricting the tube. Didymium eye glasses assist in seeing the glass during this manipulation.

To add refrigerant, first attach the constricted tube to the gas manifold. Submerge the tube in liquid nitrogen in a thermos dewar. Evacuate the sample to <40mTorr and then close the valve to the sample. Attach the refrigerant gas to the manifold with a charging hose and evacuate the hose. Purge the manifold three times by adding refrigerant and evacuating it. The third evacuation should be <60mTorr. Add refrigerant to the manifold so that the internal pressure is 800-900 mm Hg. Slowly open the tube valve to the manifold and allow the refrigerant gas to condense as it contacts the cold tube. Control the amount of added refrigerant by observing the manometer Hg fall. The difference in Hg levels can be related to the weight of condensed refrigerant. Since the specific gravities of all refrigerants are different, a refrigerant constant, which relates Hg pressure drop to refrigerant gas weight, must be determined before sample tubes are charged with refrigerant. After sufficient refrigerant has been added, fill the dewar with liquid nitrogen and evacuate the manifold to <40mTorr. Open the tube valve to eliminate non-condensable gases (such as air) from the tube and evacuate to <40mTorr.

To determine the aforementioned refrigerant constant, first prepare empty glass tubes. Accurately record their weight and constrict the tubes. Attach them to the manifold and precisely add varying amounts of refrigerant from 150-300 mm Hg. Seal and allow the tubes to warm to room temperature. Re-weigh matched tops and bottoms of each tube. Calculate the constant for each of the samples by the formula below and obtain an average.

$$C = \frac{b - a}{H} = \text{grams / mm Hg}$$

where C = refrigerant constant

a = initial weight of the tube (g)

b = final weight of refrigerant + tube (g)

H = mm of Hg pressure difference in manifold

Once the water is accurately weighed into the tube, the proper weight of refrigerant to be added based on the specified ratio can be calculated by the formula:

$$R = \frac{L(1 - P)}{P}$$

where R = refrigerant weight (g)

L = water weight (g)

P = percent water [expressed as a decimal (i.e. 40% = .40)]

The mm of Hg manometer pressure drop needed to deliver a certain weight of refrigerant can be calculated from the above equation and the refrigerant constant.

$$M = \frac{R}{C}$$

where M = mm Hg manometer pressure drop

R = refrigerant weight (g)

C = refrigerant constant (g/mm Hg)

After refrigerant has been added to the tube, proceed to seal the tube. Adjust the oxygen and MAPP gases to give a 3-4" flame. With the tube still evacuated and in liquid nitrogen, warm the constriction uniformly until it is drawn inward by the vacuum. Heat the fused portion strongly and lower the tube to produce a molten thread. Cut the thread with the flame. The tube can be annealed while in liquid nitrogen using a cooler carbon-rich flame. The annealing process

deposits carbon on the glass that must be wiped off later. Remove the tube from the liquid nitrogen.

SAFETY NOTE: Once the tube has been sealed and brought to room temperature, it is under high internal pressure and could explode at any time. When possible, keep it behind a safety shield and wear safety glasses, heavy gloves, and a face shield.

Prior to heating in the oven, the two parts of the tube are matched and re-weighed so that the actual weight of refrigerant added can be determined. Thus, the actual weight ratio of water:refrigerant in the sealed tube can be calculated.

Carefully insert the sealed tube into a protective metal sleeve and cap it. Put it into a 122ºF (50ºC) oven for 2-3 hours as a safety check. Taking appropriate safety precautions inspect the tube for hydrate formation going up and down in temperature from 0°F (-18°C) to 80°F (27°C).

The photographs in Appendix D were taken with a blue filter, 200 speed film, and a 1/30 second shutter speed and developed by subtracting 2 densities and 1 cyan to compensate for low light.

Appendix D
Photographic Evidence of Clathrate Hydrate Formation

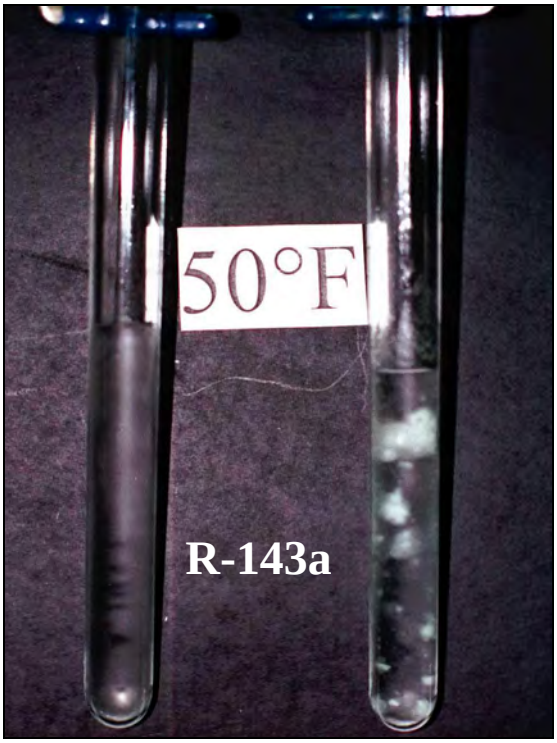
Picture 1

1% water 5% water

Picture 2

1% water 5% water

Picture 3

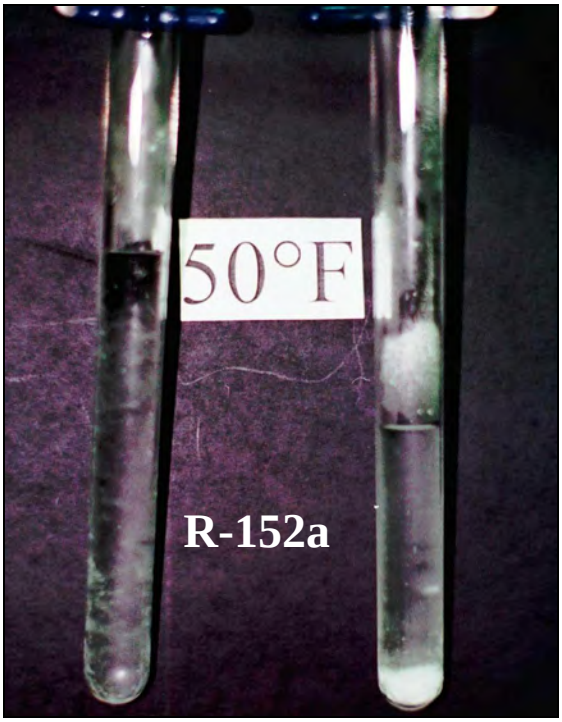


1% water 5% water

Picture 4

1% water 5% water

Picture 5

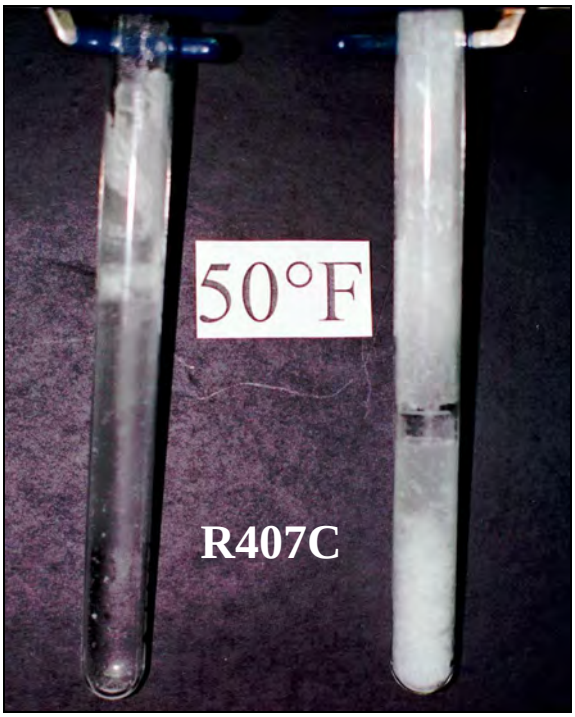


1% water 5% water

Picture 6

1% water 5% water

Picture 7



1% water 5% water

Picture 8

1% water 5% water

Picture 9

1% water 5% water

Picture 10

1% water 5% water

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(54) Title: STABLE PHARMACEUTICAL SOLUTION FORMULATIONS FOR PRESSURISED METERED DOSE INHALERS

(57) Abstract: An aerosol solution composition for use in an aerosol inhaler comprises an active material, a propellant containing a hydrofluoroalkane, a cosolvent and optionally a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler. The composition is stabilized by using a small amount of mineral acid and a suitable can having part or all of its internal metallic surfaces made of stainless steel, anodized aluminium or lined with an inert organic coating.

STABLE PHARMACEUTICAL SOLUTION FORMULATIONS FOR PRESSURISED METERED DOSE INHALERS

The invention relates to stable pharmaceutical solution to be used with pressurised metered dose inhalers (MDIs) suitable for aerosol administration. In particular, the invention relates to solution to be used with pressurised metered dose inhalers (MDIs), suitable for aerosol administration containing β_2-agonists and stable at room temperature for a pharmaceutically acceptable shelf-life.

Pressurised metered dose inhalers are well known devices for administering pharmaceutical products to the respiratory tract by inhalation.

Drugs commonly delivered by inhalation include bronchodilators such as $ß_2$-agonists and anticholinergics, corticosteroids, anti-leukotrienes, anti-allergics and other materials that may be efficiently administered by inhalation, thus increasing the therapeutic index and reducing side effects of the active material.

MDI uses a propellant to expel droplets containing the pharmaceutical product to the respiratory tract as an aerosol. Formulations for aerosol administration *via* MDIs can be solutions or suspensions. Solution formulations offer the advantage of being homogeneous with the active ingredient and excipients completely dissolved in the propellant vehicle or its mixture with suitable co-solvents such as ethanol. Solution formulations also obviate physical stability problems associated with suspension formulations so assuring more consistent uniform dosage administration.

For many years the preferred propellants used in aerosols for pharmaceutical use have been a group of chlorofluorocarbons which are commonly called Freons or CFCs, such as CCl_3F (Freon 11 or CFC-11), CCl_2F_2 (Freon 12 or CFC-12), and $CClF_2$-$CClF_2$ (Freon 114 or CFC-114).

Recently, the chlorofluorocarbon (CFC) propellants such as Freon 11 and Freon 12 have been implicated in the destruction of the ozone layer and their production is being phased out.

Hydrofluoroalkanes [(HFAs) known also as hydro-fluoro-carbons (HFCs)] contain no chlorine and are considered less destructive to ozone and these are

proposed as substitutes for CFCs.

HFAs and in particular 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227) have been acknowledged to be the best candidates for non-CFC propellants and a number of medicinal aerosol formulations using such HFA propellant systems have been disclosed.

Due to the higher polarity of the HFA propellants, in particular of HFA 134a (dielectric constant D > 9.5), with respect to CFC vehicles (D < 2.3), HFA solution formulations may suffer to a greater extent of chemical stability problems with respect to the corresponding CFC formulations.

Preparation of stable HFA solution formulations is even more critical when bronchodilator β_2-agonists belonging to the class of the phenylalkylamino derivatives are concerned; said drugs, like formoterol and salbutamol (albuterol), may suffer of inherent chemical stability problems due to their susceptibility to oxidative conditions; moreover, in the view of the presence of some functional groups like formamide, a higher polarity of the vehicle may accelerate the rate of solvolysis reactions.

As far as formoterol, the currently marketed CFC solution formulation (Foradil®) exhibits indeed a limited shelf life, i.e. 12 months at refrigerator temperature, 4± 2°C, and only 3 month at room temperature.

As far as salbutamol, no formulation as HFA solution for aerosol administration is currently on the market.

In consideration of the problems outlined, it would be highly advantageous to provide a formulation in the form of HFA solution to be administered by MDI's aimed at providing pharmaceutical doses of β_2-agonists characterised by adequate shelf-life.

OBJECT OF THE INVENTION

It is an object of the invention to provide a formulation in the form of HFA solution to be administered by MDI's for providing pharmaceutical doses of β_2-agonists into the low respiratory tract of patients suffering of pulmonary diseases such as asthma, characterised by adequate shelf-life. In particular, it is an object of the invention to provide a formulation in the form of HFA solution to be administered by MDI's for providing pharmaceutical doses of

formoterol with a greater shelf-life of that of the formulation currently on the market.

According to the invention there is provided a pharmaceutical composition comprising a β_2-agonist belonging to the class of phenylalkylamino derivatives in a solution of a liquefied HFA propellant, a co-solvent selected from pharmaceutically acceptable alcohols, solution whose apparent pH has been adjusted to between 2.5 and 5.0 by addition of small amounts of a mineral acid. The composition of the invention shall be contained in a pressurised MDI having part or all of its internal metallic surfaces made of stainless steel, anodised aluminium or lined with an inert organic coating.

In fact, it has been found that, in the case of certain active ingredients such as β_2-agonists, their chemical stability in HFA solution formulations could be dramatically improved by a proper and combined selection of the kind of cans as well as the apparent pH range. The attribution 'apparent' is used as pH is indeed characteristic of aqueous liquids where water is the dominant component (Mole Fraction > 0.95). In relatively aprotic solvents such as the HFA-ethanol vehicles used in these studies, protons are non-hydrated; their activity coefficients differ significantly from those in aqueous solution. Although the Nernst equation with respect to EMF applies and the pH-meter glass electrode system will generate a variable milli-volt output according to proton concentration and vehicle polarity, the "pH" meter reading is not a true pH value. The meter reading represents an apparent pH or acidity function (pH').

When the active ingredient was titrated with a strong acid in a model vehicle system commercially available (HFA 43-10MEE, Vertrel XF, Dupont), the pH' profile exhibits a shallow negative to about pH' = 5.5; thereafter the acidity function drops abruptly. Surprisingly the corresponding HFA formulations turned out to much more stable below pH' 5.5.

On the other hand, the use of inert containers allows to avoid the leaching of metal ions or alkali as a consequence of the action of the acid contained in the formulation onto the inner walls of the cans. Metal ions such Al^{3+} or alkali respectively deriving from the conventional aluminium or glass cans could in

turn catalyse radical oxidative or other chemical reactions of the active ingredient which give rise to the formation of degradation products.

According to a particular embodiment of the invention there is also provided a pharmaceutical composition further containing a low volatility component in such a way as to, besides increasing the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler as explained in the following, further improving the stability of the formulation. In fact, the addition of a low volatility component with a reduced polarity with respect to the co-solvent such as an ester may allow either to reduce the amount of acid to be added for adjusting the pH and diminish the polarity of the medium so limiting the possible uptake of environmental water. In the case of active ingredients such as formoterol, it is well known that the latter (e.g. humidity) could be detrimental to the stability of the active ingredient during storage. Accordingly, there is also provided a pressurised MDI for administering pharmaceutical doses consisting of an anodised aluminium container filled with a pharmaceutical composition consisting of a formoterol fumarate solution in HFA 134a as a propellant in turn containing 12% *w/w* ethanol as a co-solvent and 1.0% *w/w* isopropyl myristate as a low volatility component, the apparent pH of said solution having been adjusted to between 3.0 and 3.5 by addition of small amounts of hydrochloric acid. The expression '% w/w' means the weight percentage of the component in respect to the total weight of the composition.

The shelf-life of the formulation put in the device of the invention could be predicted to be greater than two years at the refrigerator temperature (4-10°C) and three months at room temperature.

A person sufficiently skilled in the art can easily apply the teaching of the present invention to the preparation of HFA solution formulations containing other active ingredients bearing functional groups, sensitive to hydrolytic and/or oxidative reactions, such as formamide and cathecol respectively.

WO 97/47286, EP 513127, EP 504112, WO 93/11747, WO 94/21228, WO 94/21229, WO 96/18384, WO 96/19198, WO 96/19968, WO 98/05302, WO 98/34595 and WO 00/07567 disclose HFA formulations in the form of suspensions in which β_2-agonists such formoterol and salbutamol are either

exemplified and/or claimed.

WO 99/65464 refers to HFA formulations containg two or more active ingredients in which at least one is in suspension. The preferred formulations comprises salbutamol sulphate in suspension.

In WO 98/34596, the applicant described solution compositions for use in an aerosol inhaler, comprising an active material, a propellant containing a hydrofluoroalkane (HFA), a cosolvent and further comprising a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler. Said application does not address the technical problem of the chemical stability of the active ingredient but it rather concern the drug delivery to lungs.

In the international application n° PCT/EP99/09002 filed on 23/11/99 the applicant disclosed pressurised MDI's for dispensing solution of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component characterized in that part or all of the internal surfaces of said inhalers consist of stainless steel, anodised aluminium or are lined with an inert organic coating. The examples are referred only to steroids and anticholinergic agents and no acidified solutions are envisioned. As demonstrated in the example 1 of the present application, the use of coated containers, even in the presence of an organic acid, is not sufficient for providing stable solution formulations of a phenylalkylamino derivative such as salbutamol.

EP 673240 proposes the use of acids as stabilisers preventing the chemical degradation of the active ingredient in aerosol solution formulations comprising HFAs. Most examples relate to ipratropium bromide, an anticholinergic drug and only an example is presented for a β_2-agonist, i.e. fenoterol. No exemplary formulations for salbutamol are provided. It is evident from the data reported in the example 1 of the present application, that salbutamol cannot be stabilised at all by addition of organic acids even when stored in coated cans. Furthermore, apart from ipratropium bromide, in EP 673240 no guidance is given with respect to the amount of acid which has to be added in order to stabilise the medicaments without compromising the stability of the whole composition in the can. The only hint can be found on

page 5, lines 15 to 16 which says that an amount of inorganic acid should be added to obtain a pH value from 1 to 7, so a very broad and generic range.

WO 98/34596 refers to solution formulations containing a propellant and a physiologically acceptable polymer which could help the solubilisation and the stability as well of the active ingredients.

WO 00/06121 refers to propellant mixtures for aerosol dinitrogen monoxide and a hydrofluoroalkane in the preparation of suspension and solution aerosols. The use of dinitrogen monoxide may improve the stability at storage of oxidation-sensitive active ingredients. As far as β_2-agonist such levosalbutamol sulphate, formoterol fumarate and salmeterol xinafoate, only examples referred to suspensions are reported.

WO 99/65460 claims pressurised MDI's containing stable formulations of a β-agonist drug in suspension or solution. Examples refer to solutions of formoterol fumarate containing an HFA propellant and ethanol as co-solvent, filled in conventional aluminium or plastic coated glass cans.

Samples stored under accelerated conditions (40°C, 75% relative humidity) for a very short period, one month, exhibited about 10% loss of drug. According to pharmaceutical guidelines on stability, loss of 10% of active ingredient does not meet the criteria of acceptance. Moreover, as it is evident from the data reported in Example 2 of the present application, following the teaching of WO 99/65460 stable formoterol solution formulations cannot be provided. Applicant has indeed demonstrated that the presence of low-volatility components does not substantially affect the chemical stability of the compositions. In some cases, they could even improve it.

According to a further aspect of the invention there is provided a method of filling an aerosol inhaler with a composition of the invention, the method comprising:

(a) Preparation of a solution of one or more active ingredients in one or more co-solvents optionally containing an appropriate amount of a low volatility component.

(b) Filling of the device with said solution.

(c) Adding a pre-determined amount of a strong mineral acid.

(d) Adding a propellant containing a hydrofluoroalkane (HFA).

(e) Crimping with valves and gassing.

Active ingredients which may be used in the aerosol compositions of the invention are short- and long-acting β_2-adrenergic agonists such as salbutamol, formoterol, salmeterol, TA 2005, salt thereof and their combinations with steroids such as beclomethasone dipropionate, fluticasone propionate, budesonide and its 22R-epimer. Other amino type drugs bearing functional groups sensitive to oxidative and/or hydrolytic reactions can be advantageously used.

Preferably the composition will be contained in anodised aluminium cans. Suitable coated device can also be used.

Metering valves fitted with gaskets made of chloroprene-based rubbers can preferably be used to reduce the ingress of moisture which, as previously mentioned, can adversely affect the stability of the drug during storage. Optionally, further protection can be achieved by packaging the product in a sealed aluminium pouch.

The hydrofluorocarbon propellant is preferably selected from the group of HFA 134a, HFA 227 and mixtures thereof.

The co-solvent is usually an alcohol, preferably ethanol.

The low volatility component, when present, has a vapour pressure at 25°C lower than 0.1 kPa, preferably lower than 0.05 kPa. It could be selected from the group of glycols, particularly propylene glycol, polyethylene glycol and glycerol, esters for example ascorbyl palmitate, isopropyl myristate and tocopherol esters.

The compositions of the invention may contain from 0.2 to 10% w/w of said low volatility component, preferably between 0.5 and 2.0% w/w.

Propylene glycol, polyethylene glycol, glycerol and esters are the preferred low-volatility components.

The function of the low volatility component is to modulate the MMAD of the aerosol particles and preferably to further improve the stability of the formulation. With respect to the latter aspect, particularly preferred is the use of isopropyl myristate.

The apparent pH range is advantageously comprised between 2.5 and 5.0, preferably between 3.0 and 4.5, even more preferably between 3.0 and 3.5. Strong mineral acids such as hydrochloric, nitric, phosphoric are preferably used to adjust the apparent pH.

The amount of acid to be added to reach the desired apparent pH will be pre-determined in the model vehicle reported before and it will depend on the type and concentration of the active ingredient. In the case of formoterol, an amount comprised between 3 and 3.5 µl of 1.0 M hydrochloric acid should be preferably added.

The following examples further illustrate the invention.

Example 1

Stability of salbutamol (100 µg/dose)-HFA 134a solution as such and in the presence of different organic acids.

Compositions containing 24 mg of salbutamol (100 µg/dose), 10-20% (w/w) ethanol in HFA 134a put in 12 ml epoxy phenol resin lacquered cans, with or without addition of different organic acids, were stored at 40- 50°C.

The results in term of stability expressed as percentage of remaining drug determined by HPLC, are reported in Table 1.

Table 1

Acid	% SALBUTAMOL t = 42 days	t= 1.5 months at 4°C
None	69%	-
Oleic	69-70%	-
Xinafoic	70%	-
Citric (0.41 w/w)	-	40.0
Citric (0.02 w/w)	-	55.1
30% Acetic acid (0.4% w/w)	-	49.6
30% Acetic acid (0.14% w/w)	-	73.8

The results show that the addition of organic acids does not improve the stability of salbutamol even when coated cans are used.

Example 2

Stability of formoterol (12μg/100μl) -HFA 134a compositions in epoxy-phenol resin lacquered cans.

Solution formulations were prepared by dissolving 1.44 mg of formoterol fumarate in HFA 134a in turn containing 15% w/w ethanol and 1.3% w/w glycerol. pMDIs were stored upright over the range 4-50°C for up to 28 days. Formoterol content was determined by HPLC and the percent residual concentrations calculated relative to the 12μg/shot nominal dose. The percent residual formoterol concentration is reported in Table 2. Derived Arrhenius parameters were used to estimate rate constants at ambient temperature (18-25°) and solutions stored in a domestic refrigerator (4-10°); these rate constants were used to calculate predicted shelf-life for 5% and 10% degradation of formoterol.(Table 3).

The calculated shelf-life data in Table 3 indicates that formoterol is not stable in this HFA 134a-ethanol-glycerol vehicle.

Table 2: Degradation Rate Data for Formoterol-HFA 134a pMDI Solutions (12μg/100μl)
Vehicle: HFA 134a with 1.3% w/w Glycerol, 15.0% w/w Ethanol
Epoxy-phenol lacquered cans stored upright

Time (days)	Percent Residual Conc. Formoterol				
	50°C	43°C	40°C	25°C	4°C
Initial	99.7	99.7	99.7	99.7	99.7
2	92.5	-	-	-	-
4	87.2	89.4	-	-	-
6	80.6	-	-	-	-
7	-	-	89.0	-	-
10	74.9	-	-	-	-
12	72.1	79.4	-	-	-
14	67.0	-	81.7	92.0	-
16	64.4	75.7	-	-	-
18	59.5	-	-	-	-
20	59.5	74.5	-	-	-
24	54.6	68.6	-	-	-
28	47.2	63.3	71.3	86.6	96.7
r	0.995	0.989	0.993	0.997	-
Rate Constant ($day^{-1} \times 10^2$)	2.53	1.49	1.17	0.51	0.11
Arrhenius Plot Parameters: $K = Ae^{E/RT}$					
$A = 2.28 \times 10^6\ day^{-1}$: $E = 49.4\ kJ\ mol^{-1}$; $r = 0.9985$					

Table 3: Predicted Shelf Life Data for Formoterol-HFA 134a pMDI Solutions (12μg/100μl)
Vehicle: HFA 134a with 1.3% w/w Glycerol, 15% w/w Ethanol
Epoxy-phenol lacquered cans stored upright

Temperature	Rate Constant ($day^{-1} \times 10^3$)	Shelf-Life (days)	
		$^t10\%$	$^t5\%$
4°C	1.10	95	47
10°C	1.74	60	29
20°C	3.51	30	15
25°C	4.93	21	10

Example 3

Effect of hydrochloric acid on solution pH' (acidity function)

(a)1.0 M hydrochloric acid was added incrementally to 50ml of HFA 43-10MEE (Vertrel XF) containing 20% w/w ethanol and pH' measured after each aliquot of acid. Figure 1 shows the resultant titration curve normalised to the usual fill volume of a pMDI can (12ml). The pH' profile exhibits a shallow negative slope to about pH'=5.5; thereafter the acidity function drops abruptly.

(b) Experiment (a) was repeated with formoterol formulations containing a lower concentration of ethanol (12% w/w) and with the addition of 1.0% isopropyl myristate. The resultant pH profile, for replicate bulk solutions, shown in Figure 2 is similar in shape with the abrupt fall in pH' per unit increment of acid again commencing at about pH' = 5.5. However, only about half the acid is required to achieve the same reduction in pH'. This is largely due to the reduction in ethanol content; Figure 2 also shows similarity in the profiles obtained with and without isopropyl myristate.

Example 4

Effect of pH' on Stability of Formoterol Solutions in HFA 43-10MEE containing 20% w/w ethanol

Aliquots of 1.0 M hydrochloric acid were added to 12ml of formoterol solution in glass vials. After measurement of pH, valves were crimped on and the vials stored upright at 50°C. Vial samples containing different

concentrations of acid were assayed for residual formoterol after 10 and 20 days storage. The pH' of a third vial was determined after 40 days storage. Results are shown in Table 4. Table 4 shows changes in pH on storage; this is probably largely associated with leaching of alkali from the soft glass of the vials. However, overall consideration of the pH' and formoterol content data implies that the stability of a solution formulation of the drug in HFA can be improved by the addition of mineral acid to provide a formulation with pH' between 2.5-5.0.

Table 4: pH' and Formoterol Content of Formoterol-Vertrel XF/HFA Solutions (12μg/100μl)
Vehicle: Vertrel XF/HFA with 20% Ethanol and Hydrochloric Acid
St Gobain glass vials stored upright

Acidity Function (Ph')		**Percent Residual Conc. Formoterol**		
Initial	**40 days**	**Initial**	**10 days**	**20 days**
1.8	2.8	100	4.8	Nil
2.1	4.4	100	75.1	70.7
2.6	4.2	100	97.2	86.7
3.3	4.2	100	97.1	89.9
5.6	6.6	100	95.8	92.1
7.4	6.7	100	85.4	67.2

Example 5

Stability of acidified formoterol–HFA 134a solutions in anodised cans

Formoterol formulations (12μg/100μl) were prepared by dissolving 1.44 mg of formoterol fumarate in HFA 134a containing 12% *w/w* ethanol with and without 1.0% *w/w* isopropyl myristate. The latter was included as a non-volatile excipient with the potential for increasing MMAD if so desired. It also improves the solubility of formoterol in the vehicle and reduces polarity of the vehicle compared to the addition of glycerol.

pMDI cans containing 3.1-3.4μl 1.0 M hydrochloric acid were set down on storage, upright and inverted, at 4°C to 50°C and samples taken for analysis of formoterol content at appropriate intervals.

Stability data obtained after 70 days of storage are given in Table 5.

A matrix of formulations containing 1.44 mg (12μg/100μl) formoterol fumarate were prepared in HFA 134a containing 12.0% *w/w* ethanol with or without 1.0% *w/w* isopropyl myristate as non-volatile excipient. Aliquots of drug concentrate were transferred to anodised cans and 3.15-3.35μl of 1.0M hydrochloric acid added prior to crimping with 50μl valves and gassing between 22 and 28 replicates at each acid strength were prepared.

To determine residual formoterol, 30 x 50μl shots were discharges into DUSA tubes. The acid range selected was anticipated to give pH' values of 3.0-3.5 and to determine the formulation sensitivity to small changes in acid concentration. Cans were placed on stored upright and inverted (valve up and down respectively) at 25-50°C.

Table 5 shows the results obtained at 40° and 50° after 11-40 day's storage. Each value (expressed as per cent nominal drug concentration) is obtained from a different can.

Initial values were obtained for two cans of each acid strength. Inspection of the data shows all assay values to within the reproducibility of the HPLC assay and independent of acid strength. A similar conclusion was drawn for the storage time point replicates, i.e., independent of acid strength (3.2-3.3μl) or whether cans were stored upright or inverted. Consequently for kinetics calculation the mean value for initial (n=10) and subsequent time points (n=6) was used.

In Table 6 are reported the Arrhenius parameters together with estimated shelf lives at 4, 10 and 25°C. The $t_{5\%}$ is predicted to be greater than 3 months at ambient temperature and approximately 2 years at 4°C.

Table 5: Stability Data for Formoterol Fumarate Solutions (12µg/100µl) in HFA
134a containing 12.0% Ethanol ± 1.0% Isoproyl Myristate
(values are expressed as percent nominal)
Anodised cans fitted with 50µl valves/30 doses collected per can
Different cans assessed at each condition
Cans stored upright (* inverted)

1.0M HCl	STORAGE CONDITION/No isopropyl myristate							
µl per Can	Initial		40°C; 40 days		50°C; 11 days		50°C; 33 days	
	1st Can	2nd Can	1st Can	2nd Can	1st Can	2nd Can	1st Can	2nd Can
3.15	99.8	99.6	-	-	-	-	-	-
3.20	100.8	99.7	96.0	93.2*	96.7	96.5	88.5	89.9*
3.25	97.9	98.8	93.9	94.3*	96.4	96.5	92.2	91.5*
3.30	97.3	98.9	93.7	93.7*	97.0	89.1	90.9	92.8*
3.35	100.0	98.3	-	-	-	-	-	-
Mean	99.1		94.1		95.4		91.0	
C.V.	1.1%		1.0%		3.2%		1.8%	

1.0M Hcl	STORAGE CONDITION/1.0% isopropyl myristate							
µl per Can	Initial		40°C; 33days		50°C; 11 days		50°C; 31 days	
	1st Can	2nd Can	1st Can	2nd Can	1st Can	2nd Can	1st Can	2nd Can
3.15	101.1	99.3	-	-	-	-	-	-
3.20	97.0	100.2	94.4	93.2*	93.8	93.6	90.6	92.7*
3.25	101.4	100.2	98.6	95.0*	96.1	95.9	91.6	89.7*
3.30	99.9	100.8	92.8	95.3*	95.6	95.7	90.0	89.6*
3.35	99.2	97.2	-	-	-	-	-	-
Mean	99.6		94.9		95.1		90.7	
C.V.	1.5%		2.2%		1.2%		1.4%	

Table 6: Shelf Life Prediction for Acidified Formoterol Fumarate Solution (12μg/100μl) in HFA 134a containing 12% w/w Ethanol ± 1.0% w/w isopropyl Myristate (IPM)

Anodised aluminium cans

TIME (days)	FORMOTEROL FUMARATE (percent nominal)			
			40°C	
	Nil IPM	1% IPM	Nil IPM	1% IPM
0	99.1	99.6	99.1	99.6
11	95.4	95.1	-	-
31	-	90.7	-	-
33	91.0	-	-	94.9
40	-	-	94.1	-
Rate Const. ($day^{-1} \times 10^3$)	2.52	2.94	1.29	1.46

Arrhenius Parameters	Frequency Factor (day^{-1})	Activation Energy ($kJ\ mol^{-1}$)
Nil IPM	3.19×10^6	56.3
1% w/w IPM	9.63×10^6	58.9

TEMPERATURE	Nil IPM			1.0% w/w IPM		
	Rate Const. (day^{-1})	$t_{10\%}$ (days)	$t_{5\%}$ (days)	Rate Const. (day^{-1})	$t_{10\%}$ (days)	$t_{5\%}$ (days)
4°C	7.8×10^{-5}	1344	657	7.8×10^{-5}	1360	664
10°C	1.3×10^{-4}	802	392	1.3×10^{-4}	789	386
25°C	4.4×10^{-4}	240	117	4.4×10^{-4}	225	110

CLAIMS

1. An aerosol composition which comprises an amino type drug bearing a functional group sensitive to oxidative and/or hydrolytic reaction in a solution of a liquefied HFA propellant, a co-solvent selected from pharmaceutically acceptable alcohols, wherein the pH of the solution has been adjusted to between 2.5 and 5.0 by addition of small amounts of a mineral acid such as hydrochloric, nitric or phosphoric acid.

2. A composition according to claim 1, wherein the pH of the solution has been adjusted between 3.0 and 3.5.

3. A composition according to claims 1-2, wherein the solution includes a low volatility component with a vapour pressure at 25°C not more than 0.1 kPa, preferably not more than 0.05 kPa.

4. A composition according to any preceding claim, wherein the solution includes at least 0.2% by weight of the low volatility component and not more than 10% by weight.

5. A composition according to claims 1-4, wherein the cosolvent is an alcohol, preferably ethanol.

6. A composition according to any preceding claim, wherein the low volatility component is selected from a glycol or an ester.

7. A composition according to claim 6, wherein the low volatility component is isopropyl myristate.

8. A composition according to any preceding claim, wherein the propellant includes one or more HFAs selected from the group comprising HFA 134a and HFA 227.

9. A composition according to any preceding claim wherein the active ingredient is a β_2-agonist selected from salbutamol, formoterol, salmeterol and TA-2005, salts thereof or their combination with steroid such as beclomethasone dipropionate, fluticasone propionate, budesonide and its 22R-epimer.

10. A pressurised metered dose inhaler for aerosol administration consisting of a container having part or all of its internal metallic surfaces made of stainless steel, anodised aluminium or lined with an

inert organic coating, containing a composition according to claims 1-9.

11. A method of filling the inhaler of claim 10, the method comprising:

(a) preparation of a solution of one or more active ingredients in one or more co-solvents optionally containing an appropriate amount of a low volatility component;

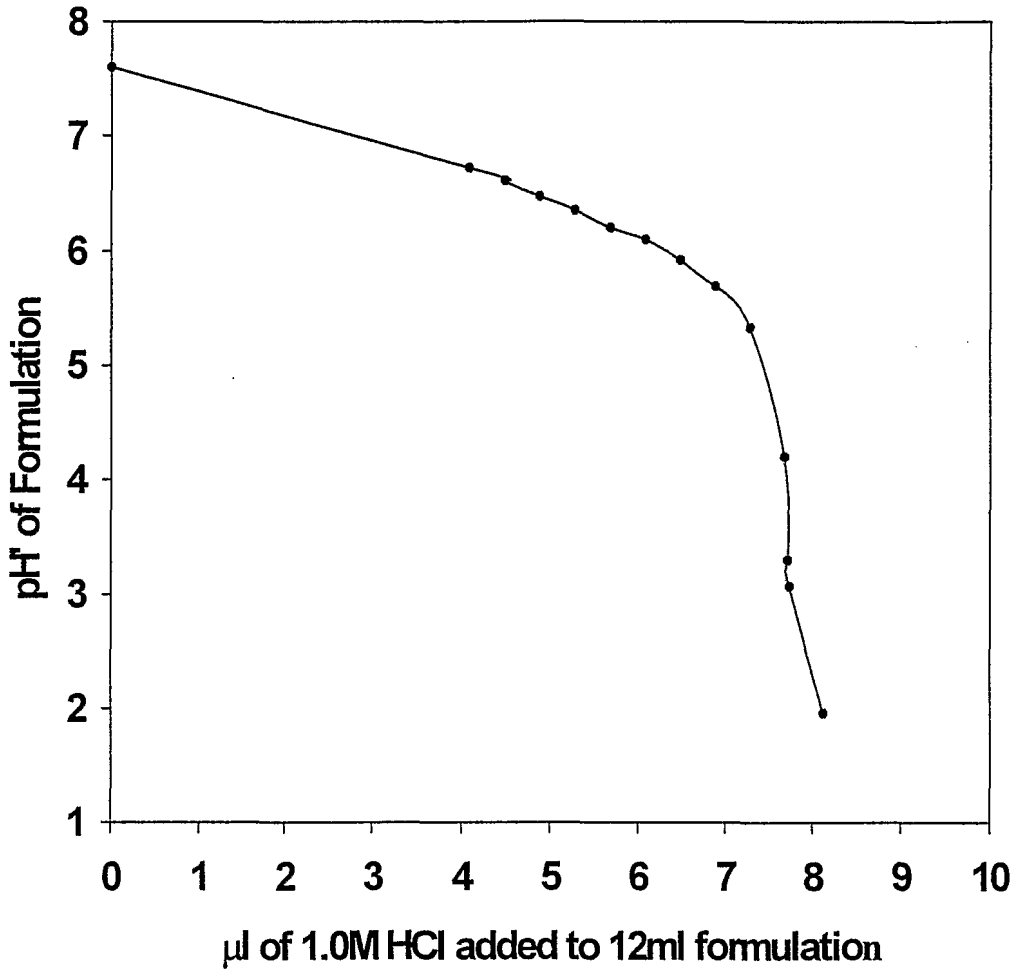
(b) filling the device with said solution ;

(c) adding a pre-determined amount of a strong mineral acid ;

(d) adding a propellant containing a hydrofluoroalkane (HFA);

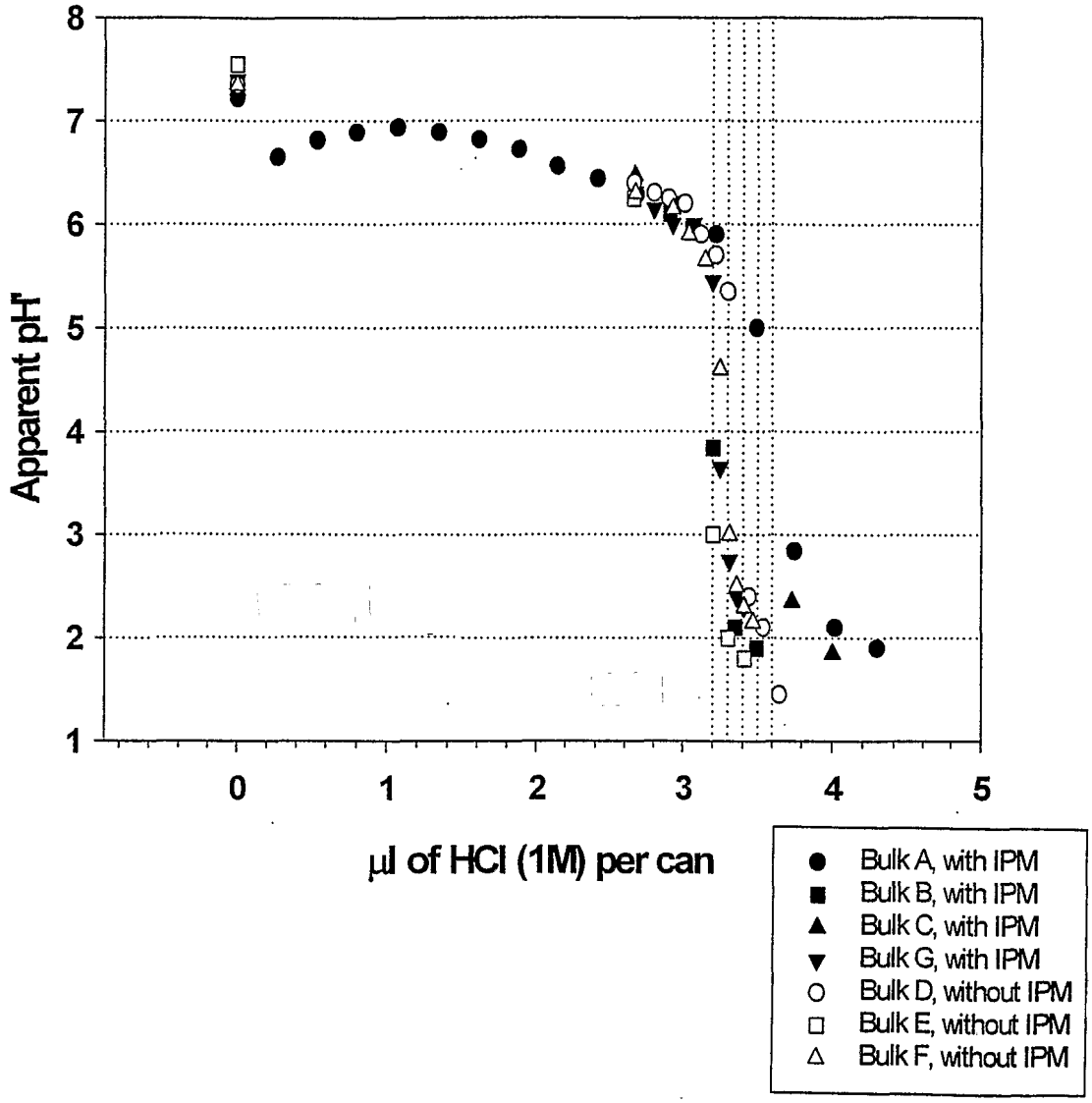
(e) crimping with valves and gassing.

Fig. 1



Effect of hydrochloric acid on Acidity Function (pH') of Formoterol Fumarate Solution (12µg/100µl) in Vertrel XF/HFA containing 20% w/w Ethanol.

Fig. 2



Effect of hydrochloric Acid on Acidity Function (pH') of Formoterol Fumarate Solution (12µg/100µl) in Vertrel XF/HFA containing 12% w/w Ethanol

(IPM = Isopropyl Myristate)

INTERNATIONAL SEARCH REPORT

Int ›nal Application No
PCT/EP 00/04635

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/12 B65D83/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K B65D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 13262 A (JAGER PAUL D ;KONTNY MARK J (US); NAGEL JURGEN H (DE)) 23 June 1994 (1994-06-23) cited in the application page 4, paragraph 4 -page 5, paragraph 1 page 4, last paragraph -page 6, paragraph 2 page 9, last paragraph -page 10, last paragraph page 12, last paragraph -page 15, last paragraph page 13; table 1 page 18; table 4 --- -/--	1,3-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2001	13/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

INTERNATIONAL SEARCH REPORT

Inl onal Application No
PCT/EP 00/04635

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 23065 A (BOEHRINGER INGELHEIM PHARMA ;HOCHRAINER DIETER (DE); ZIERENBERG BE) 27 April 2000 (2000-04-27) page 1, line 3 - last line page 2, paragraph 3 page 5, paragraph 4 -page 6, paragraph 1; claim 1; example 3 ---	1,2,9
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T	WO 00 30608 A (BRAMBILLA GAETANO ;LEWIS DAVID (IT); VENTURA PAOLO (IT); GANDERTON) 2 June 2000 (2000-06-02) cited in the application page 1, paragraph 1 page 2, line 7 - line 18 page 2, last paragraph -page 3, paragraph 1 page 4, last paragraph -page 5, last paragraph page 7, line 12 - line 25 page 8, line 26 - line 28 page 9, line 8 - line 12 page 9, line 27 -page 10, line 5; claims; examples 1,3-7 ---	1-11
A	WO 96 32099 A (GLAXO WELLCOME INC ;ASHURST IAN C (US); HERMAN CRAIG S (US); LI LI) 17 October 1996 (1996-10-17) page 2, line 12 - line 32 page 3, line 16 - line 25 page 5, line 6 - line 28 page 6, line 5 - line 19; claims 1,2,11,14-17; examples -----	10

Continuation of Box I.2

Present claims 1-8 relate to a product which has only been defined by reference to an "amino-type drug". The term "amino-type drug" as used in the present independent claim 1 and in dependent claims 2-8 defines the product by a chemical group. However, a product cannot be sufficiently characterised by a chemical group as is done by an expression like "amino-type drug", because it is impossible to know which compositions are encompassed in this expression.

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product only by reference to the expression "amino type drug". Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products mentioned in claim 9, and those prepared in examples 1, 2, 4 and 5, and the concept of " amino-type drug".

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

– information on patent family members

Int onal Application No
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Information on patent family members

In onal Application No
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Pago PSE No: 629301
CUS: 1300870962

Patente PCT
COMPOSICIÓN FARMACÉUTICA

Detalle del pago

Id.	Rentístico	Concepto y Servicio	Cant.	Val. Unit.	Subtotal
1	50005-01-03	Modificaciones / Correcciones al registro Patente PCT (DESCUENTO INTERNET)	1	$ 176,000	$ 176,000
		TOTAL			$ 176,000

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