

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
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DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 5
ACT: 519 PRESENTACION	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
LUIS FELIPE CASTILLO GIBSON

Asunto: Radicación: 12-67890- -6
 Trámite: 11
 Evento: 378
 Actuación: 519
 Oficio: 11963
 Folios: 5

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/US2010/054040				
Fecha de Presentación Internacional	26/10/2010				

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Radicado No. 12-067890-00000-0000	25/04/2012
Reivindicaciones:	Radicado No. 12-067890-00000-0000	25/04/2012
Oposiciones:	Radicado No. 12-067890-00004-0000	Procaps S.A. 12/12/2012
Prioridad:	US 61/254,923	26/10/2009

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque ésta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del capítulo primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. Para el caso de la presente solicitud se estudiarán las reivindicaciones 1 a 43 (Radicado No. 12-067890-00000-0000).

Título de la solicitud: “FORMULACIÓN OFTÁLMICA Y MÉTODO DE FABRICACIÓN DE LA MISMA”.

El problema planteado en esta solicitud consiste en la necesidad de desarrollar una formulación de un agonista A_1 con estabilidad incrementada sin necesidad de preparar un liofilizado para una subsecuente reconstitución.

Para resolver este problema técnico la solicitud en estudio proporciona una formulación oftálmica que comprende una suspensión acuosa de un agonista A_1 , un surfactante y un preservante y un proceso para preparar la formulación.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/7076; A61P27/02

4. Excepción a la Patentabilidad (Art 20 D 486 literales (a) – (d))

El objeto de las reivindicaciones 31 a 34 no es patentable de acuerdo con el Art citado.

5. De la solicitud de patente

Titulo

El título no corresponde con el objeto de la solicitud porque no divulga el objeto de la materia reclamada en la presente solicitud, por lo cual se sugiere al solicitante hacer la corrección necesaria.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 carece de concisión debido a que abarca un indefinido número de formulaciones posibles, debido al uso de términos funcionales que no limitan el objeto de la solicitud, tales como: un agonista A_1 , tensioactivo, y un conservante. Adicionalmente, la solicitud carece de información que permita establecer que todas las composiciones obtenidas son estables, y por otra parte, no existe fundamento para afirmar que todos los agentes agonistas A_1 poseen problemas de estabilidad.

Las expresiones “a niveles que no son irritantes o molestos al ojo” y “aproximadamente” son ambiguas y no limitan el alcance de la solicitud.

6. Unidad de invención (Art 25 D 486)

La solicitud no cumple con el requisito de unidad de invención porque se refiere a 2 grupos inventivos.

Los grupos inventivos están definidos por las siguientes características esenciales:

1. Composiciones oftálmicas de un agonista A1, un surfactante y un conservante.
2. Proceso para preparar una formulación oftálmica.

Se sugiere presentar las solicitudes divisionales que considere necesarias, o limitar la solicitud inicial a una sola invención, eliminando de ella las otras invenciones.

7. Análisis de la Oposición

Argumentaciones de Procaps S.A

La opositora presenta el documento EP1110554 publicado el 27 de junio de 2001 el cual se refiere a composiciones farmacéuticas para el tratamiento de enfermedades de los ojos, que contienen como ingrediente activo los derivados de 2-aluiniladenosina que tienen un unión de acetileno en la posición 2-de la base adenina los cuales son agonistas de los receptores A1. La formulación de estos compuestos en gotas para los ojos se da a conocer en el mismo documento EP1110554, incluyendo agentes isotónicos tales como cloruro de sodio y glicerina, estabilizadores tales como edetato sódico, conservantes tales como cloruro de benzalconio y parabenos, adyuvantes de solución, tales como Polisorbato 80 (agente tensioactivo) reguladores del pH tales como fosfato de hidrógeno disódico, dihidrógeno fosfato de sodio, ácido bórico, tetraborato de sodio, ácido clorhídrico e hidróxido de sodio. El ejemplo 1 del documento muestra una composición de gotas para los ojos que contiene 2 - (1-octinil) adenosina, polisorbato 80 (tensioactivo), cloruro de benzalconio (conservante) con cloruro sódico (agente isotónico) y dihidrógeno fosfato de sodio y fosfato disódico de hidrógeno (reguladores de pH) en agua esterilizada. Concluye la opositora que la presente solicitud carece de novedad con respecto a la información divulgada en D1.

Respuestas del Solicitante

El solicitante no radicó respuesta a la oposición

Respuesta del Examinador Técnico

El documento presentado en la oposición desvirtúa la novedad del objeto de esta solicitud; por lo cual se considerará dentro del examen de patentabilidad.

8. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: 26 de octubre de 2009, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha Publicación
D1	EP 1110554	"MEDICINAL COMPOSITIONS FOR TREATING EYE DISEASES"	27/06/2001
D2	Pharmaceutical Manufacturing Handbook. Editorial Wiley-Interscience. New Jersey, 2008	"CRITICAL ASPECTS OF LIQUIDS MANUFACTURING PROCESS"	2008

D1^[1] divulga composiciones para el tratamiento de enfermedades oftálmicas que comprenden un agonista A1, un surfactante y un preservante (Pág. 7, Párr. 34 y Ejemplo 1).

D2^[2] divulga las características fundamentales para el desarrollo de formas farmacéuticas en suspensión entre las que se encuentra un tamaño de partícula entre 1 a 50 micrómetros (Pág. 329).

9. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en una formulación oftálmica que comprende una suspensión acuosa de una partícula fina de un agonista A1, un agente tensioactivo y un conservante.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1
Una formulación oftálmica que comprende una suspensión acuosa de una partícula fina de un agonista A1	Gotas para los ojos que contienen derivados de 2-alquililadenosia (Párrafos [0035] y [0036], Ejemplo 1)
un agente tensioactivo y	Adyuvante de solubilidad como polisorbato 80 (Párr. [0036])
Un conservante	Un conservante como cloruro de benzalconio. (Párr. [0036])

Las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en el documento D1, el cual enseña gotas para los ojos que contienen derivados de 2-alquilil adenosina que tienen actividad agonista sobre A1 a pesar de tener mayor selectividad sobre A2 junto con otros excipientes tales como un adyuvante de solubilidad como polisorbato 80 y un conservante como el cloruro de benzalconio (Párrafos [0035] y [0036] y Ejemplo 1).

En consecuencia, la reivindicación 1 y sus dependientes no son nuevas, según lo divulgado en el documento D1.

Nivel inventivo (Art18 D486)

Las reivindicaciones 1 y 2 consisten en una formulación oftálmica que comprende una suspensión acuosa de una partícula fina de un agonista A1, un agente tensioactivo y un conservante

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1	D2
Una formulación oftálmica que comprende una suspensión acuosa de una partícula fina de un agonista A1	Gotas para los ojos que contienen derivados de 2-alquililadenosia (Párrafos [0035] y [0036], Ejemplo 1)	Formas farmacéuticas en suspensión

1[URL:http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=EP&NR=1110554A1&KC=A1&FT=D&ND=&date=20010627&DB=&locale=en_EP

2[URL:http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=6387889B1&KC=B1&FT=D&ND=3&date=20020514&DB=EPODOC&locale=en_EP

un agente tensioactivo y	Adyuvante de solubilidad como polisorbato 80 (Párr. [0036])	Los surfactantes mejoran la estabilidad física de la suspensión (Pág. 329)
Un conservante	Un conservante como cloruro de benzalconio. (Párr. [0036])	Un conservante adecuado para formas líquidas oftálmicas como el cloruro de benzalconio (Pág. 336)
Comprende partículas finas menores a 50 micrómetros	No los divulga	Las partículas en las suspensiones están entre 1 a 50 micrómetros (Pág. 329)

El documento D1 se considera el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulgan una composición que comprende derivados de 2-alquiniil adenosina que tienen actividad agonista sobre A1 a pesar de tener mayor selectividad sobre A2 junto con otros excipientes tales como un adyuvante de solubilidad como polisorbato 80 y un conservante como el cloruro de benzalconio (Párrafos [0035] y [0036] y Ejemplo 1)

La diferencia entre la invención, definida en la reivindicación 1 y el producto de D1 consiste en que la presente solicitud divulga que las partículas del agonista A1 tienen un tamaño de partícula menor a 50 micrómetros.

El efecto que logra el incluir estos compuestos es que permiten obtener composiciones oftálmicas en suspensión para administración tópica estables.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: cómo modificar la composición conocida en D1 para lograr composiciones para uso tópico oftálmico con adecuada estabilidad.

Sin embargo, el documento D2 enseña que en las formulaciones farmacéuticas en suspensión las partículas son usualmente muy finas con tamaños entre 1 a 50 micrómetros (Pág. 329). Igualmente, la anterioridad indica que existen métodos para proveer estabilidad física a una suspensión, entre los que se encuentran el uso de surfactantes como el más exitoso.

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría un tamaño de partícula inferior a 50 micrómetros como lo indica el documento D2 en la composición divulgada en el documento D1 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

La reivindicación 35 reclama un proceso para preparar una formulación oftálmica.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D2
Un proceso para preparar una formulación oftálmica que comprende:	Aspectos críticos para la manufactura de líquidos (Págs. 320 a 338)
a. Moler la forma del agonista A1 a tamaños de partícula menores de 50 micrómetros	El tamaño de partícula en la materia prima para preparar la formulación debe menor a 10 micrómetros. (Pág 737)
b. Esterilizar el agonista A1 molido	Esterilización por radiación gamma. (Pág. 119)

c. Suspender asépticamente las partículas del agonista A1 en una suspensión acuosa que comprende un agente tensioactivo y un conservante	En relación con mejorar la vida útil de la suspensión se pueden agregar conservantes adecuados como el cloruro de benzalconio (pág. 336) y surfactantes que mejoran la estabilidad física de la suspensión (Pág. 329)
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El documento D2 se considera el estado de la técnica cercano porque divulga las actividades fundamentales y consideraciones a tener en cuenta en la manufactura de suspensiones tópicas oftálmicas indicando que el tamaño de partícula debe ser inferior a 10 micrómetros (Pág. 737), la pertinencia de la adición de conservantes y surfactantes para mejorar la estabilidad (Págs. 336 y 329) y consideraciones de seguridad general tales como esterilidad, toxicidad ocular e irritación y cantidad de conservante utilizado.

El proceso reivindicado difiere del D2 en que no se divulga de manera secuencial el conjunto de etapas para lograr la composición en suspensión.

El efecto logrado por el proceso reivindicado consiste en el desarrollo de una formulación que comprende un agonista A1 más estable.

Por lo tanto, el problema técnico objetivo a resolver consiste en cómo aplicar los conceptos de elaboración de formulaciones líquidas para lograr una suspensión estable de un agonista A1.

De manera que el estado de la técnica proporciona información suficiente a la persona del oficio normalmente versada en la materia para desarrollar el proceso de la presente solicitud.

Conclusión:
La reivindicación 35 cumple el requisito de novedad (Art. 16), y no con el requisito de nivel inventivo (Art. 18).

10. Conclusión

Los requisitos de patentabilidad de la presente solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	EP 1110554	1 a 30 1-30	Novedad Nivel Inventivo
D2	Pharmaceutical Manufacturing Handbook. Editorial Wiley-Interscience. New Jersey, 2008	1-30 y 35 a 43	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



MARIA DEL SOCORRO PIMIENTA CORBACHO
Directora de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2013-07-16

Elaboró: Emilse Cano Urrego

Revisó: Lyna Del Carmen Mordecay Dunoyer

PHARMACEUTICAL MANUFACTURING HANDBOOK

Production and Processes

SHAYNE COX GAD, PH.D., D.A.B.T.

Gad Consulting Services
Cary, North Carolina

 **WILEY-INTERSCIENCE**
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some that, since the in-feed side of the tunnel is typically in ISO 7 or 8 space, a greater differential is required; however, this is not true since the cooling zone is ISO 5, and the heating zone is certain to be sterile and is also ISO 5 in terms of particulate air quality. Their in-feed is often direct from a glass washer, which may be remote from the main preparations area utilized for washing, wrapping, and sterilizer loading.

2.1.6.3 Gas and Vapor Sterilization

The sterilization of materials using noncondensing gases (ethylene oxide, chlorine dioxide, or ozone) or condensing vapors such as hydrogen peroxide is a supplementary process intended for items that cannot be exposed to heat. The utilization of gas/vapor designs is coming into increased use as a supportive technology for isolation technology for presterilized items such as syringes and stoppers that must be introduced into the isolators aseptic zone. Air locks using these agents can be utilized in similar fashion for the supply of materials to manned clean rooms. Control over agent concentration or injection mass, relative humidity, and temperature may be required for these systems. There are different types of vapor processes available, and users should generally follow the cycle development strategy suggested by the manufacturer of the equipment they have chosen. Specific temperature and humidity ranges may be required for some vapor processes to assure appropriate efficacy [25, 26].

2.1.6.4 Radiation Sterilization

The use of radiation within a parenteral facility would have been considered unthinkable prior to the start of the twenty-first century. While γ irradiation is typically a contracted service provided off-site, electron beam sterilization advances can make the installation of an in-house (and generally an in-line) system a real possibility. An in-line system would be utilized similarly to the gas/vapor systems described above for treatment of external surfaces for entry into either a clean room or isolator-based aseptic processing facility. The use of this same technology for terminal sterilization is also possible [1]. Association for the Advancement of Medical Instrumentation (AAMI)/ISO 11137 provides widely accepted guidance on the development and validation of radiation sterilization processes.

2.1.6.5 Sterilization by Filtration

Filters are utilized to sterilize liquids and gases by passage through membranes that retain microorganisms by a combination of sieve retention, impaction, and attractive mechanisms [27]. In contrast with the other forms of sterilization that are destructive of the microorganisms, filters rely on separation of the undesirable items (microorganisms as well as nonviable particles) from the fluid. Because filtration requires passage of the fluid from the “dirty” (upstream) side of filter to the clean (downstream) side of the filter, the downstream piping and equipment must be both “clean” and sterile prior to the start of the filtration process. This will ordinarily require the use of SIP procedures or sterilization followed by aseptic assembly.

Sterilizing filtration of parenterals is a complex and often inadequately considered subject, and numerous controls are required on the filter, fluid, and sterilizing/

tions with closure systems, physical consequences of moisture loss, and microbial contamination control [6].

4.3.4 CRITICAL ASPECTS OF LIQUIDS MANUFACTURING PROCESS

4.3.4.1 Physical Plant

Heating, Ventilation, and Air Conditioning System The manufacturer has to warrant adequate heating, ventilation, and air conditioning in places where labile drugs are processed [6].

The effect of long processing times at suboptimal temperatures should be considered at the production scale in terms of the consequences on the physical or chemical stability of individual ingredients and product. A pilot plant or production scale differs from laboratory scale in that their volume-to-surface-area ratio is relatively large. Thus, for prolonged suboptimal temperatures, jacketed vessels or immersion heaters or cooling units with rapid circulation times are absolutely necessary [2].

For heat-labile drugs, uncontrolled temperature increments can activate auto-oxidation chains when the drug product ingredients react with oxygen and generate free radicals but without drastic external interference. Vitamins, essential oils, and almost all fats and oils can be oxidized. A good example of a heat-labile drug solution is clindamycin, which has to be stored at room temperature and away from excess heat and moisture [19]. Auto-oxidation chains are finished when free radicals react with each other or with antioxidant molecules (quenching). The tocopherols, some esters of gallic acid, as well as BHA and BHT (butylated hydroxyanisole and butylated hydroxytoluene) are common antioxidants used in the pharmaceutical industry [1].

Isolation of Processes To minimize cross-contamination and microbiological contamination, the manufacturer may develop special procedures for the isolation of processes. The level of facilities isolation depends on the types of products to be manufactured. For instance, steroids and sulfas require more isolation than over-the-counter (OTC) oral products [6]. To minimize exposure of personnel to drug aerosols and loss of product, a sealed pressure vessel must be used to compound aerosol suspensions and emulsions [21]. An example of cross-contamination with steroids was the controversial case of a topical drug manufactured for the treatment of skin diseases. High-performance liquid chromatography/ultraviolet and mass spectrometry (HPLC/UV, HPLC/MS) techniques were used by the FDA for the detection of clobetasol propionate, a class 1 superpotent steroid, as an undeclared steroid in zinc pyrithione formulations. The product was forbidden and a warning was widely published [22].

Dust Removal System The efficiency of the dust removal system depends on the amount and characteristics of dust generated during the addition of drug substance and powdered excipients to manufacturing vessels [6]. Pharmaceutical industries usually generate some type of dust or fume during processing. Important factors for selecting dust collectors are maintenance, surrogate test, economics, and containment. In addition, reentrainment of the fine particles, vertical or horizontal position, efficiency, pressure resistant, service life time, as well as sealing capacity to work

through the bag are significant factors concerning filter selection of dust removal systems. Some examples of dust collection applications in the manufacture of liquid dosage forms are handling and pulverization of raw materials, spray dryers, and general room ventilation [23].

Air Filtration System The efficiency of the air filtration system has to be demonstrated by surface or air-sampling data where the air is recirculated [6]. To monitor the levels of contamination in the air, there are commercial automatic samplers for microbiological contamination or gas presence. Air trace environmental samplers for pharmaceutical industries are based on the slit-to-agar impaction technique for the presence of viable microorganisms. Automatic samplers for compressed gas analyze the presence of a specified gas in 1 m³ by absorbing air at a fixed flow rate for a sampling period of 1 h or a different adjusted time. These solutions to the sampling needs of the pharmaceutical industry are robust, require low maintenance, and are easy to use. This allows for validation of sampling data at the moment of application filling to support the process control. Sampling time and selection of microbiological growth media or analysis technique are important components to consider when developing a sampling plan [24].

4.3.4.2 Equipment

Sanitary Design Pumps, valves, flowmeters, and other equipment should be easily sanitized. Some examples of identified sources of contamination are ball valves, packing in pumps, and pockets in flowmeters [6].

The sanitary design and performance of equipment make it accessible for inspection, cleaning, and maintenance. It has to be cleanable at a microbiological level and its performance during normal operations should contribute to sanitary conditions. The materials used in the design have to assure hygienic compatibility with other equipment, the product, the environment, other systems such as electrical, hydraulics, steam, air, and water, as well as the method and products used for cleaning and sanitation. The equipment should be self-draining to assure product or liquid collection. Small niches, for example, pits, cracks, corrosion, recesses, open seams, gaps, lap seams, protruding ledges, inside threads, bolt rivets, and dead ends, as well as inaccessible cavities of equipment such as entrap and curlers must be eliminated whenever possible; otherwise they have to be permanently sealed. Enclosures, for example, push buttons, valve handles, switches, and touch screens, should be prepared for a hygienic design of maintenance. Standards have been developed by the American Meat Institute [25].

Standard Operating Procedures for Cleaning Production Equipments Current GMPs are defined as the basic principles, procedures, and resources required to guarantee an environment appropriate for manufacturing products of adequate quality [26]. To minimize cross-contamination and microbiological contamination, it is GMP for a manufacturer to create and pursue written standard operating procedures (SOPs) to clean and sanitize production equipment in a way that avoids contamination of in-progress and upcoming batches. When the drug is known as a potent generator of allergic reactions, such as steroids, antibiotics, or sulfas, cross-contamination becomes an issue of safety [20]. In addition, validation and data analysis procedures,

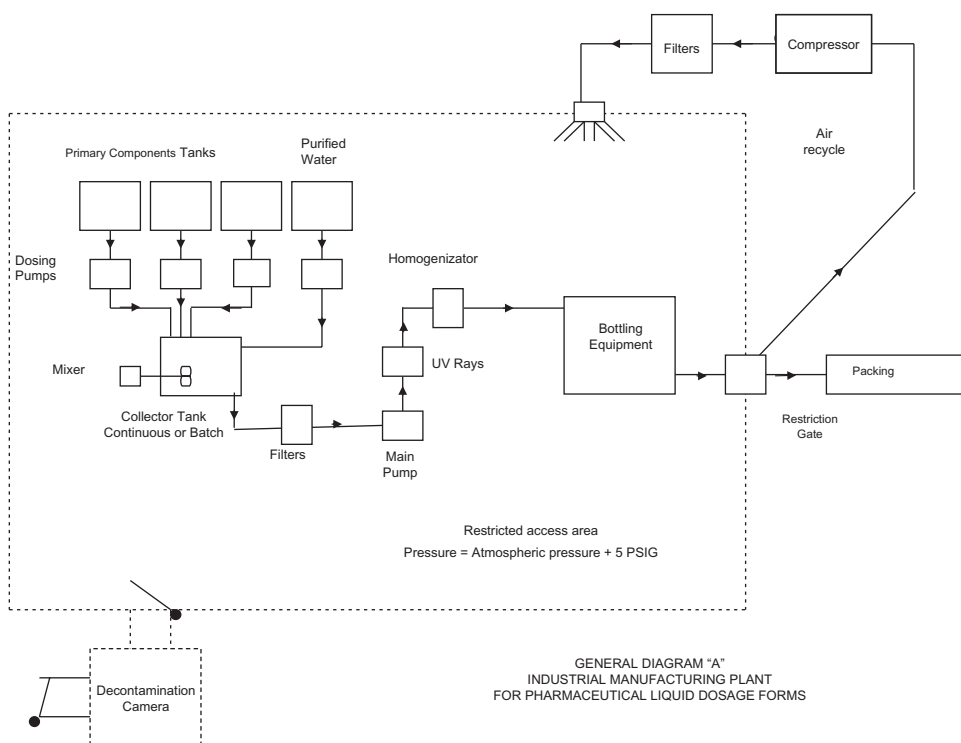


FIGURE 1 Mixing and filling lines for pharmaceutical dosage forms. Positive indoor pressure of 5 psi over outdoor pressure assures constant airflow from inside to outside in order to reduce entrance of contaminating agents.

including drawings of the manufacturing and filling lines [6], are especially important for clean-in-place (CIP) systems, as indicated in Figures 1 and 2.

Many companies have problems with standardizing operating procedures for cleaning steps and materials used [6]. Appropriate SOPs are necessary to determine the scope of the problem in investigations about possible cross-contaminations or mix-ups. The best approach to validate a SOP is to test it, use it as a training tool, and observe the results obtained by different persons. This includes the worst-case situation in order to enhance the step-by-step writing methodology as well as standardizing the materials used. A typical SOP contains a header to present the SOP title, date of issue, date of last review, total number of pages, responsible person, and approval signature. Typically, a SOP includes position of responsible person, SOP purpose and scope, definitions, equipment and materials, safety concerns, step-by-step procedure, explanation of critical steps, tables to keep data, copies of forms to fill, and references [26]. The forms to keep the records must show the date, time, product, and lot number of each batch processed. However, the most important points of the SOP are equipment identity, cleaning method(s) with documentation of critical cleaning steps, materials approved for cleaning that have to be easily removable, names and position of persons responsible for cleaning and inspection, inspection methods, and maintenance and cleaning history of the equipment [20].

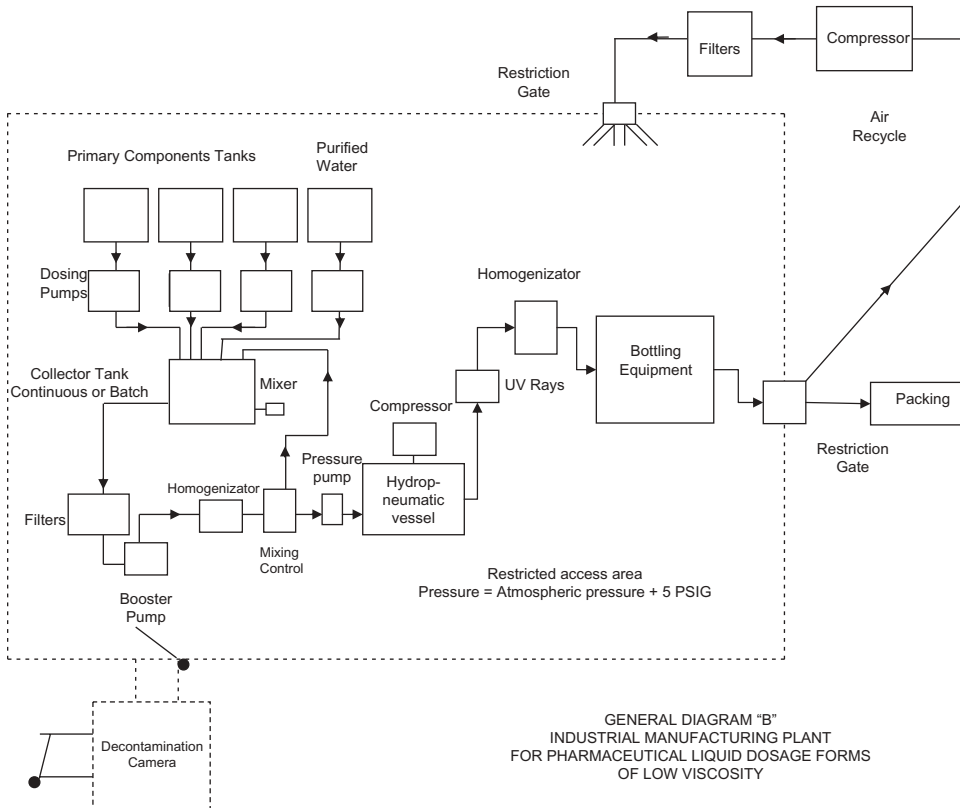


FIGURE 2 Mixing and filling lines for pharmaceutical dosage forms. Using this hydro-pneumatic system, instead of the mechanical system in Figure 1, the liquid moves by the pressure generated in a compressed air tank.

Cleaning and Sanitizing Transfer Lines Pipes should be hard, easily cleaned, and sanitized. To avoid moisture collection and microbiological contamination, hoses should be stored in a way that allows them to drain rather than be looped. For example, transfer lines are an important source of contamination when flexible hoses are handled by operators, lying on the floor, and after they are placed in transfer or batching tanks [6].

Heat is considered one of the most efficient physical treatments for sanitizing pharmaceutical equipment and could be used for sanitizing hoses that have already been cleaned. The recirculation of hot water at a temperature of 95°C for at least 100 min allows bacteria elimination [14].

Due to the important amount of insoluble residues left on piping and transfer lines after emulsion manufacturing, such as topical creams and ointments, equipment cleaning becomes difficult to address. To avoid cross-contamination, some manufacturers have decided to dedicate lines and hoses to specific products.

However, these decisions have to appear in the written production protocols and SOPs [20].

Sampling Cleaned Surfaces for Presence of Residues The cleaning method is validated by sampling the cleaned surfaces of the equipment for the existence of residues. The equipment characteristics and residue solubility are factors to support the selection of the sampling method to be used [6]. There are two acceptable general types of sampling methods: direct surface sampling by swabbing of surfaces and rinse sampling with a routine production in-process control. Although surface residues will not be identical on each part of the surface, statistically the most advantageous is direct surface sampling because it allows evaluation of the hardest areas to clean as well as insoluble or “dried-out” residues by physical removal. The type of sampling material and solvent used for extraction from the sampling material should be validated in order to determine their impact on the test data. The second method, rinse sampling, is used for larger surfaces or inaccessible systems. Contaminants that are physically occluded and insoluble residues are disadvantages of the rinse sampling method. To validate this cleaning process, direct measurement of the contaminant in the rinse water has to be tested instead of a simple test for water quality. Routine production in-process control is used as indirect testing for large equipment that has to be cleaned by the rinse sampling method. The uncleaned equipment has to give an unacceptable result for the indirect test [27].

Establishing Appropriate Limits on Levels of Postequipment Cleaning Residues Very low levels of residue are possible to be determined since technological advances offer more sensitive analytical methods. The manufacturer should know the toxicological information of the materials used and potential amounts of residues after exposure to the equipment surface. Accordingly, the manufacturer has to establish proper limits of residues after equipment cleaning and scientifically justify these limits. The established limits must be clinically and pharmaceutically safe, realistic, viable, and verifiable [20]. The sensitivity of the analytical method will determine the logic of the established limits since absence of residues could indicate a low sensitivity of the analytical method or a poor sampling procedure. Sometimes thin-layer chromatography (TLC) screening must be used in addition to chemical analyses. Some practical levels established by manufacturers include 10ppm of chemicals, 1/1000 of the biological activity levels met on a normal therapeutic dose, and no visible residues of particles determined organoleptically [27].

Connections Connectors and manifolds should not be for common use. For example, sharing connectors in a water supply, premix, or raw material supply tanks may be a source of cross-contamination [6].

Time between Completion of Manufacturing and Initiation of Cleaning The time that may elapse from completion of a manufacturing operation to initiation of equipment cleaning should also be stated where excessive delay may affect the adequacy of the established cleaning procedure. For example, residual product may dry and become more difficult to clean [20].

SOPs are an example of deficiency in many manufacturers regarding time limitations between batch cleaning and sanitization [6]. Lack of communication between

departments responsible for the production at different levels is the main cause of time control problems. Typically each department, from human resources to finances, manufacturing, and warehouse, has its own computer system optimized for the particular ways that the department does its work. Therefore, time control becomes a primordial issue when labile materials are transferred from one department to another [28].

To facilitate communication between different departments, some useful softwares have been developed. For example, ERP is an integrated approach which may have positive payback if the manufacturer installs it correctly. An ERP is a type of software that can improve communication between planning and resources. The software attempts to integrate all departments and functions in a company onto a single computer system that can serve each particular need, such as finance, human resources, manufacturing management, process manufacturing management, inventory management, purchasing management, quality management, and sales management. Each department has its own software, except now the software is linked together, so that, for example, someone in manufacturing can look into the maintenance software to see if specific batch cleaning and sanitization have been scheduled or realized and someone in finance can review the warehouse software to see if a specific order has been shipped. The information is online and not in someone's heads or on papers that can be misplaced. People in different departments may see the same information, update it if they are allowed to do, and make right decisions faster. However, the software is less important than the changes companies make in the ways they work. Reorganization and training are the keys of ERP's success to fix integration problems. There are three different ways to install an ERP: big bang, franchising strategy, and slam dunk. Big bang is the most ambitious way whereby companies install a single ERP across the entire company. By the franchising strategy, departments do not share many common processes across, whereas slam dunk is focused on just a few key processes [28].

Weight in Formulations Flow properties of liquids rarely vary due to their constant density at a constant temperature. Oral solutions and suspensions are formulated on a weight basis (gravimetry) in order to be able to measure the final volume by weight before filling and packing. Volumetric measurements of liquid amounts to be used for manufacturing liquid dosage forms have shown greater variability than weighted liquids. For instance, the inaccurate measurement of the final volume by using dip sticks or a line on a tank may cause further analytical errors and potency changes [6].

The importance of selecting gravimetry instead of volumetry to measure liquid amounts in the pharmaceutical industry of liquid dosage forms is well illustrated by the volume contraction of water–ethanol and volume expansion of ethyl acetate–carbon disulfide liquid mixtures as well as a CS₂–ethyl acetate system. The National Formulary (NF) diluted alcohol is a typical example of the volume nonadditivity of liquid mixtures [29]. This solution is prepared by mixing equal volumes of alcohol [U.S. Pharmacopeia (USP)] USP and purified water (USP). The final volume of this solution is about 3% less than the sum of the individual volumes because of the contraction due to the mixing phenomenon [1]. In addition, molecular interactions of surfactants in mixed monolayers at the air–aqueous solution interface and in mixed micelles in aqueous media also cause some contraction of volume upon mixing [30].

Location of Bottom Discharge Valve in Batching Tank The bottom discharge valve should be located exactly at the bottom of the tank. In some cases valves have been found to be several inches to a foot above the bottom of the tank [6].

For a tank suspected of having substantial deposits at the bottom, a fiber-optic camera can be inserted in the tank to provide a view and positive confirmation of the tank bottom condition. These camera and light vision systems are sanitary equipment able to provide a computational real-time visual inspection of the inside tank under process conditions or pressure vessel. In addition, they are used to control several parameters during the manufacturing process, such as product level and thickness, solids level, uniformity of suspensions, foam, and interface and/or cake detection [31].

Batching Equipment to Mix Solution Ingredients of solutions have to be completely dissolved. For instance, it has been observed that some low-solubility drugs or preservatives can be kept in the “dead leg” below the tank, and the initial samples have reduced potency [6]. When there is inadequate solubility of the drug in the chosen vehicle, the dose is unable to contain the correct amount of drug in a manageable size unit, that is, one teaspoonful or one tablespoonful. Thus, ingredients as well as handling and storage conditions should be chosen to manage the problem [14].

In solutions, the most important physical factors that influence the solubility of ingredients are type of fluid, mixing equipment, and mixing operations. Generalized Newtonian fluids are ideal fluids for which the ratio of the shear rate to the shear stress is constant at a particular time. Unfortunately, in practice, usually liquid dosage forms and their ingredients are non-Newtonian fluids in which the ratio of the shear rate to the shear stress varies. As a result, non-Newtonian fluids may not have a well-defined viscosity [32].

When all the ingredients are miscible liquids, the combination and distribution of these components to obtain a homogeneous mixture are called blending. Whenever possible, ingredients should be added together and the impeller mixer often is located near the bottom of the vessel [21]. Mixing of high-viscosity materials requires higher velocity gradients in the mixing zone than regular blending operations. In fact, the fundamental laws of physics regarding the performance of Newtonian fluids in the production process may be studied using computational tools. For example, VisiMix is a software that is routinely used to calculate shear rates [2].

Finally, if it is determined that there is a bigger problem of insolubility coming from the formulation, then addition of cosolvents, surfactants, as well as the preparation of the ionized form of an acid or base, drug derivatization, and solid-state manipulation are approaches to manipulating the solubility of the drug [14].

Batching Equipment to Mix Suspension In the case of suspensions, the flow necessary to overcome settling in a satisfactory suspension depends on the mixing equipment and is predicted by Stokes's law. Thus, to use the Stokes's law, suspensions are considered as Newtonian fluids if the percentage of solids is below 50%. Mixing equipment uses a mechanical device that moves through the liquid at a given velocity. Dispersing and emulsifying equipment is categorized as “high-shear” mixing equipment. The maximum shear rate with such equipment occurs very close to the

mixing impeller. Therefore, the diameter of the impeller and the impeller speed directly influence the power applied by the mixer to the liquid [21].

Batching Equipment to Mix Emulsion The most common problems of mixing emulsions are removing “dead spots” of the mixture and scrapping internal walls of the mixer. Dead spots are quantities of ingredients that are not mixed and become immobile. Where dead spots are present, that quantity of the formula has to be recirculated or removed and not used. If the inside walls of the mixer keep residual material, operators should use hard spatulas to scrape the walls; otherwise the residual material will become part of the next batch. In both cases, the result may be nonuniformity. Stainless steel mixers have to include blades made of hard plastic, such as Teflon, to facilitate the scrapping of the mixer walls without damaging the mixer. Scraper blades should be flexible enough to remove internal material but not too rigid to avoid damaging the mixer [20]. The mixing will be successful if the macroscale mixing offers sufficient flow of components in all areas in the mixing tank and the microscopic examination shows a correct particle size distribution [33].

4.3.4.3 Particle Size of Raw Materials

Raw materials in Solution The types of raw materials used to be part of solutions are presented in Table 1. They have different purposes and can be cosolvents, electrolytes, buffers, antioxidants, preservatives, coloring, flavoring and sweetener agents, among others.

Particle Size of Raw Materials in Solution Particle size is affected by the breaking process of the particle, crystal form, and/or salt form of the drug. The particle size can affect the rate of dissolution of raw materials in the manufacturing process. Raw materials of a finer particle size may dissolve faster because they have a larger surface area in contact with the solvent than those of a larger particle size when the product is compounded [6]. Mixing faster causes the particle to break down and dissolve more quickly. In addition, hydrated particles are less soluble than their anhydrous partners [37].

TABLE 1 Solutions: pharmaceutical excipients

Purpose	Agent
Protecting the active product ingredients	- Buffers - Antioxidants - Preservatives
Maintaining the appearance	- Colorings - Stabilizers - Cosolvents - Antimicrobial preservatives - Electrolytes
Taste/Small Masking	- Sweeteners - Flavorings

Source: From ref. 4, 34, 35, 36

Solid drugs may occur as pure crystalline substances of definite identifiable shape or as amorphous particles without definite structure. In addition, when a drug particle is broken up, the total surface area is increased as well as its rate of dissolution. The amorphous form of a chemical is usually more soluble than the crystalline form while the crystalline form usually is more stable than the amorphous form [37]. Processing conditions used for providers to obtain raw materials can dramatically impact their quality and stability; for instance, the presence of different polymorphs may depend on the thermal history of freezing, concentration of solvents, and drying conditions [38]. The polymorphism of a crystalline form is the capacity of a chemical to form different types of crystals, depending on the conditions of temperature, solvents, and time followed for its crystallization. Among different polymorphs, only one crystalline form is stable at a given temperature and pressure. Over time, the other crystalline forms, called metastable forms, will be transformed into stable forms. Transformations longer than the shelf-life of metastable forms into stable forms of a drug are very common in final products and compromise its stability and efficacy to different extents depending on quality control [37].

While the metastable forms offer higher dissolution rates, many manufacturers use a particular amorphous, crystalline, salt, or ester form of a drug with the solubility needed to be dissolved in the established conditions, for instance, to prepare a chloramphenicol ophthalmic solution [39]. Thus, the selection of amorphous or crystalline form of a drug may be of considerable importance to facilitate the formulation, handling, and stability [37].

However, the dissolution rate of an equal sample of a slowly soluble raw material usually will increase with increasing temperature or rate of agitation as well as with reduce viscosity, changes of pH or nature of the solvent. In addition, other alternative mechanisms to enhance the solubility of insoluble drugs are: 1) hydrophilization: the reduction in contact angle or angle between the liquid and solid surface [40], which can be accessed by intensive mixing of the hydrophobic drug with a small amount of methylcellulose solution [41]; 2) the formation of microemulsions: by covering small particles with surfactants to obtain micromicelles that are visible only in the form of an opalescence; and, 3) the formation of complexing compounds: by adding a soluble substance to form soluble reversible complexes. However, the last method is used with some restrictions [42].

Raw Materials in Suspension The types of raw materials used to be part of suspensions are presented in Table 2. They have different purposes and can be wetting agents, salt formation ingredients, buffers, polymers, suspending agents, flocculating agents, electrolytes, antioxidants, poorly soluble Active Product Ingredients, preservatives, coloring, flavoring and sweetener agents, among others.

Particle Size of Drug in Suspension The physical stability of a suspension can be enhanced by controlling the particle size distribution [43]. Uncontrolled changes of drug particle size in a suspension affect the dissolution and absorption of the drug in the patient. Drug substances of finer particle size may be absorbed faster and bigger particles may not be absorbed. Aggregation or crystal growth is evaluated by particle size measurements using microscopy and a Coulter counter [21] or preferably techniques that allow samples to be investigated in the natural state. Allen [44] offers an academic and industrial discussion about particle characterization.

TABLE 2 Suspensions: pharmaceutical excipients

Purpose	Agent
Facilitating the connection between Active Product Ingredient and vehicle	- Wetting agents particle size ($>0.1\mu\text{m}$) - Salt formation ingredients - Sugars
Protecting the Active Product Ingredients	- Buffering-systems - Polymers - Antioxidants - Poorly soluble drugs
Maintaining the suspension appearance	- Colorings - Suspending agent - Flocculating agent - Antimicrobial preservatives
Masking the unpleasant taste/smell	- Electrolytes - Sweeteners - Flavorings - Poorly soluble Active Product Ingredient

Source: From ref. 4, 34, 35, 36

Powder properties and behavior, sampling, numerous potential particle size measuring devices, available equipment as well as surface and pore size are his principal themes.

Particles are usually very fine ($1\text{--}50\mu\text{m}$). For instance, topical suspensions use less than $25\mu\text{m}$ particle size [6]. The particle size of the drug is the most important consideration in the formulation of a suspension, since the sedimentation rate of disperse systems is affected by changes in particle size. Finer particles become interconnected and produce particle aggregation followed by the formation of nonre-suspendable sediment, known as caking of the product. The two main causes of aggregation and caking are energetic bonding and bonding through shared material. A statistical wide distribution of particle sizes gives more compact packing and energetic bonding than narrower distributions. It has been observed that heat treatments can cause agglomeration of particles, not only due to energetic bonding but also by formation of crystal bridges. Also, when the application of shear forces to mix and homogenize the suspension uses too high energy inputs, then the probability for aggregation increases [43].

Examples of oral suspensions in which a specific and well-defined particle size specification for the drug substance is important are phenytoin suspension, carbamazepine suspension, trimethoprim and sulfamethoxazole suspension, and hydrocortisone suspension [6].

There are some useful methods to improve the physical stability of a suspension, such as decreasing the salt concentration, addition of additives to regulate the osmolarity, as well as changes in excipient concentrations, unit operations in the process, origin and synthesis of the drug substance, polymorphic behavior of the drug substance crystals, and other particle characteristics. However, methods based on changes of the particle properties and the surfactants used are the most successful [43].

TABLE 3 Emulsions: pharmaceutical excipients

Purpose	Agent
Particle Size	- Solid particles (10 nanometers to 5 micrometers size) - Droplet particles (0.1–1.0 micrometers size)
Protecting the Active Product Ingredients	- Buffering-Systems - Polymers - Antioxidants - Distribution pattern (O/W, W/O)
Maintaining the appearance	- Colorings - Emulsifying agents - Penetration enhancers - Gelling agents - Stabilizers - Antimicrobial preservatives
Taste/smell Masking	- Sweeteners - Flavorings - Relation oil vs. water

Source: From ref. 4, 34, 35, 36

To approach physical stability problems of suspensions, effectiveness and stability of surfactants as well as salt concentrations must be checked with accelerated aging. In addition, unit operations affecting particle size distribution, surface area, and surfactant effectiveness should be approached, taking into account that different types of distributions, for instance, volume or number weighted, give a different average diameter for an equal sample [43].

Raw Materials in Emulsions The types of raw materials used to be part of emulsions are presented in table 3. They have different purposes and can be buffers, polymers, emulsifying agents, penetration enhancers, gelling agents, stabilizers, antioxidants, preservatives, coloring, flavoring and sweetener agents, among others.

Particle Size in Emulsions When a solid drug is suspended in an emulsion, the liquid dosage form is known as a coarse dispersion. In addition, a colloidal dispersion has solid particles as small as 10 nm–5 μ m and is considered a liquid between a true solution and a coarse dispersion [44].

4.3.4.4 Compounding: Effects of Heat and Process Time

Oxygen Oxygen removal for processing materials that require oxygen to degrade is possible by methods such as nitrogen purging, storage in sealed tanks, as well as special instructions for manufacturing operations [6]. For instance, sealing glass ampules containing a liquid dosage form with heat under an inert atmosphere is a packing mechanism used to prevent oxidation. Some aspects of oxygen sensitiveness that should be taken into account are the necessity of water and headspace deoxygenation in ampules before sealing, the avoidance of multidose vials that facilitate oxygen contact with the product after opened, and rubber stoppers for vial sealing that are permeable to oxygen as well as release additives to catalyze oxidative reac-

tions. Rubber stoppers soften and get sticky over time because all rubber products degrade as sulfur bonds induced during vulcanization revert. Connors et al. [45] present the oxygen content of water at different temperatures and an interesting discussion of calculations for the case of captopril as an oxygen-sensitive drug.

Dissolution of Drugs in Solutions Although some compounds, such as poloxamers, decrease their aqueous solubility with an increase in temperature [46], usually, drugs dissolve more quickly when the temperature increases because particle vibration is augmented and the molecules move apart to form a liquid. Chemical instabilities by oxidation due to high temperature or prolonged periods of heat exposure can occur when trying to increase the dissolution of poorly soluble raw materials. To control such instabilities, charts of time and amount of temperature treatments to dissolve materials as well as tests of dissolution are required [6]. In addition, precipitations and other reactions may occur between salts in solution and can be anticipated by using heat-of-mixing data and activation energy calculations for decomposition reactions. Connors et al. [45] provide examples of calculations about effects of temperature on chemical stability of pharmaceuticals in solution. Regarding the instability of the product, the reasons to limit temperature amounts can go from controlling final concentration changes to controlling burn-on/fouling when too-high temperatures are applied [45]. Usually salts are more soluble in water and alcohol than weak acids or bases. The reason salts are not always the best choice to increase the solubility of a drug is its permeability. Oral drug absorption depends not only on solubility and dissolution but also on permeability through the cellular membrane. Drugs have to be able to dissolve not only in the aqueous fluids of the body before reaching the intestinal wall but also in the lipophilic environment of the cellular membrane in order to reach the internal part of the cell and interfere with its functionality. Therefore, the cosolvent approach is essential if the drug presents problems in dissolving in the media. The dielectric constant of a solvent is a relative measure of its polarity. Comparing the hydroxyl–carbon ratio of the solvent molecule allows establishing the relative polarity of the cosolvent as determined by its dielectric constant [47]. Remington describes the formulations of some solutions, such as the ferrous sulfate syrup, amantadine hydrochloride syrup, phenobarbital elixir, and theophylline elixir [1].

Potency of Drugs in Suspension To avoid degradation of the suspended drug substance by high temperature or prolonged periods of heat exposure, it is necessary to record the time and amount of temperature treatments on charts [6]. The rate of dissolution of a suspended drug increases with the increase in temperature. The potency stability of a suspended drug depends on the concentration of the dissolved drug since drug decomposition occurs only in solution [48]. The goal is to avoid the dissolution of suspensions. Changing the pH of the vehicle or replacing the drug with a less soluble molecule may result in enhanced potency stability of the suspended drug [48].

For instance, when the chemical stability of a suspension of ibuprofen powder and other ibuprofen–wax microspheres was studied with a modified HPLC procedure for three months, the amount of drug released from the microspheres was affected by the medium pH, type of suspending agent, and storage temperature without observing chemical degradation of the drug [49].

Temperature Uniformity in Emulsions During the preparation of emulsions, heat may be increased as part of the manufacturing protocol or mixing operation system. Temperature measurements should be monitored and documented continuously using a recording thermometer if the temperature control is critical or using a hand-held thermometer if it is not a critical factor. Temperature may be critical in the manufacturing process depending on the thermosensitivity of the drug product and excipients as well as the type of mixer used. To guarantee the temperature uniformity during the mixing operation, manufacturers may consider the relation between the container size, mixer speed, blade design, viscosity of the contents, and rate of heat transfer [20].

Fong-Spaven and Hollenbeck [50] studied the apparent viscosity as a function of the temperature from 25 to 75°C of an oil–water emulsion stabilized with 5% triethanolamine stearate (TEAS) using a Brookfield digital viscometer. They observed that the viscosity decreased when the temperature reached about 48°C, but surprisingly viscosity increased to a small peak at 54°C and then continued decreasing after that peak. The viscosity peak was attributed to a transitional gellike arrangement molecular structure of TEAS that is destroyed as soon as the temperature continues increasing, the TEAS crystalline form reappears, and viscosity again decreases [36].

Microbiological Control To avoid chemical instabilities that yield microbiological and physical instabilities, as a result of high temperature or prolonged periods of exposure, it is necessary to record the time and amount of temperature treatments on charts [6].

Product Uniformity Charts of storage and transfer operation times for the bulk product are required to control the risk of segregation. Transfers to the filling line and during the filling operation are the most critical moments to keep the suspension uniformity [6]. The implementation of an ERP for time scheduling is the best solution for time control and organization of resources. However, it could be difficult due to the reluctance of people to change [10]. The constant flow of the liquid through the piping, the constant mixing of the bulk product in the tank, as well as the transfer of small amounts near the end of the filling process to a smaller tank during the filling process may minimize segregation risks [6].

Final Volume Excess heating produces variations of the final volume over time [6]. Although increasing solute concentration can elevate the boiling point and reduce evaporation of water, changes in drug concentration are undesirable because they yield different final products. Regarding the instability of the product, the reasons to limit temperature amounts can go from controlling final concentration changes to controlling burn-on/fouling when too-high temperatures are applied [36].

A solution is a liquid at room temperature that passes into the gaseous state when heated at very high temperature, forming a vapor with determined vapor pressure, through a process called vaporization. The kinetic energy is not evenly distributed between the molecules of the liquid. When the liquid is in a closed container at a constant temperature, the molecules with the highest kinetic energy leave the surface of the liquid and become gas molecules. Some of the gas molecules remain as gas and others condense and return to the liquid. When, at a determined temperature,

the rate of condensation equals the rate of vaporization, the equilibrium vapor pressure is reached. However, vapor pressure increases with increases in liquid temperature, resulting in more molecules leaving the liquid surface and becoming gas molecules [51].

Storage Charts of time and temperature of storage are important to control the increased levels of degradedness [6]. Shelf life is defined as the amount of time in storage that a product can maintain quality and is equivalent to the time taken to reach 90% of the composition claim or have 10% degradation. The availability of an expiration date is assumed under specified conditions of temperature. Based on zero- and first-order reaction calculations, Connors et al. [45] show the estimation methods to determine the shelf life of a drug product at temperatures different from the one specified under standard conditions.

4.3.4.5 Uniformity of Oral Suspensions

Keeping the particles uniformly distributed throughout the dispersion is an important aspect of physical stability in suspensions. Based on Stokes's law for dilute suspensions where the particles do not interfere with one another, there are different factors that control the velocity of particle sedimentation in a suspension, for instance, particle diameter, densities of the dispersed phase and the dispersion medium, as well as viscosity of the dispersion medium [36]. Remington describes the formulation of trisulfapyrimidines oral suspension [1]. In addition, Lieberman et al. [42, 48] are also good sources of typical formulations for suspensions.

Viscosity Depending upon the viscosity, many suspensions require continuous or periodic agitation during the filling process [6].

Segregation in Transfer Lines When the stored bulk of a nonviscous product is transferred to filling equipment through delivery lines, some level of segregation is expected. The manufacturer has to write the procedures and diagrams for line setup prior to filling the product [6]. Delivery lines of suspensions increase the tendency of particles of the same size to assemble together. However, slightly increasing the global mixing in the lines can easily reverse the segregation without enhancing the global mixing [52]. Shear stress versus rate of shear can be plotted to determine the flow pattern of a specific suspension as pseudoplastic, Newtonian, or dilatant. The type of flow is determined by the slope of the plot. While shaking increases the yield stress and causes particles flow, the cessation of shear and rest rebuilds the order of the system. A good-quality suspension is known as a thixotropic system and is obtained when the particles at rest avoid or show reduced sedimentation. The rheogram of a thixotrope system presents a typical hysteresis or curve representing different shear stresses over time [33].

Quality Control The GMPs for suspensions include testing samples at different checkpoints in the procedure, at the beginning, middle, and end, as well as samples from the bulk tank. The uniformity will be successful only if, on microscopic analysis, the components are dispersed to the expected particle size distribution established by product development. Visual and microscopic examinations should consist of looking for verification of foam formation, segregation, and settling, although testing

for viscosity is important to determine agitation during the filling process. Samples used for tests should not be combined again with the lot [6, 33].

4.3.4.6 Uniformity of Emulsions

Remington describes the following three typical formulas of emulsions: type A gelatin, mineral oil emulsion (USP), and oral emulsion (O/W) containing an insoluble drug [1]. In addition, Lieberman et al. [42, 50] are also good sources of typical formulations for emulsions. The components of the emulsion system may present physical and chemical instabilities reflected on the distribution of an active ingredient, component migration from one phase to another, polymorphic changes in components, and chemical degradation of components [33].

Solubility The soluble active ingredient should be added to the liquid phase that will be its carrier vehicle. Data of solubility have to be determined as part of the process validation. Potency uniformity has to be tested by demonstrating satisfactory distribution in the emulsified mix [20].

Particle Size Regarding globule diameter in emulsions, the size–frequency distribution of particles in an emulsion over time may be the only method for determining stability [36]. Drug activity and potency uniformity of insoluble active ingredients depend upon control of particle size and distribution in the mix [6]. In addition, aggregation of the internal phase droplets, formation of larger droplets, and phase separation are categorized as emulsion system instabilities that are reflected in the particle size distribution of the emulsion. The measurement of particle size distribution over time allows the characterization of the emulsion stability and determines the rheological behavior of the emulsion. Well-accepted approaches to determine particle size distribution include microscopy, sedimentation, chromatography, and spectroscopy. However, these analyses are problematic in a multiphase emulsion [33].

Crystalline Form Uncontrolled temperature or shear can induce changes in component crystallinity or solubility. For this reason, analytes originally present in each phase of the product should be counted as well possible interactions with the container or closure and the processing equipment analyzed. Some techniques used to obtain information about the emulsion system and its components are microscopic examination, macro- and microlaser Raman, and rheological studies [33]. The FDA guidance offers the following example: “in one instance, residual water remaining in the manufacturing vessel, used to produce an ophthalmic ointment, resulted in partial solubilization and subsequent recrystallization of the drug substance; the substance recrystallized in a larger particle size than expected and thereby raised questions about the product efficacy” [20].

4.3.4.7 Microbiological Quality

Microbial Specifications These specifications are determined by the manufacturer. The USP Chapters 61, 62, and 1111 present the microbial limits to assess the significance of microbial contamination in a dosage form [53]. However, the USP

does not determine specific methods for water-insoluble topical products. The microbial specifications are presented as a manufacturer's document that details the methods to isolate and identify the organisms as well as the number of organisms permitted and action levels to be taken when limits are exceeded and the potential causes are investigated [6]. The *Pharmaceutical Microbiology Newsletter* (PMF) presents several articles to discuss topics such as microbial identification, methods, data analysis, and preservation as well as topics related to USP and FDA regulations [54]. To minimize the differences about microbial limits and test methods, the USP is trying to harmonize the standards with the European Pharmacopoeia (EP) [55].

Microbial Test Methods The selected microbial test methods determine specific sampling and analytical procedures. When the product has a potential antimicrobial effect and/or preservative, the spread technique on microbial test plates must be validated. In addition, the personnel performing the analytical techniques have to be qualified and adequately trained for this purpose [6].

Usually, total aerobic bacteria, molds, and yeasts are counted by using a standard plate count in order to test the microbial limits. The microbial limit test may be customized by performing a screening for the occurrence of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Pseudomonas cepacia*, *Escherichia coli*, and *Salmonella* sp. [56].

Investigation of Exceeded Microbiological Limits A high number of organisms may indicate deficiencies in the manufacturing process, such as excessive high temperature, component quality, inadequate preservative system, and/or container integrity. Information about the health hazards of all organisms isolated from the product has different meanings depending on the type of dosage form and group of patients to be treated. For instance, in oral liquids, pseudomonads are usually a high-risk contamination. Examples presented by the FDA are Nystatin antifungal suspension, used as prophylaxis in AIDS patients [57]; antacids, with which *P. aeruginosa* contamination can promote gastric ulceration [58]; and the presence of *Pseudomona putida*, which could indicate the presence of other significant contaminants such as *P. aeruginosa* [6].

Deionizer Water-Monitoring Program Deionizing systems must be controlled in order to produce purified water, required for liquid dosage forms and USP tests and assays [1]. The monitoring program has to include the manufacturer's documentation about time between recharging and sanitizing, microbial quality and chlorine levels of feed water, establishment of water microbial quality specifications, conductivity monitoring intervals, methods of microbial testing, action levels when microbial limits are exceeded, description of sanitization and sterilization procedures for deionizer parts, and processing conditions such as temperature, flow rates, use and sanitization frequency, and regenerant chemicals for ion exchange resin beds [6, 59].

Effectiveness of Preservative Manufacturing controls and shelf life must ensure that the specified preservative level is present and effective as part of the stability program [6]. Depending on the type of product, the selection of the preservative system is based on different considerations, such as site of use, interactions,

spectrum, stability, toxicity, cost, taste, odor, solubility, pH, and comfort. The USP and other organizations describe methods to validate the preservative system used in the dosage form. Compounds used as preservatives are alcohols, acids, esters, and quaternary ammonium compounds, among others. For instance, to preserve ophthalmic liquid dosage forms, these products are autoclaved or filtrated and require an antimicrobial preservative to resist contamination throughout their shelf life, such as chlorobutanol, benzalkonium chloride, or phenylmercuric nitrate [1].

4.3.4.8 Filling and Packing

Constant Mixing during Filling Process Due to the tendency of suspensions to segregate during transport through transfer lines, special attention is required on suspension uniformity during the filling process. Appropriate constant mixing of the bulk to keep homogeneity during the filling process and sampling of finished products and other critical points are indispensable conditions to assure an acceptable quality level during the filling and packing process [20].

Mixing Low Levels of Bulk Near End of Filling Process Constant mixing during the filling process includes mixing low levels of bulk near the end of the filling process. Large-size batches of bulk suspension require the transfer of the residual material to a smaller tank in order to assure appropriate mixing of components before filling and packing the containers [20].

Potency Uniformity of Unit-Dose Products Products manufactured have to be of quality at least as good as the established acceptable quality level (AQL). The quality level should be based on the limits specified by the USP. However, when the bulk product is not properly mixed during filling and packing processes, liquid dosage forms, and specially suspensions, are not homogeneous and unit-dose products contain very different amounts of the active component and potency. For these reasons, finished products have to be tested to assure that the final volume and/or weight as well as the amount of active ingredient are within the specified limits [6].

Calibration of Provided Measuring Devices Measuring devices consist of droppers, spoons for liquid dosage forms, and cups labeled with both tsp and mL. Measuring devices have to be properly calibrated in order to assure the right amount of ingredients per volume to be administered [6].

Container Cleanliness of Marketing Product The previous cleanliness of containers filled with the product will depend on their transportation exposure, composition, and storage conditions. Glass containers usually carry at least mold spores of different microorganisms, especially if they are transported in cardboard boxes. Other containers and closures made with aluminum, Teflon, metal, or plastic usually have smooth surfaces and are free from microbial contamination but may contain fibers or insects [45]. Some manufacturers receive containers individually wrapped to reduce contamination risks and others use compressed air to clean them. However, the cleanliness of wrapped containers will depend on the provider's guarantee of the manufacturing process and compressed-air equipment may release vapors or oils that have to be tested and validated [6].

4.3.4.9 Stability

The typical stability problems are color change, loss of active component, and clarity changes for solutions; inability to resuspend the particles and loss of significant amounts of the active component for suspensions; and creaming and breaking (or coalescence) for emulsions [1]. These instabilities are usually related to the following:

Active and Primary Degradant. A liquid dosage form is stable while it remains within its product specifications. When chemical degradation products are known, for stability study and expiration dating, the regulatory requirements for the primary degradant of a active component are chemical structure, biological effect and significance at the concentrations to be determined, mechanism of formation and order of reaction, physical and chemical properties, limits and methods for quantitating the active component and its degradant molecule at the levels expected to be present, and pharmacological action or inaction [45]. Examples of drugs in liquid dosage forms that are easily degraded are vitamins and phenothiazines [6].

Interactions with Closure Systems. Elastomeric and plastic container and closure systems release leachable compounds into the liquid dosage form, such as nitrosamines, monomers, plasticizers, accelerators, antioxidants, and vulcanizing agents [44]. Each type of container and closure with different composition and/or design proposed for marketing the drug or physician's samples has to be tested and stability data should be developed. Containers should be stored upright, on their side, and inverted in order to determine if container–closure interactions affect product stability [6, 45].

Moisture Loss. When the containers are inappropriately closed, part of the vaporized solvent is released and the concentration and potency of the active component may be increased [6].

Microbiological Contamination. Inappropriate closure systems also increase the possibilities of microbial contamination when opening and closing containers [6].

4.3.4.10 Process Validation

Objective Process validation has the objectives of identifying and controlling critical points that may vary product specifications through the manufacturing process [6].

Amount of Data To validate the manufacturing process, the manufacturer has to design and specify in the protocol the use of data sheets to keep information about the control of product specifications from each batch in-process as well as finished-product tests. Some formats are common to different products, though each type of product has some specific information to be kept on special sheets. Thus, the amount of data varies from one type of product to another [6].

Scale-Up Process Data obtained using special batches for the validation of the scale-up process are compared with data from full-scale batches and batches used for clinical essays [6].

Product Specifications The most important specifications or established limits for liquid dosage forms are microbial limits and test methods, medium pH, dissolution of components, viscosity, as well as particle size uniformity of suspended components and emulsified droplets. Effectiveness of the preservative system depends on the dissolution of preservative components and may be affected by the medium pH and viscosity. In addition, dissolved oxygen levels are important for components sensitive to oxygen and/or light [6].

Bioequivalence or Clinical Study In the patient, the general or systemic circulation is responsible for carrying molecules to different tissues of the body. To assure the expected bioactivity of a product, the amount of drug that reaches the systemic circulation per unit of time is analyzed and is known as bioavailability. Bioequivalence is the comparison of the bioavailability of a product with a reference product. While oral solutions may not always need bioequivalence studies because they are considered self-evident, suspensions usually require bioequivalence or clinical studies in order to demonstrate effectiveness. However, OTC suspension products such as antacids are exempt from these studies [6].

Control of Changes to Approved Protocol The manufacturing process of a specific product is validated and approved internally by the quality control unit and externally by the FDA. Any change in the approved protocol has to be documented to explain the purpose and demonstrate that the change will not unfavorably affect product safety and efficacy. Factors include potency and/or bioactivity as well as product specifications. However, the therapeutic activity and uniformity of the product are the main concerns after formulation and process changes [20].

4.3.5 LIQUID DOSAGE FORMS*

Douche A liquid preparation, intended for the irrigative cleansing of the vagina, that is prepared from powders, liquid solutions, or liquid concentrates and contains one or more chemical substances dissolved in a suitable solvent or mutually miscible solvents.

Elixir A clear, pleasantly flavored, sweetened hydroalcoholic liquid containing dissolved medicinal agents; it is intended for oral use.

Emulsion A dosage form consisting of a two-phase system comprised of at least two immiscible liquids, one of which is dispersed as droplets (internal or dispersed phase) within the other liquid (external or continuous phase), generally stabilized with one or more emulsifying agents. (Note: Emulsion is used as a dosage form term unless a more specific term is applicable, e.g. cream, lotion, ointment.).

Enema A rectal preparation for therapeutic, diagnostic, or nutritive purposes.

Extract A concentrated preparation of vegetable or animal drugs obtained by removal of the active constituents of the respective drugs with a suitable menstrua, evaporation of all or nearly all of the solvent, and adjustment of the residual masses or powders to the prescribed standards.

*The definitions in this section are from ref. 11.