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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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ASUNTO	Radicación	10 001 028
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	25 - 19173
	Folios	030

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional			
Vía PCT (Fase Nacional)	☒	Capítulo I	☒
No. Solicitud Internacional	PCT/US08/065722		
Fecha de Presentación Internacional	04/Junio/2008		

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:	Folios 35 a 61	06/Enero/2010
Reivindicaciones:	Folios 62 a 64	06/Enero/2010
Oposiciones:	Folios 116 a 152	Procaps 19/Julio/2011
	Folios 153 a 171	Lafrancol 21/Julio/2011
Respuesta del solicitante:	Folios 176 a 183	05/Diciembre/2011
Prioridad:	CL 1634-2007	06/Junio/2007

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta 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

Título de la solicitud: "COMPOSICIÓN FARMACÉUTCA QUE CONTIENE UNA
Expediente 10 001 028 1er Art 45

HORMONA DE ESTEROIDE, UN EXCIPIENTE ADHESIVO DE MUCOSA, FORMADO POR LA COMBINACIÓN DE QUITOSÁN Y CARBOXIPOLIMETILENO, UN AGENTE DE DESINTEGRACIÓN, UN DILUYENTE Y UNA MEZCLA DE LUBRICANTES”.

El problema planteado en esta solicitud consiste en la necesidad de suministrar un sistema de liberación vaginal con un menor índice de desintegración /disolución, previniendo la acumulación de residuos en la cavidad vaginal.

Para resolver este problema técnico la solicitud en estudio proporciona una composición de acuerdo la reivindicación 1, (pág. 28, Fl. 62).

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61F 6/06.

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las Reivindicaciones 1 y sus dependientes no son claras porque la expresión: “por lo menos”, es imprecisa, lo cual no permite distinguir la invención del estado de la técnica. Asimismo, las expresiones “un agente de desintegración”, “un agente diluyente” y “una mezcla de lubricantes”, no especifican a que componente se refiere, ya que estos no se definen por su estructura o nombre químico sino por su función dentro de la composición.

La reivindicación 11, se caracteriza por un resultado a alcanzar, lo cual no limita la composición porque la invención no queda definida por el resultado a alcanzar, puesto que la reivindicación incluiría no sólo la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Se sugiere reemplazarlo por las características esenciales, estructurales o funcionales, que contribuyen a la obtención de ese efecto.

La reivindicación 12 que depende de la 1, menciona que los lubricantes están presentes en una proporción entre 0.01% y 3.5%, lo cual no es consistente con la cantidad mencionada en la reivindicación 1 porque el valor de 0.01% está por fuera del rango mencionado en la reivindicación 1.

5. Análisis de las Oposiciones

Argumentaciones de Procaps S.A.

Argumenta la opositora que los documentos WO970792 y US2004132690 afectan la patentabilidad de la presente solicitud porque el primero, revela la administración transdérmica/transmucosal de una composición farmacéutica comprimida sólida caracterizada por contener una hormona esteroide que es progesterona y puede estar asociada a estradiol o un excipiente adhesivo mucoso formado por carboxipolimetileno (carbómero), un agente de desintegración, un diluyente y una mezcla de lubricantes. El segundo documento, enseña de forma particular en los Expediente 10 001 028 1er Art 45

párrafos 1,24 y 25, una composición farmacéutica que contiene gel a base de quitosano para la administración vaginal, donde dicho documento revela adicionalmente la posibilidad de usar no sólo quitosano sino sus derivados con el fin de mejorar la biocompatibilidad y biodegradabilidad de la composición. Tomando estos documentos como los más cercanos, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia incluir gel a base de quitosano para la administración vaginal como se enseñó en el primer documento en una composición farmacéutica comprimida como la presentada en el primer documento, con el fin de mejorar la biocompatibilidad y la biodegradabilidad de la composición. Por lo anterior dicha solicitud colombiana 10-001028, no puede pretender un monopolio por patente ya que no cumple con dos de los tres requisitos necesarios para su protección.

Argumentaciones de Laboratorios Lafrancol S.A.

Argumenta la opositora que la solicitud 10-001028 no cumple los requisitos materiales de patentabilidad establecidos en el Título II, capítulo I de la decisión 486 de 2000, lo anterior ya que la composiciones y combinaciones farmacéuticas apropiadas para la administración vaginal de esteroides, para que sean utilizadas en una terapia de reemplazo hormonal, durante la menopausia y para soportar la fase lútea de ciclos de fertilización in vitro; y donde adicionalmente dichas composiciones y combinaciones se caracterizan por la incorporación de polímeros y combinaciones desintegradoras, las cuales permiten una adherencia de mucosa adecuada y biodisponibilidad e hormonas en el endometrio, son prácticas y eventos totalmente conocidos en la industria farmacéutica, de manera que no existe novedad ni nivel inventivo por lo tanto no se debe conceder un beneficio patentario. También argumenta que las composiciones de las cuales se hace referencia que involucra agentes terapéuticos como: progesterona y estradiol, que están plenamente identificadas en el sector químico-farmacéutico, por lo cual se anexan copias del documento "The Merck Index". Además, menciona que se pretende solicitar beneficio patentario para objetos que ya se encuentran plenamente identificados en el mercado; de manera que la solicitud en estudio no cumple con los requisitos esenciales para acceder al derecho patentario por cuanto no se encuentran presentes la novedad, el nivel inventivo. Asimismo, afirma que las combinaciones de productos conocidos y su variación, bien sea en uso, forma, dimensión o de materia, no se consideran invenciones por cuanto no son susceptibles de aplicación industrial, nivel inventivo y novedad, luego no pueden acceder a beneficios patentarios.

A la oposición de Procaps S.A, el solicitante responde que el documento WO970792 muestra una composición sólida en forma de parche transdérmico y la reclamada es en forma de comprimidos sólidos los cuales permiten la administración de ingredientes activos en estado micronizado de manera vaginal, de tal forma que los excipientes utilizados en la invención que son diferentes a los usados en la anterioridad citada, no permiten derivar de manera obvia los excipientes usados en la composición de la invención. Por otro lado, resulta poner de presente que la composición divulgada en el documento US2004132690, comprende quitosano o un derivado de este con carbómer 974, con ácido láctico, para obtener un gel con propiedades bioadhesivas para administrar transmucosalmente en la vagina;

señalándose como problema técnico de la anterioridad, formular composiciones, para combatir las infecciones vaginales; mientras que la solicitud hace uso de progesterona y estradiol como agentes activos. En conclusión, este último documento no le resta nivel inventivo a la solicitud por que el excipiente mucoadhesivo utilizados en ambas es diferente, al igual que la vía de administración y los agentes activos. Igualmente menciona, que por las diferencias entre los documentos citados como anterioridades y la invención, no se pueden considerar como anterioridades válidas capaces de afectar la novedad, el nivel inventivo y la aplicación industria.

A la oposición de Laboratorios Lafrancol S.A., el solicitante responde que la parte opositora se limita a listar los documentos en que se divulgan los componentes progesterona y estradiol por separado y no como las composiciones acá reivindicadas; por lo tanto no es válido argumentar que cada uno por separado e conocido u obvio, pues la invención esta dada por la relación (combinación especial) entre ellos que no había sido anticipada en el estado del arte y que además solucione un problema técnico, como en el presente caso. Además, argumenta que los documentos listados por la oposición no son relevantes para el estudio de nivel inventivo porque se refieren a la progesterona y estradiol por separado y tampoco presentan enseñanzas o sugerencias relacionadas con una composición farmacéutica sólida de uso intravaginal que presente las características para alcanzar una buena adhesividad en una parte del cuerpo caracterizada por su difícil administración.

De acuerdo con lo expuesto por Procaps S.A, esta Superintendencia considera que los documentos por ellos presentados, no desvirtúan la Novedad ni el Nivel Inventivo del objeto de esta solicitud, por lo cual no se considerarán dentro del Examen de Patentabilidad, declarando infundada la oposición.

Por su parte, esta Superintendencia considera que los argumentos del opositor Lafrancol S.A., sustentados con los documentos citados antes, no son relevantes para desvirtuar el objeto de la presente solicitud de invención por lo tanto no se tomarán en cuenta para el presente análisis de patentabilidad, declarando infundada la oposición.

6. 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: Junio 6 de 2007 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Nº	Documento	Título	Fecha de Publicación*
D1	*artículo	Development and in vitro evaluation of a mucoadhesive vaginal delivery system for progesterone	Octubre 10 de 2001
D2	*artículo	The use of mucoadhesive polymers in vaginal delivery	Septiembre 22 de 2005

D1¹ (págs. 323-332) divulga composiciones en forma de tabletas de progesterona para entrega por vía vaginal.

D2² (págs. 1692-1712) divulga el uso de polímeros, entre otros como el chitosan, para usar como vehículo en composiciones en forma de tabletas para administrar por vía vaginal.

7. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en una composición farmacéutica comprimida sólida para administración vaginal caracterizada porque contiene, por lo menos, una hormona esteroide, un excipiente adhesivo de mucosa, formado por la combinación de chitosan y carboxipolimetileno, un agente de desintegración, un diluyente y una mezcla de lubricantes, en donde por lo menos uno de ellos está presente en una relación entre 0.05% y 3.5% p/p.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1	D2
Composición comprimida sólida vaginal caracterizada porque contiene	Composición tabletas vaginales caracterizada porque contiene	Composición tabletas vaginales caracterizada porque contiene
1-Por lo menos una hormona esteroide	Progesterona (abstract)	No menciona
2-Un excipiente adhesivo de mucosa formado por la combinación de chitosan y carboxipolimetileno(carbopol)	Carbopol 974 (abstract)	Chitosan Carbopol
3-Agente de desintegración	Celulosa microcristalina (abstract)	No menciona cual desintegrante
4- Un diluyente	No menciona cual diluyente	No menciona cual diluyente
5-Mezcla de lubricantes, En relación de 0.05% y 3.5% p/p	No menciona cual lubricante	No menciona cual lubricante

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1, porque D1 divulga una composición en forma de tabletas que comprende 30 a 50 mg de progesterona (abstract, pág.329), carbopol 974(abstract, pág.324) y celulosa microcristalina (abstract).

La diferencia entre la invención, definida en la reivindicación 1 y la composición de D1 es que menciona la combinación de chitosan-carbopol, a cambio de sólo el carbopol en la composición conocida.

Aunque exista esta diferencia, no se observa ningún efecto sorprendente.

1http://www.sinab.unal.edu.co:2053/science?_ob=ArticleListURL&_method=list&_ArticleListID=2140766244&_sort=r&_st=13&view=c&_acct=C000055778&_version=1&_urlVersion=0&_userid=1998314&md5=55cc5f0851e195cc7b5f709ba514f549&searchtype=a

2 <http://144.206.159.178/ft/18/595516/12296009.pdf>
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Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: “cómo modificar la composición de D1 para lograr una tableta alternativa para el mismo fin”

Sin embargo en D2, se divulgaba la utilización de polímeros entre otros como el chitosan y el carbopol que muestran propiedades mucoadhesivas, como excipientes en una tableta vaginal, para la entrega de agentes activos por esta vía (págs. Abstract, 1702-1704 y1707).

Se aclara que la composición reclamada menciona un agente de desintegración, un diluyente, mezcla de lubricantes y que aunque los documentos D1 y D2 no los mencione no quiere decir que no los contenga, por el contrario estos excipientes son bien conocidos que hacen parte de una forma farmacéutica como lo es un comprimido³ en proporciones comprendidas en los rangos reclamados, así desintegrante 5%, 10 -15% y -4% (pág.2476); diluyente 5-15%(pág.2474); lubricantes 0.1 a 5%(pág.2475).

Por otro lado en la descripción se aprecian ejemplos de 6 composiciones y la gráficas 1, 2 y 3 muestran una mayor disolución para las composiciones 4, 5 y 6, que tienen el desintegrante almidón glicolato y menor tamaño que las composiciones 1,2 y 3 que no tienen este desintegrante y que tienen un mayor tamaño. La anterior comparación es obvia ya que se espera un mayor porcentaje de disolución en tabletas que contienen un desintegrante y un menor tamaño frente a las que no contienen este componente y son mucho más grandes.

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría el chitosan mencionado en D2 en la tableta de D1 y un diluyente y una mezcla de lubricante que son bien conocidos como excipientes en la fabricación de comprimidos, para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Puesto que las reivindicaciones dependientes 2 –12 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	*artículo	1-12	Nivel Inventivo
D2	*artículo	1-12	Nivel Inventivo

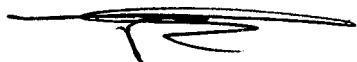
En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días

3 Farmacia práctica de Remington, Alfonso R. Gennaro. 19a Edición 1995 tomo II. comprimidos (págs.. 2472-2477)
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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.

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.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 23 OCT. 2012

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OK

Development and in vitro evaluation of a mucoadhesive vaginal delivery system for progesterone

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Abstract

The purpose of the present study was to design a novel carrier system based on a mucoadhesive polymer exhibiting improved properties concerning drug delivery to the vaginal mucosa. This was reached by the covalent attachment of L-cysteine to commercially available polyacrylic acid (Carbopol 974P). Mediated by a carbodiimide, increasing amounts of L-cysteine were covalently linked to the polymer. The resulting thiolated polyacrylic acid conjugates (NaC974P-Cys) displayed between 24.8 and 45.8 μmol thiol groups per gram of polymer. Because of the formation of intra- and/or intermolecular disulfide bonds, the viscosity of an aqueous thiolated polymer gel (3%) increased about 50% at pH 7.0 within 1 h. In oscillatory rheological measurements, it was shown that this increase in viscosity is mainly due to the increase in elasticity. Tensile studies carried out on freshly excised cow vagina demonstrated a significant ($P < 0.05$) increase in the total work of adhesion (TWA) compared to the unmodified polymer. An amount of 24.8 μmol thiol groups per gram of polymer resulted in a 1.45-fold increase in the TWA, whereas an amount of 45.8 μmol showed an even 2.28-fold increase. These improved mucoadhesive properties can be explained by the formation of disulfide bonds between the thiolated polymer and cysteine rich subdomains of the mucus layer. The release rate of the model drug progesterone from tablets based on microcrystalline cellulose serving as the reference was approximately 1% per hour, whereas it was 0.58% per hour for the unmodified polymer (NaC974P) and 0.12% per hour for the thiolated polymer (NaC974P-Cys). Therefore, this thiolated polymer is a promising carrier for progesterone providing a prolonged residence time and a controlled drug release. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Carbopol–cysteine conjugate; Thiomers; Oscillatory rheometry; Progesterone

1. Introduction

Natural progesterone administered orally shows poor bioavailability due to its intensive hepatic

metabolism. This greatly limits the efficacy of peroral administration. Therefore, it was chosen as a good candidate for a controlled vaginal application form. The vaginal route of administration has many advantages compared to other routes [1]. The vaginal epithelium is permeable to a wide range of drugs, like hormones, antimycotics, peptides and proteins. The vagina provides a promising site of systemic drug delivery because of its large surface area and its rich blood supply. In addition, a prolonged contact of

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a delivery system with the vaginal mucosa may be achieved more easily than at other absorption sites like the rectum or intestinal mucosa. However, despite all the advantages of a vaginal application, changes in the membrane during the menstrual cycle and postmenopausal period must be taken into account. In postmenopausal women, the reduced epithelial thickness may increase the original absorption rates of drugs [2]. Over the last three decades considerable attention has been focused on the development of novel and controlled delivery systems providing a long-term therapeutic concentration of drugs following a single dose. Many drug delivery systems are based on mucoadhesive polymers that are able to swell rapidly when placed in an aqueous environment and, therefore, exhibited a controlled drug release. Since the first presentation of the concept of mucoadhesion, many attempts have been undertaken to improve the adhesive properties of such polymer systems [3–6]. One approach to reach this goal is to immobilise thiol groups into the polymer system that are capable of forming covalent bonds with the mucus layer. This has been proved by mucin binding studies [7]. These bonds are responsible for the much higher adhesive properties on porcine mucosa. The thiol groups are supposed to interact with cysteine rich sub-domains of mucus glycoproteins via disulfide exchange reactions [8]. To date several polymer conjugates with thiol groups have been synthesised and evaluated for peroral drug delivery [9,10]. The aim of the present study was the development of a mucoadhesive vaginal delivery system for the model drug progesterone. As dosage forms tablets were designed to improve the adhesion to the vagina in order to prolong the residence time and consequently to obtain a release of progesterone. A better patient compliance may also be achieved by this delivery system. New conjugates of a polyacrylic acid polymer with cysteine were synthesised and the effects of covalently bound cysteine on the rheological properties of these new polymers should be determined using oscillatory rheometry. Furthermore, mucoadhesion tests were performed on cow vagina. Release studies of progesterone from these newly generated conjugates were also carried out to investigate the influence of the thiol groups on the release rate.

2. Materials and methods

2.1. Materials

Polyacrylic acid (C974P) (Carbopol 974P, BF Goodrich, Becksville, OH, USA) was neutralised with NaOH as described previously [11]. Progesterone, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC), was obtained from Sigma (St. Louis, MO, USA); L-cysteine hydrochloride monohydrate from Sigma-Aldrich (Steinheim, Germany) and microcrystalline cellulose (Elcema^R G 250, Degussa, Germany). All other chemicals used were of reagent-grade.

2.2. Synthesis of the polyacrylic acid conjugates

First, 250 mg of the sodium salt of polyacrylic acid (NaC974P) were hydrated in 62.5 ml of demineralised water for 1 h. The carboxylic acid moieties of the polymer were activated for 45 min with EDAC in a final concentration of 50 mM. Thereafter, 62.5 mg, 125 and 250 mg, respectively, of L-cysteine hydrochloride monohydrate were added to the reaction mixture. The pH value was adjusted to 5 by adding 1 M NaOH or 1 M HCl, respectively. The reaction mixture was then incubated for 3 h at room temperature. The resulting conjugates were isolated by dialysing at 10°C in the dark against 0.2 mM HCl at pH 3.0, two times against the same medium but containing 1% NaCl and two times exhaustively against 1 mM HCl. The pH value of the dialysed polymer–cysteine conjugates was then adjusted to pH 4.5 with 1 M NaOH and lyophilised. A polymer being prepared and isolated in exactly the same way as the polyacrylic acid–cysteine conjugates but omitting EDAC during the coupling reaction served as the control for all studies. The polymer–cysteine conjugates and controls were stored at 4°C until further use.

2.3. Determination of the thiol group content

The amount of thiol groups on the polymer–cysteine conjugate was determined by iodometric microtitration (1 mM iodine; indicator: starch). Three milligrams each of the conjugates and control were

hydrated in 1.0 ml of demineralised water. Finally, the thiol group content was analysed by microtitration after acidification with 1 M HCl to pH 3.0 [12].

2.4. Oscillatory rheology

Oscillatory shear experiments were performed on a Haake rheometer Rotovisco RT20 (Haake, Karlsruhe, Germany; thermo controller Haake F6/8). The rheometer was a thermostatically controlled cone/plate 35 mm in diameter and a 2° angle. Throughout the experimental period, the plate temperature was maintained at $37 \pm 1.5^\circ\text{C}$. The sample amount was approximately 1.5 g. By this modus, the induced response (strain) when a sinusoidal stress is applied to the sample, is measured. After the identification of the linear viscoelastic region, samples were investigated over a frequency of 1–10 Hz (ν). The parameters obtained are the complex modulus G^* consisting of the elastic modulus G' and the viscous modulus G'' , and the dynamic viscosity η' which are calculated by:

$$G' = G^* \cos(\delta)$$

$$G'' = G^* \sin(\delta)$$

$$\eta' = G''/\omega$$

The dynamic viscosity is defined as G''/ω , where ω is the angular velocity of oscillatory stress, which is related to the oscillatory frequency by the relationship $\omega = 2\pi\nu$. The related phase angle is expressed as δ .

In order to determine the relation of the thiol group content to viscosity, a combined measurement was performed. According to our hypothesis inter- and/or intrachain disulfide bonds within the polymer can be generated within NaC974P–Cys. This cross-linking is the reason for the excellent cohesiveness of the polymer itself. The formation of the disulfide bonds can be proved indirectly by measuring the decrease of the thiol groups and increase of viscosity. Hydrogels [3% (m/m)] of the NaC974P–Cys conjugates and of the control at a pH of 7.0 were prepared separately. At time 0 one aliquote of about 0.1 g of the gel was used for iodometric titration in

order to analyse the thiol group content as described above and another aliquote of about 1.5 g of hydrogel was applied on the rheometer and measured in oscillatory modus. The sample was left on the plate of the rheometer and protected from evaporation by parafilm. Oscillatory measurements with exactly the same parameters were performed hourly. The experiment time was 4 h. Parallel to this the rest of the hydrogel sample was left in a bottle on a shaking water bath at 37°C and exactly at the same time points as the viscosity was determined the amount of thiol groups present was analysed titrimetrically. Each experiment was performed three times.

2.5. Tensile studies

The adhesive strength of the polymer–cysteine conjugate and the control was evaluated with an adhesion test using a validated adhesive strength-measuring device. A previously reported method for measuring mucoadhesion was adapted [13]. Instead of porcine mucosa, cow vaginal mucosa was used. A 30-mg aliquot of each of the lyophilised NaC974P–Cys conjugates and controls were compressed to test tablets as described below. The tablets were attached to the cow vaginal mucosa in the following manner: The tablet was attached to a stainless steel flat disc (5 mm in diameter, 0.3 g in weight in the system), which was hung by a nylon thread (15 cm) from a laboratory stand. The vaginal mucosa was fixed to a glass tissue mount using a cyanoacrylate adhesive. The tissue mount and fixed mucosa was placed in a beaker and 100 mM phosphate buffered saline (PBS) pH 6.0 was added sufficiently to immerse mount and the tissue. The beaker was placed on a balance, then carefully raised by a mobile platform until the vaginal membrane came in contact with the tablet. The contact was determined when the nylon thread holding the tablet became bent. After a 30-min incubation at 25°C , the mucosa was pulled down from the tablet at a rate of 0.1 mm s^{-1} . Data points were collected every second by a personal computer (WINWEDGE software: TAL Technologies, Philadelphia, PA, USA) linked to the balance. Data were transferred to EXCEL 97 (Microsoft, USA) and the

force–distance curve, i.e., the total work of adhesion (TWA) was calculated. Each experiment was performed six times.

2.6. Release studies and analytical procedure

Release studies with the model drug progesterone were performed. For each tablet, 95 mg of the polymer–cysteine conjugate were hydrated in 15 ml of demineralised water. Following a 30-min waiting, 5 mg of progesterone were added, homogenised and lyophilised. These 100-mg polymer–drug lyophilisates were compressed (Hanseaten Type EI, Hamburg, Germany) into 8-mm diameter flat-faced discs. The tablets were prepared in the same way with the unmodified polyacrylate (NaC974P). Further tablets with microcrystalline cellulose were fabricated. For this purpose, progesterone and microcrystalline cellulose were mixed and directly compressed. The *in vitro* release rate from these drug delivery systems was conducted. The dosage forms were placed in 25-ml beakers (Schott Duran, Germany) containing 20 ml of release medium (100 mM PBS, pH 6.0). The vessels were closed, placed on a shaking water bath (GFL 1092; 100 rev/min) and incubated at $37 \pm 0.5^\circ\text{C}$. Sink conditions were maintained during this study. Aliquots of 2 ml were withdrawn every 30 min for 6 h. The medium was replaced with an equal volume of release medium equilibrated to temperature. Released progesterone was assayed for progesterone content by HPLC (Perkin Elmer, USA).

The samples were assayed for progesterone content at a flow-rate of 1 ml/min with an UV detector (series 200 LC235C, Perkin Elmer) at a detection wavelength of 240 nm. The stationary phase was a Nucleosil 100 5C₁₈ column (240×4.6 mm). Any polymer residues were held back on a pre-column (Nucleosil 100-5C₁₈, 40×4.0 mm). The mobile phase was methanol–water (90:10). Samples (20 µl) were injected by an autosampler (ISS-200, Perkin Elmer). The retention time for progesterone was approximately 4.4 min. Calibration curves were prepared on the basis of peak area measurements. The linearity interval established in the receptor phase was between 0.01 and 54.5 µg/ml ($r^2 = 0.999971$).

2.7. Data analysis

The results are expressed as the mean of 3–6 experiments $\pm$ S.D. as indicated in the text. For statistical data analysis the *t*-test with $P < 0.05$ as a minimal level of significance was used.

3. Results

3.1. Synthesis

The synthesis of the conjugates was mediated by a carbodiimide reaction (Fig. 1). Cysteine was covalently bound to carbopol (NaC974P) by forming amide bonds between the primary amino group of the amino acid and the carboxylic moieties of the polymer. Recently, cysteine has been covalently attached to polycarbophil (PCP), another representative polyacrylate [7]. PCP is an acrylic acid derivative cross-linked by divinyl glycol, whereas NaC974P is cross-linked to a different extent by allyl ethers of either sucrose or pentaerythrol. This explains the changes in the three-dimensional structure of the polymer. The molar ratio of polymer/cysteine varied from 1:1 to 2:1 and 4:1, respectively. The corresponding coupling rates are listed in Table 1. Results demonstrated that the lowest amount of added cysteine led to the highest coupling rate. A reason for this observation can be seen in the increasing concentration of thiol groups, disturbing the carbodiimide mediated coupling reaction. Thiol groups are known to form very stable intermediate products with EDAC which can be only slightly attacked by nucleophiles [14].

3.2. Viscosity

At all times the modified and unmodified polymer gels exhibited a pseudoplastic behaviour, namely a decrease in viscosity at an increasing shear rate. According to our working hypothesis [9], the formation of disulfide bonds can be proved indirectly by measuring the decrease in thiol groups [15] and, consequently, by the increase in viscosity. As we know that thiolated polymers are viscoelastic systems [13], the set up for measuring viscosity was

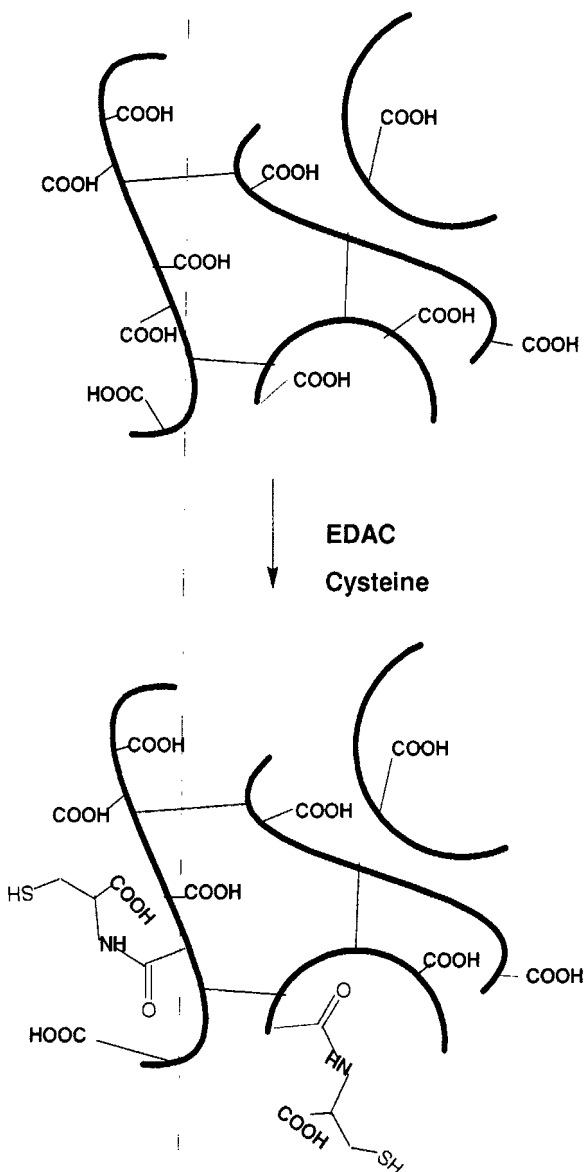


Fig. 1. Scheme of synthesis of NaC974P-Cys conjugates. EDAC = 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride.

done in an oscillatory mode. This means the cone of the rheometer is moved back and forward in a sinusoidal motion. For the thiolated polymer as well as for the control the following parameters were measured as a function of oscillatory frequency (ν , Hz), storage or elastic modulus (G'), loss modulus (G''), $\tan \delta$ and dynamic viscosity (η). The data of polymer-conjugates as well as of controls are pre-

sented in Figs. 2 and 3. G' is a measure for the recoverable energy stored elastically in the system, whereas G'' is a measure for the energy dissipated as viscous flow representing the real and imaginary parts of the complex dynamic shear modulus, respectively. In comparison to the control there is an increase in G' of the thiolated polymers whereas G' of the thiolated polymer is not significantly different (Fig. 2). The increase in G' of the conjugates after 1 h of observation is very high and significant, whereas the control does not show any significant difference in G' values after 1 h. As shown in Fig. 3, the dynamic viscosity of the thiolated polymer gels at an oscillation frequency of 1 Hz is about 1.7-fold higher than of the controls after 1 h. This means that the increase in viscosity is mainly due to the increase in G' , the elastic modulus or storage modulus. $\tan \delta$ is the ratio G''/G' and the dynamic viscosity is defined as G'/ω , where ω is the angular velocity of oscillatory stress, which is related to the oscillatory frequency by the relationship $\omega = 2\pi\nu$. The smaller $\tan \delta$, the higher the elasticity is and vice versa. In general, a value of $\tan \delta$ smaller than one indicates a dominating G' . However, as depicted in Fig. 3 the values of $\tan \delta$ of the control are also smaller than one, demonstrating that the modified as well as the unmodified polyacrylic acid gels are viscoelastic [16]. The covalent attachment of cysteine to NaC974P caused a further decrease of $\tan \delta$ after 1 h as shown in Fig. 3.

The average η values at 1 Hz of three samples were extracted from the resultant graph to allow a comparison between the different materials. However, this approach does not describe the complete viscoelastic characteristics of each sample. A comparison of the decrease in the thiol group content and the viscosity over a period of 4 h (Fig. 4) shows an increase in viscosity only within the 1st h and afterwards the viscosity values remain similar, whereas a further decrease in thiol groups could be observed over the whole examination time.

3.3. Mucoadhesion

Tensile studies carried out with NaC974P-Cys conjugates showed a significant improvement in the total work of adhesion (TWA) compared to the

Table 1
Protocol of the synthesis of NaC974P–Cys conjugates

POLYMER	pH ^a	NaC974P (mg/62.5 ml)	Cyst (mg/ml)	EDAC (mM)	Thiol groups (μmol/g)
NaC974P–Cys 0.3%	5	250	4	50	24.8±9.3
NaC974P–Cys 0.54%	5	250	2	50	45.0±8.4
NaC974P–Cys 0.55%	5	250	1	50	45.8±7.5
Control	5	250	1–4	–	0.0±0.0

^a pH during the coupling reaction.

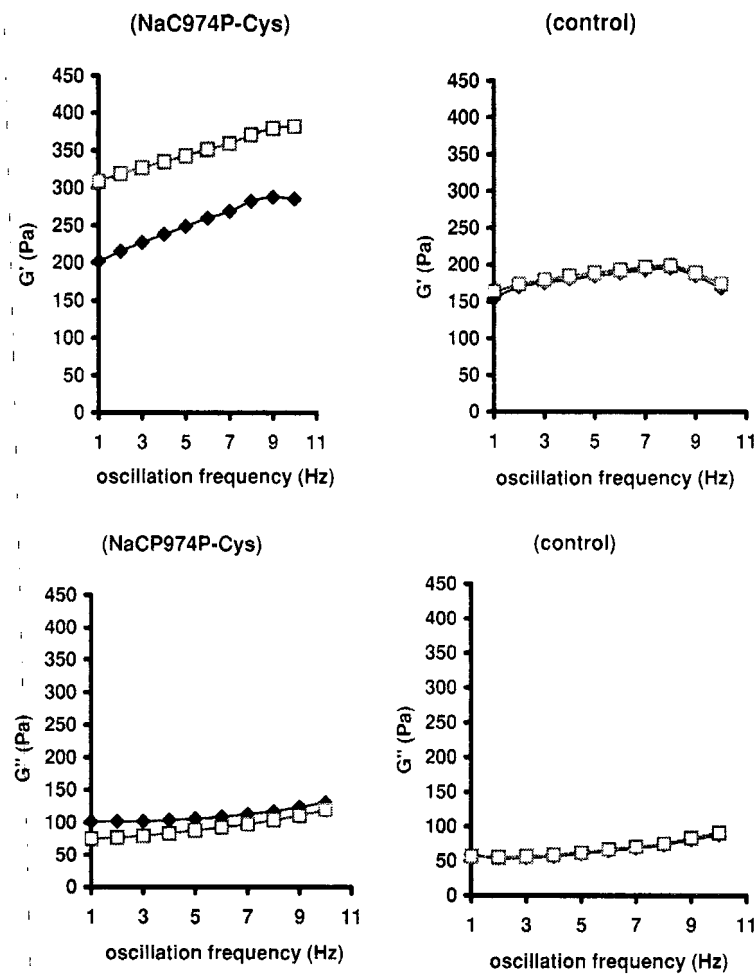


Fig. 2. Comparison of the effect of oscillatory frequency on the storage modulus G' and loss modulus G'' between 3% (w/w) NaC974P–Cys gels and control gels at 37°C. —♦—, Start of measurement at time 0; —□—, measurement after 1 h; data are the means of three experiments.

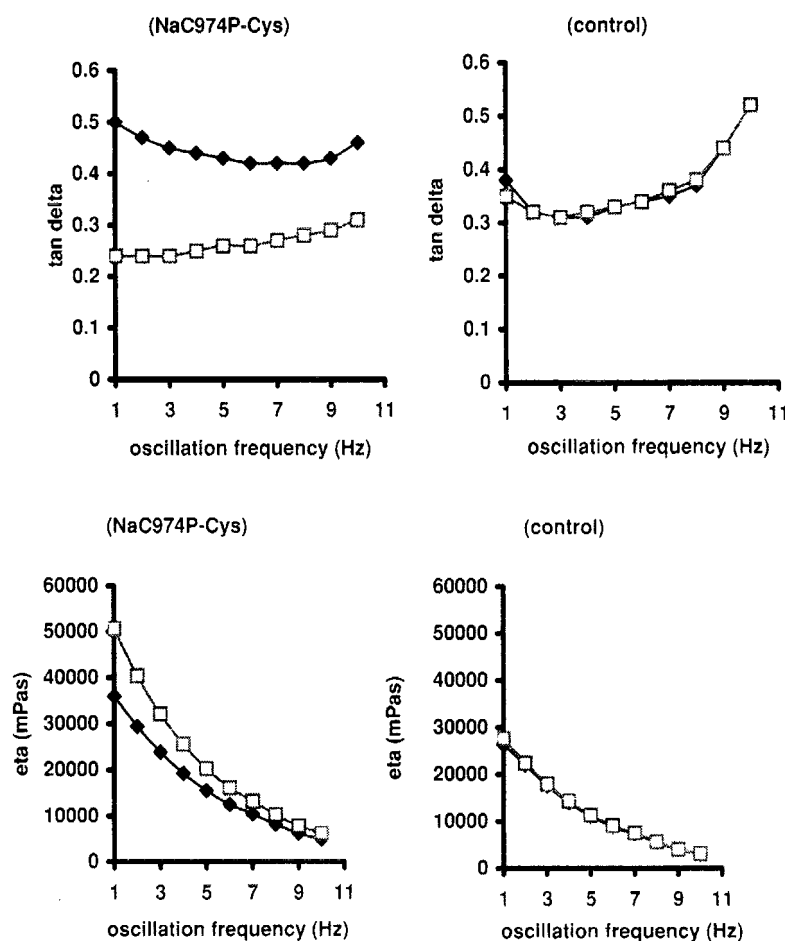


Fig. 3. Comparison of the effect of oscillatory frequency on the $\tan \delta$ and dynamic viscosity η between 3% (w/w) NaC974P-Cys gels and control gels at 37°C. —♦—, Start of measurement at time 0; —□—, measurement after 1 h; data are the means of three experiments.

controls (Fig. 5). The more cysteine was covalently bound to the polymer, the higher the determined TWA was.

3.4. Release studies

A comparison of the release rates from tablets based on the unmodified NaC974P, modified NaC974P-Cys and microcrystalline cellulose is given in Fig. 6. The incorporation of progesterone in both polymer-matrices, modified and unmodified, reduced the initial drug release over 6 h. The release from the NaC974P-Cys tablets was significantly slower than that from the NaC974P- matrix. In order to achieve suitable plasma levels, 30–50 mg of progesterone have to be applied [17]. It would have been possible to prepare 300-mg tablets with 30–50

mg of progesterone but with respect to in vivo studies in rats, we performed the release experiments with 5 mg of progesterone per tablet. Our experiments showed that the covalently bound cysteine caused a higher cohesiveness of the tablet and, therefore, a slow release of the model compound. These results are in good agreement with the disintegration time of the tablets: where the Elcema tablets disintegrated within 5 min, the tablets based on the unmodified polymer needed more than 5 h and the tablets based on the modified polymer required more than 10 h (data not shown). One reason for the slow release may be the possibility of forming disulfide bonds within the tablet so consequently a better cohesiveness is guaranteed. Bioadhesive polymers are hydrophilic macromolecules with substituents capable of forming hydrogen bonds, in

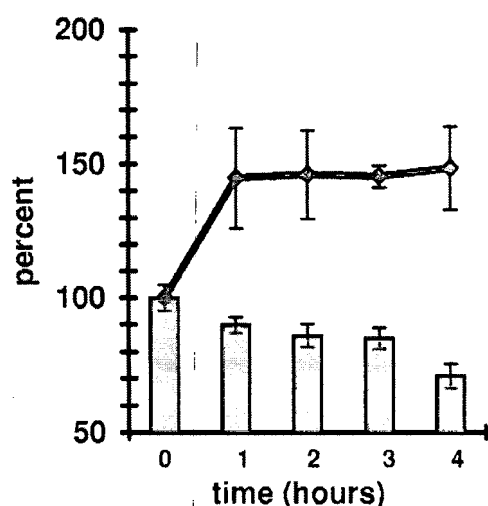


Fig. 4. Decrease in thiol group content indicated as bars versus the increase in viscosity indicated as $-\diamond-$ at 1 Hz at pH 6.0. Values of viscosity or thiol groups at the starting point are indicated as 100%. $N=3$; mean $\pm$ S.D.

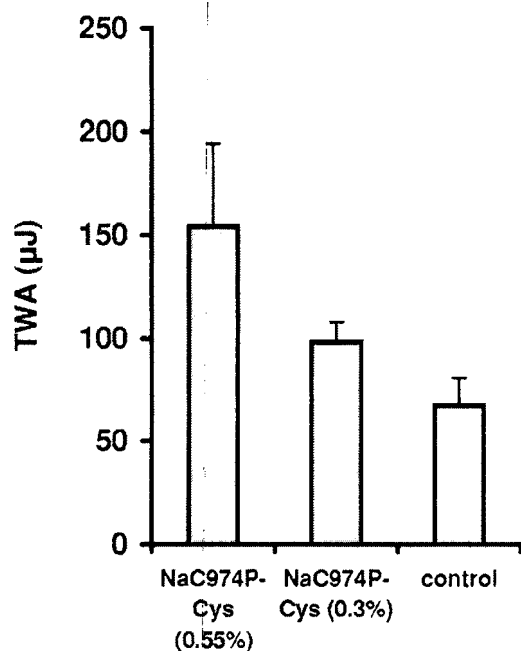


Fig. 5. Comparison of the total work of adhesion (TWA) of the unmodified NaC974P (control) and two different NaC974P-Cys conjugates. Represented values are the mean $\pm$ S.D. ($N=6$) of the TWA determined in tensile studies with compacted discs on freshly excised cow vagina at pH 6.0.

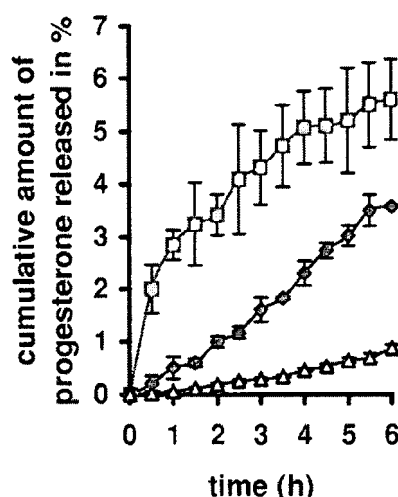


Fig. 6. Release profiles of progesterone from tablets based on $(-\diamond-)$ NaC974P; $(-\wedge-)$ NaC974P-Cys (0.3% thiol groups); $(-\blacksquare-)$ microcrystalline cellulose (Elcema). Studies were carried out in 100 mM PBS, pH 6.0; $N=3$, mean $\pm$ S.D.

particular carboxyl groups, and in our case additional thiol groups are available which stabilise the polymeric network by forming disulfide bonds.

4. Discussion

Cysteine was covalently bound to NaC974P by forming amide bonds between the primary amino group of the amino acid and the carboxylic moieties of the polymer. This modification caused a significant increase in the viscoelastic properties of the swollen polymer. The viscoelasticity of mucoadhesive polymers has a great influence on their adhesive properties and cohesiveness. By adsorbing, swelling and capillary effects, mucoadhesive polymers are supposed to take water from the underlying mucosal tissue leading to a strong adhesion [18]. Progesterone is an interesting compound and has already been administered vaginally. It has been used for many years for a variety of gynaecological problems such as luteal phase defect, premenstrual syndrome (PMS), endometrical hyperplasia, dysfunctional uterine bleeding and endometriosis [17,19]. Also modern infertility treatments have expanded the use of physiological progesterone. However, androgenic activity, inherent in the synthetic compounds limits their use in infertility treatment and for pregnancy

supports due to the possible teratogenic side effects [17]. Natural progesterone shows no androgenic activity and, thus, it is extensively used in assisted reproduction also over a long time period. The major problem with natural progesterone is its route of administration. Oral intake is the most convenient, however, rapid and extensive intestinal metabolism prevents adequate absorption [20]. Moreover, liver metabolism results in metabolites that induce side effects. Intramuscularly injection assures reliable absorption but is related to poor compliance. Therefore, the interest in non-invasive application forms increases. One possible route may be the transdermal route. For this purpose, progesterone was embedded in a matrix system with special adherence to the skin [15]. The problem with the transdermal route is the very high progesterone level, which is required. For this reason, the vaginal route has become the most effective way to deliver natural progesterone. The vaginal mucosa has a good absorption potential. The drug can be administered easily and the first pass metabolism by the liver can be avoided. However, cyclic changes in the histology and physiology of the vaginal mucosa may have an effect on the drug absorption.

Another problem in vaginal delivery is the rapid removal of inserted systems by the normal cervical mucus. Therefore, the vaginal progesterone used in infertility treatment required multiple daily administrations of topical preparations like suppositories. The development of a vaginal gel (Crinone®) with sustained release was a breakthrough in vaginal application systems. Toner [21] showed in a study with 345 women that crinone (8%) administered once or twice a day had the same effect as an i.m. application. Crinone-vaginal gel consists of the mucoadhesive polymer polyacrylic acid. On the other hand, Wilding et al. [22] investigated the vaginal spreading and clearance of a radiolabelled pessary and polycarbophil gel in six post-menopausal healthy female volunteers over a 6-h period of time using the technique of γ -scintigraphy and found in one case 80% retention and in another 2% retention of the product. Therefore, no significant retention could be shown in this study.

There is a possibility that the improved mucoadhesion of tablets consisting of NaC974P-Cys conjugates may lead to a prolonged residence time but this

has to be confirmed by in vivo studies in the near future. As a consequence, satisfactory plasma levels could be achieved which would be of great benefit. Also the aesthetic qualities of the delivery system are important. Leakage of a liquid or semisolid system and permanent problems with parts of disintegrated tablets decrease the compliance of such systems. Recently, dissolution studies of vaginal bioadhesive tablets based on different well-established polymers exhibited good vaginal adhesion on cow vagina [3]. The results of this study showed the highest detachment force of tablets based on HPMC. The swelling behaviour of the tablets containing HPMC lasted 6 h.

We achieved an improved mucoadhesion on the vaginal mucosa as well as an improvement of the cohesiveness of such dosage forms by modifying the polyacrylic acid polymers by a covalent attachment of cysteine.

5. Conclusion

NaC974P-Cys, a thiolated polymer, is a novel matrix for vaginal delivery systems and exhibits the advantage of good cohesiveness within polymer tablets and a good mucoadhesion on cow vagina. In release studies, a controlled progesterone release could be demonstrated from NaC974P-Cys tablets compared to tablets consisting of microcrystalline cellulose or unmodified NaC974P. Hence, this thiolated polymer is a promising candidate as a matrix for vaginal delivery systems exhibiting controlled release properties.

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References

- [1] J.L. Richardson, L. Illum, The vaginal route of peptide and



The use of mucoadhesive polymers in vaginal delivery[☆]

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Abstract

The vagina is an important area of the reproductive tract and serves as a potential route of drug administration. Beside locally acting drugs it is also of importance for systemic drug delivery, uterine targeting or even vaccination. Currently available dosage forms have several limitations, therefore novel concepts and dosage forms are needed. In this field mucoadhesive polymers will play a major role. After discussion of the anatomy and physiology of the vagina this review highlights the most important studies based on mucoadhesive polymer-systems like poly(acrylates), chitosan, cellulose derivatives, hyaluronic acid derivatives, pectin and traganth, starch, poly(ethylene glycol), sulfated polysaccharides, carrageenan, Na-alginate and gelatine. © 2005 Elsevier B.V. All rights reserved.

Keywords: Poly(acrylates); Chitosan; Cellulose derivatives; Hyaluronic acid; Pectin; Traganth; Starch; Sulfated polysaccharides; Carrageenan; Na-alginate

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1. Introduction

Apart from local effective drugs the vagina provides also a promising site for systemic drug delivery, because of its large surface area and rich blood supply [1]. This route of administration offers advantages compared to other routes. Considerable progress has been made in this research area over the past few years and, at present, the anatomy and physiology, microflora and secretions of the vagina are well understood [2]. In contrast the scientific knowledge regarding the possibilities of drug delivery via the vagina is limited. To date, there are only a limited number of vaginal dosage forms available, although various possibilities are presently being explored. The currently available vaginal delivery systems have limitations, such as leakage, messiness and low residence time, which contribute to poor subject or patient compliance. Attempts are being made to develop novel vaginal drug delivery systems that can meet the clinical as well as the requirements of the patients.

However, despite all the advantages of a vaginal application, changes of the membrane during the menstrual cycle and postmenopausal must be taken into account. In postmenopausal women the reduced epithelial thickness may change the original absorption rates of drugs significantly [3]. During the last three decades considerable attention has been focused on the development of novel and controlled delivery

systems providing a long-term therapeutic concentration of drugs following a single dose.

Beside novel drug loaded inserts which are on the market, hydrogel systems with higher retention time are existing. Many drug delivery systems are based on so called 'mucoadhesive' polymers. Mucoadhesion is another version of the bioadhesion because the target is still the underlying tissue. These polymers are able to swell rapidly when placed in aqueous environment and therefore exhibiting a controlled drug release. Since the first presentation of the concept of mucoadhesion, many attempts have been undertaken to improve the adhesive properties of such polymer systems [4–10]. Consequently, the therapeutic efficacy of locally acting drugs can be improved by their increased availability at the target membrane.

Rational design of future formulations need to include attention to vehicle properties that optimise vaginal coating and retention. It should be taken into account that formulations interact with the vaginal fluids and cause changes in viscosity. The interactions depend upon the specific macromolecules which are the thickening agents for gels or important auxiliary agents in tablets. Therefore, these macromolecules, such as poly(acrylates), cellulose-derivatives, chitosan and many others, are very important excipients for future formulations. This review will focus on the various aspects and potential of such mucoadhesive polymers for vaginal drug delivery.

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In addition to being gender specific, the vaginal route is less preferable in terms of convenience depending on the dosage form. Another disadvantage is the influence of the estrogen concentration on the permeability of the vaginal membrane, which can influence the pharmacokinetics of drugs designed for systemic action [38,39]. The amount of vaginal fluid of an adult woman was reported to be in the range of 2–3 g/24 h [40] and this amount is decreasing with increasing age. This volume may also affect the vaginal absorption of drugs. As a drug must be in solution before it can be absorbed the presence of a film of moisture will be an advantage but in contrast to this the presence of a thick cervical mucus may present also a barrier to drug absorption and a very high amount of vaginal fluid may lead to the removal of a dosage form. Finally the pH of the fluid may affect the drug absorption too as it can be supposed that unionised forms will be preferable absorbed.

2.6. Vaginal absorption of drugs

On one hand physiological factors like cyclic changes, thickness and porosity of the epithelium and volume, viscosity and pH of the vaginal fluid and on the other hand physicochemical properties of drugs like molecular weight, lipophilicity and ionization affect the absorption across the vaginal epithelium [15]. Drugs are transported across the vaginal membrane by the transcellular route, intracellular route or vesicular and receptor-mediated transport mechanisms [15]. A physical model of the vaginal membrane as a transport barrier has been described [41]. Moreover, an absorption of drugs targeted for local action in the vagina is not desirable.

2.6.1. Animal models

In a review article different animal models are described [42]. A number of animal models have been employed in the study of vaginal absorption of drugs [43]. Until now studies with mice, rats, rabbits, monkeys, dogs and sheep are performed. The permeability of the different vaginal epithelia may vary. Because of the sufficient availability rodents are used with the disadvantage of significant thickness changes during the oestrus cycle leading to different absorption rates. To overcome this problem, researchers used ovariectomised rats with subsequent hormo-

nal treatment. Only few studies compare different species. The antiviral trisodium phosphonoformate was investigated in dogs and rabbits and the absolute bioavailability after vaginal administration was 14% and 34%, respectively [44] whereas the bioavailability after topical administration was 3% and 12%, respectively. This can be an indication that also the absorption rates of women and animals may differ. Richardson and Illum believe that the sheep is the most promising animal model for the study of vaginal absorption [43].

2.7. Novel concepts in vaginal drug delivery

The composition of vaginal dosage forms will be the focus of interest in the future. Novel forms are liposomes, vaginal rings [45,46], cubic gels [47], formulations based on polystyrene [48] and formulations based on silicone elastomers [49]. One interesting group of auxiliary agents is the mucoadhesive polymers, which are basis of new designed systems [50,51].

3. Mucoadhesive polymers

3.1. Definition of mucoadhesion with respect to the vagina

The target for the interaction of 'mucoadhesive' excipients is the mucus. In higher organisms mucus is a highly viscous product which forms a protective coating over the lining of hollow organs in contact with external media. Mucus is a mixture of large glycoproteins (mucins), water, electrolytes, epithelial cells, enzymes, bacteria, bacterial products and various other materials depending on the source and location of the mucus [52]. Based on the structure of mucin several mechanisms have been proposed to explain the interaction of a mucoadhesive polymer and a biological surface [53,54]. The so-called 'mucoadhesion' is another version of the bioadhesion because the target is still the underlying tissue in our case the vagina. The vaginal epithelium is usually considered to be a mucosal surface, although it has no goblet cells and lacks the direct release of mucin. Some secretions from higher up the tract may reach the vagina via uterine fluid or follicular fluid at ovula-

tion. Vaginal discharge is a mixture of several components including transudates through the epithelium, cervical mucus, exfoliating epithelial cells, secretions of the Bartholin's glands, leukocytes, endometrial and tubal fluids [2,55]. The adhesion work of a bioadhesive system, fixed on a biological tissue like excised cow vagina [8] is a good indicator of its bioadhesive power. Furthermore, it seemed that the testing medium has an influence on the bioadhesiveness [56].

3.2. The cervical mucus

The cervical mucus contains inorganic and organic salts, mucins, proteins, carbohydrates, urea and fatty acids (lactic and acetic acids). Estrogens and sexual stimulation increase vaginal fluid secretion. Wolf et al. [57] analysed the human cervical mucus by collecting from seven donors during the follicular, ovulatory and luteal phases of the ovulatory menstrual cycle. Individual mucus samples were solubilized and fractionated on sepharose columns into excluded mucins and low-molecular-weight proteins. Mucin fractions were highly purified, as evidenced by the presence of a single N-terminal amino acid residue, threonine and by the absence of contaminating plasma proteins. Amino acid compositions of mucins isolated during different menstrual phases of a single donor or from different donors were similar. Mucin carbohydrate compositions were also similar, except for the sialic acid-to-fucose ratio, which varied significantly between donors but not within the menstrual cycle of a single donor. An analysis of variance was applied to evaluate the contribution of mucin composition to viscoelasticity, as quantitated by microrheometry. Viscoelasticity was dependent on the donor, on the percent nondialyzable solids and on the mucin content but not on the phase of the menstrual cycle during which the sample was collected. These findings suggest that mucus function (viscoelasticity) is reflected in carbohydrate composition and/or structure and that this menstrual relationship is unique for each donor. Furthermore, the absence of menstrual phase-dependent differences in mucins suggests that mucin concentration and not composition changes in response to alterations in the hormonal milieu.

Based on these insights other scientific studies deal with artificial mucus. The compositions of such media are based on natural constituents of human vaginal

secretions. In choosing the ingredients for these media, the goal of such work is to reproduce the behaviour of natural cervical mucus that influence drug release and distribution. These synthetic formulations have been developed with viscosity, 'spinnbarkeit' and pH comparable to that reported for human cervical mucus. One formulation [58] contains guar gum crosslinked with borate ion, mucin and a mixed preservative system in pH 7.4 (0.1 M phosphate buffer). The guar gum source, mucin concentration and method of preparation were shown to be critical factors in the performance of the formulation. The combination of the guar gum, sodium borate, and gastric mucin (0.5%) resulted in a viscous fluid that mimicked fresh mucus from a viscosity perspective. The addition of the phosphate buffer achieved a pH of 7.4, similar to that of human cervical mucus. This synthetic cervical mucus is consistent with the reported physical attributes of human cervical mucus [58]. Another composition was developed to simulate the fluid produced in the human vagina [59]. All these experiments are interesting with respect to mucoadhesive drug delivery systems.

The addition of synthetic polymers to cervical mucus with ionic characteristics caused significant changes in the structure of mucus gels when visualized by scanning electron microscopy [60]. Mucin is negatively charged due to the sialic acid residues on the carbohydrate-rich regions of the molecules. While anionic molecules such as poly(acrylic acid) with a molecular weight of 3 000 000 interacted little with the mucin gel (Fig. 2), both poly(ethylene)glycol with a molecular weight of 3350 which is nonionic, and polyvinyl pyridine (molecular weight 40 000) which is cationic, form interactions with mucin, leading to regions with high fiber density. The addition of poly(ethylene)glycol with a molecular weight of 3350 to human cervical mucus caused the formation of fiber patches, where the fibers appeared to coalesce due to hydrogen bonding between poly(ethylene)glycol and mucin. The addition of the cationic polyvinyl pyridine to human cervical mucus had a significant effect on the fiber network. With increasing concentration of poly(vinylpyridine) the fibers appear to aggregate together leaving holes in the fiber network adjacent to regions with very small interfiber spacing (Fig. 3). The fiber aggregation is likely due to electrostatic interactions between the polymer and the mucin.

systems have been utilized for this purpose. The compounds have almost exclusively been delivered to the vaginal epithelium. The presence of a mucus-covered cervix in women provides an opportunity as an alternative for such drug delivery. An obvious application is the delivery of drugs that destroy or render dysfunctional, spermatozoa and pathogens such as viruses and bacteria. In principle, a reservoir of a compound in the cervical mucus could achieve other physiological goals, as well. Katz [61] reported about the critical problem of understanding the mechanisms of drug entry and permeation through the cervical mucus. This problem is only partially understood at present, and salient biophysical concepts are presented which will aid in further studies. He concluded that there are good prospects for improved utilization of the cervical mucus for drug delivery, but that their realization will require improved understanding of the mechanisms of drug transport and bioactivity within the mucus.

3.3. *Polymers*

Several bioadhesive polymers have been reported for different mucosal sites such as the buccal cavity, stomach and intestine [62]. An increasing interest has been shown for vaginal bioadhesive tablets [63]. With respect to their facilitated and shorter registration, the polymers which were already in use as pharmaceutical excipients were tested for their mucoadhesive properties. The necessary assemblies have been designed to measure the bioadhesion characteristics of polymers and formulations in a mucus environment. Smart et al. [64] published a list of mucoadhesive polymers together with a rank order of their mucoadhesive force. Their in-vitro test system consisted of a homogenised mucus which was obtained by scraping guinea-pig intestines. The force required to detach a glass plate coated with the test polymer from this mucus gel was measured. In general the polymers had a high molecular weight and hydrophilic functional groups. Several groups of polymers have been tested as vaginal delivery systems.

3.3.1. *Poly(acrylates)*

In most of the vaginal preparations poly (acrylic acid) derivatives have been used as bioadhesive polymers. A good overview over the pharmaceutical used

acrylic polymers is given by Dittgen et al. [65]. In this review modern applications of poly(acrylates) in pharmacy like in ocular, buccal, vaginal and cervical delivery are adequately discussed. These polymers are the most investigated bioadhesive polymers for vaginal applications.

3.3.1.1 Vaginal dryness The vaginal dryness and pain is a problem of women due to the decreasing hormone levels at the onset of menopause. The use of mucoadhesive gels offers a good alternative to a hormone replacement therapy with a risk of cancer. Several products are on the market. In a study on postmenopausal women, a bioadhesive formulation, Replens[®] gel which consists of 1–3% polycarbophil gel was shown to be retained in the vaginal cavity for 3–4 days [51]. However, contradictory reports were obtained when the same formulation was studied for retention in-vivo in the human vagina by a scintillation method [66]. There was a lack of significant retention of the gel in five out of the six volunteers studied. The lack of significant retention of these products in most of the volunteers was rather disappointing. Moreover γ -scintigraphy is an unrenounceable technique to assess novel formulations with optimised long lasting retention in the vagina for topical or systemic drug delivery [67].

Another study was designed to compare the vaginal deposition and moisturization of two vaginal moisturizers. Summer's Eve[®], based on pectin, and Replens[®], based on polycarbophil, in a double-blind crossover study design. Fifty-one female patients were each randomly assigned to one of two treatment groups. After a 1-week washout period, the products were used for 2 weeks. After another 1-week washout period, product assignments were switched. Colposcopy examinations were performed at the beginning and at the end of each product use. Of the forty-seven patients completing the study 87% were found to have no vaginal residue after Summer's Eve vaginal moisturizer, while only 53% were found to have no vaginal residue after using Replens vaginal moisturizer. No difference in relief of vaginal dryness or in product acceptance was found between the two products. This study showed that the use of Summer's Eve[®] vaginal moisturizer, based on pectin, resulted in significantly less vaginal residue compared to Replens[®] vaginal moisturizer, based on polycarbo-

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carbophil. Based on the balance between the mucoadhesiveness and syringeability, mixtures composed of different ratios poloxamer 407/poloxamer 188/polycarbophil had good properties. In vitro sustained release of clotrimazole from the mucoadhesive preparation was observed. In vivo antifungal activity of clotrimazole which was tested against *Candida albicans* vaginitis in female rats was significantly prolonged after vaginal delivery by this mucoadhesive system. At 10 days post-dose, the c.f.u. (colony forming units) of *C. albicans* was more than 10^4 -fold decreased in the mucoadhesive treated groups. Moreover, the vaginal delivery of clotrimazole enhanced the viability of epithelial cells without affecting the morphology of vaginal mucosa. These results indicate that clotrimazole containing vaginal mucoadhesive systems can be further developed for safe, convenient, and effective treatment of vaginal candidiasis with reduced dosing interval [86].

3.3.1.5. Systemic drug delivery via the vagina. A big problem in vaginal drug delivery is the rapid removal of inserted systems by the normal cervical mucus. Therefore, vaginal progesterone used in infertility treatment required multiple daily administrations of topical preparations like suppositories. The development of a vaginal gel (Crinone[®]) with sustained release was a breakthrough in vaginal application systems. Toner [87] showed in a study with 345 women that administered Crinone (8%) once or twice a day had the same effect as an i.m. application. Crinone-vaginal gel consists of the mucoadhesive polymer polycarbophil. In comparison of Utrogest[®] capsules, which were originally designed for oral administration but are used routinely as a vaginal preparation, with this new preparation Crinone[®] in a prospective randomized study, Crinone[®] 8% had a clear advantage over Utrogest[®] as it resulted in less vaginal discharge and fewer application difficulties. In this study a number of patients noted that Crinone[®] 8% was easier to apply and less time consuming to use than Utrogest[®] [88]. Studies of Casanas-Roux et al. in postmenopausal women [89] suggest that the sustained release effects of Crinone[®] are clinically relevant. Contradictory to this Brown et al. [90] investigated the vaginal spreading and clearance of a radiolabelled pessary and polycarbophil gel in six postmenopausal healthy female volunteers over a 6-h per-

iod of time using the technique of γ -scintigraphy and found in one case 80% retention and in another 2% retention of the product thus no significant retention could be shown in this study.

One possibility to improve mucoadhesion is the use of thiolated poly(acrylates) which are synthesised e.g. of carbopol 974P by coupling with cysteine. These conjugates used for vaginal tablets provided a prolonged residence time in-vitro on cow vagina [8]. The tablet-cohesiveness could be tremendously increased and subsequently also the disintegration time. The release of progesterone was retarded compared to the unmodified polymer. Because the tablet remains as one piece, the women would have no problems with parts of disintegrated tablets in the vagina. Therefore the compliance should be improved.

Beside the hormones, peptide and polypeptide drugs are interesting groups for possible vaginal delivery. One representative is the luteinizing-hormone-releasing hormone (LH-RH), which act on the ovaries to enhance the secretion of steroids and facilitate ovulation. Richardson and Illum summarized the data about vaginal absorption [43].

Han et al. [28] tried to find a rational dosage form for vaginal mucosal delivery of LH-RH. Vaginal absorption of LH-RH was estimated by measuring its ovulation inducing effect in rat and in vitro vaginal membrane permeation study in the rabbit. The effects of different hydrogel bases, such a polycarbophil and pemulen (polymeric poly(acrylates)) compared with solutions on vaginal membrane permeation of LH-RH were investigated. Additionally peptidase inhibitors like sodium laurate, disodium-EDTA and sodium tauro-24,25-dihydrosusidate were added to a LH-RH hydrogel delivery system and LH-RH solutions. A polycarbophil hydrogel formulation showed 3.4 times increase in LH-RH vaginal membrane permeability compared with a solution formulation. Vaginal membrane permeability from the polycarbophil was greater than that from pemulen hydrogels. This may be due to the large bioadhesive values. The results suggest that the enzyme inhibition effect of the used peptidase inhibitors can result in substantial enhancement of vaginal absorption. By administration of polycarbophil hydrogels containing LH-RH the ovulation inducing activity was 3.3 times greater than the solutions. The bioadhesive hydrogels as well as pep-

tidase inhibition significantly improved absorption of LH-RH. The ovulation inducing activity of polycarbophil hydrogel containing LH-RH was comparable with s.c. administration in ovulation inducing activity.

The release rates of LH-RH from tablets based on carbopol 974P-cysteine conjugate showed also a retardation [9] like with progesterone. One explanation for the slow release rates may be the formation of disulfide bonds during the swelling which cause a higher cohesiveness. Due to the results the carbopol 974P-cysteine proved to be interesting as tool for the vaginal administration of (poly)peptide drugs. An improved inhibitory activity towards vaginal membrane bound aminopeptidase N could be additionally achieved by carbopol 974P-cysteine. Inhibitory effects towards other metalloproteases being present on vaginal tissue may be possible [9].

Insulin has been administered over different routes of application like transdermal, nasal and also vaginally. For systemic delivery, insulin suspended in a poly(acrylic acid) gel base was observed to facilitate the rate of vaginal absorption in diabetic rats and rabbits. When insulin was administered via the vagina in the gel preparation, (0.1%, pH 6.5) to rats and rabbits, plasma insulin reached a peak and hypoglycemic effects were observed. However, plasma insulin quickly diminished after 1 h and levels returned to normal after 3 h [91].

3.3.2. Chitosan

In contrast to the poly(acrylates) chitosan is a natural polycationic copolymer consisting of glucosamine and *N*-acetylglucosamine units. It is mostly obtained by deacetylation of chitin derived from the exoskeleton of crustaceans. Chitosan has valuable properties as a biomaterial because it is considered to be biocompatible, biodegradable and non-toxic [92]. The cationic character and the potential functional groups make it an attractive biopolymer for many biomedical and pharmaceutical applications. As a pharmaceutical excipient, chitosan has been used in various formulations, like powders, tablets, emulsions, and gels. Furthermore, a controlled release of incorporated drugs can be guaranteed [93,94]. Chitosan also shows mucoadhesive properties and antimicrobial activity [95,96].

The use of natural polymers is valuable based on proven biocompatibility and safety. Chitosan pos-

sesses favorable properties and hence has applications in the pharmaceutical and biomedical fields [97,98]. It is a promising bioadhesive material at physiological pHs. This polymer possesses OH and NH₂ groups that can give rise to hydrogen bonding. These properties are considered essential for mucoadhesion [99,100]. Moreover, chitosan is suited for repeated adhesion, since it did not become inactivated after the first contact and no drop in mucoadhesion resulted [101]. A general observation is the sustained release behavior of chitosan at a concentration of 50% of tablet weight [102,103]. Formation of interpolymer complexes of chitosan with alginate and sodium carboxymethylcellulose (CMC) was investigated [104,105]. Meshali and Gabr reported that drug release from in situ polyion complexes affords more sustained effect than the preformed complexes [106]. Polymer blends can combine attributes of different polymers to give a superior quality for the dosage form. Moreover, polyionic interaction of chitosan with anionic polymers will permit a considerable reduction of chitosan concentration in tablet [107].

One study accounts for the possible use of chitosan in mixtures of different ratios with anionic polymers for the preparation of mucoadhesive tablets to be used as a vaginal delivery system for metronidazole [108].

By the introduction of thiol groups to chitosan the mucoadhesive properties could be strongly improved while maintaining its biodegradability [109]. Chitosan was thereby modified by attaching thioglycolic acid (TGA) onto the primary amino groups of the polymer via an amide bond formation [10]. The excellent bioadhesion could result in an increased residence time of a drug at the site of absorption by interacting with the mucosa [110,111]. As chitosan is also known to exhibit antimicrobial activity the chitosan-TGA conjugate would be ideal as a matrix for the mainly cationic antimycotics for treating mycotic infections in the vagina. A common microbial problem in the vulvovaginal tract is the infection with *C. albicans* [112]. Approximately 75% of women will have a vaginal infection with a *Candida* strain during their life and about 40–50% of them will suffer a second one and a small percentage will show a chronic course [113]. By the introduction of thiol groups the bioadhesive properties of chitosan could be significantly improved. The addition of clotrimazole led thereby to a further increase in bioadhesion on mucosal tissue.

Due to the immobilisation of thiol groups, the cohesive properties of the polymeric carrier matrix were strongly improved, avoiding an irritating vaginal secretion of eroded polymer fragments. A dependence on the amount of covalently attached thiol groups to the controlled release of clotrimazole was shown. The improved bioadhesive and cohesive properties of tablets comprising chitosan-TGA conjugates in combination with the controlled release of clotrimazole are promising vehicles for vaginal dosage forms in the treatment of genitourinary infections. Furthermore chitosan-4-thio-butyl amidin-conjugates (chitosan-TBA) could be of advantage for mucoadhesive vaginal drug delivery systems [114].

3.3.3. Cellulose-derivatives

Within the listed polymers displaying mucoadhesive properties especially sodium carboxy methylcellulose had excellent mucoadhesive properties [64].

Gynol II, a contraceptive Jelly[®], contains sodium carboxymethylcellulose as a mucoadhesive polymer and is used as a spermicidal contraceptive in conjunction with barrier methods of contraception.

In many studies cellulose derivatives were compared to poly(acrylates) and found to be almost equivalent compared to them. El-Kamel et al. compared the dissolution rates of metronidazole vaginal tablets based on sodiumcarboxymethyl-cellulose (NaCMC), methylcellulose (MC), hydroxypropyl-methylcellulose (HPMC) and HPMC/NaCMC mixtures and Carbopol 934, in different ratios. Following rank order of drug dissolution rates was obtained for the single polymer tablets in water: MC > NaCMC > Carbopol > HPMC. Swelling studies indicated an increase in swelling and mucoadhesion and gave the same rank order. Adhesion behavior of tablets prepared from NaCMC/HPMC (2:1) was intermediate between that of NaCMC and HPMC tablets. Generally, the presence of drug increased the adhesiveness of the formulation [115]. In comparison of the cellulose derivatives with carbopol they can be valuable alternatives.

In another study bioadhesive acyclovir vaginal tablets were prepared by using poly(acrylic acid), methylcellulose (MC), carboxymethylcellulose (CMC), hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC) as bioadhesive polymers in different concentrations by direct com-

pression and wet granulation techniques. The swelling behavior of these vaginal tablets in distilled water and lactic solution, the acyclovir release rate in lactic solution and bioadhesion to cow vagina were investigated. Swelling of the tablets containing HPC, CMC and MC was very rapid and caused disintegration of the tablets. The swelling behavior of the tablets containing HPMC lasted 6 h in lactic acid solution. The maximal detachment force from the vaginal tissue was found to depend on the concentration and type of the bioadhesive polymer. The tablets containing HPMC needed the highest detachment force [4].

New dosage forms for the antimycotic clotrimazole were developed by including bioadhesive polymers (polycarbophil, HPMC, and sodium hyaluronate) into pessaries made of semisynthetic solid triglycerides. These polymers hold the delivery systems in the vaginal tract for a few days without any toxic effects or important physiological modifications, prolonging the permanence of the drug on the vaginal mucosa. The technology controls demonstrated that the presence of the polymers did not have any influence on the characteristics of the pessaries. On the other hand, an increased adhesion of the pessaries with increased concentration of mucoadhesive polymers could be measured in an *in vitro* test. The mucoadhesive affected the drug permanence by modification of the drug distribution along the simulated application site. In conclusion, the development of new formulations showed good technological and adhesion properties and a sufficient adhesive power of the dosage form on the target site. Among the employed bioadhesive polymers, the best behavior in the performed test was by polycarbophil at its maximum concentration [116].

The absorption rates of released PGE₂ (prostaglandin E₂) from vaginal tablets, gel and pessary bases in 27 patients have been measured by means of serial plasma 15-keto-PGE₂ levels. The results showed a good absorption of MC-gels [117].

MacKenzie et al. compared the diffusion rates of prostaglandin E₂ of different viscous solutions used in clinical practice for inducing abortion. Of those which are currently in use, dextran solutions seem to be more appropriate since the prostaglandin release was almost linear over 2 h while release from NaCMC was more rapidly as the release from methyl hydroxyethyl cellulose. By increasing the viscosity it would be possi-

ble to improve the vaginal retention and with it the clinical results. A slow sustained linear release of prostaglandin could be achieved by the combination of different polymers [118].

A topical disk-like dosage form for treatment of cervical carcinoma was prepared by direct compression of a mixture of bleomycin-HCl and the combination of hydroxypropyl cellulose and carbopol. In a clinical study the released amount of bleomycin-HCl increased dramatically from this formulation. In 3 of 9 patients no cancerous focus was found after local therapy using 90–195 mg bleomycin-HCl and the remaining foci found in the other 6 patients were very few. Moreover, the normal mucosa was not affected by bleomycin-HCl [119].

Many patents dealing with similar application have been patented, e.g. an amoxicillin-containing vaginal tampon-like device was developed containing semi-synthetic glycerides (Suppocire AS2) HPMC and diethylene glycol monoethyl ether (Transcutol) [120]. An almost identical preparation from the technological point [121] except of the active compound has been reported for the intravaginal administration of bisphosphonates. They are used for treatment of osteoporosis and related bone and skeleton diseases and for prevention of bone breakdown and loss of bone mass and strength.

3.3.4. Hyaluronic acid and derivatives

Hyaluronic acid microspheres as vaginal drug delivery systems are suggested for the systemic delivery of calcitonin by the vaginal route [5]. A further development of such microspheres were based on hyaluronan esters. They have been evaluated as a novel delivery system for the vaginal administration of salmon calcitonin. Acute vaginal administration of the hyaluronan-microspheres resulted in pronounced hypocalcaemia in rats [122] and daily administration for 2 months was shown to prevent bone loss in a rat model for osteoporosis [123]. Quantification of the extracted peptide *in vivo* confirmed that the biological activity of salmon calcitonin was unaffected by the microsphere preparation process [5].

A combination of hyaluronic acid and HEC can repair vaginal dryness to some extent [124]. One interesting use of hyaluronic acid is in combination with the Doederlein's bacillus in order to normalize the bacterial flora. The advantage of formulating with

hyaluronic acid could be a higher retention and a more effectiveness of the Doederlein's bacillus [125].

3.3.5. Pectin and tragacanth

One interesting patent deals with an aqueous solution for a vaginal douche consisting of a fungicidal fungistatic drug, a surfactant as a penetrating agent, and/or a bioadhesive gum such as tragacanth, pectin, dextran and xanthan to hold the drug to the vaginal wall. Thus, a solution contained ketokonazole, pectin, nonyl phenol-9 and polyethylene glycol [83].

From sixteen different formulations based on bioadhesive polymers for vaginal delivery the highest bioadhesive strength, the highest swelling volume and the lowest pH reduction were obtained with a bioadhesive tablet consisting of a mixture of carbopol 934 and pectin 2:1 [126].

3.3.6. Starch

Insulin was administered vaginally to sheep as an aqueous solution and as a lyophilized powder within bioadhesive starch microspheres [15]. The effect of lysophosphatidylcholine (LPC) on the vaginal absorption of insulin from both formulations in the sheep was studied. While the vaginal absorption of insulin from insulin solution was minimal, the addition of LPC resulted in a rapid rise in plasma insulin and a pronounced fall in plasma glucose levels. The absolute bioavailability of the peptide from the latter solution was 13%. The hypoglycemic response to vaginally administered insulin was also improved using the microsphere delivery system, compared to insulin solution alone, and was further enhanced by LPC. Vaginal absorption of insulin from each formulation appeared to be influenced by the estrous cycle and was thought to correlate with changes in vaginal histology [15]. To increase the bioavailability additional absorption enhancers were co-administered [127].

3.3.7. Poly(ethylene glycol)

The use of poly(ethylene glycol) offers a number of possibilities for controlled drug release in dependence of physical properties such as molecular weight (3000–8000), specific hydrates and changing diffusion coefficient of crystalline/rubbery hydrogels which affect the diffusion of drugs through the water swollen matrix and across the polymer boun-

dary. The advantage of starting with a dry, drug-impregnated polymer is to obtain the desirable zero order release rate. Drugs have been classified into five groups showing different release profiles. The effects of design and loading on the release profile are described presenting the first clinical results of morphine loaded hydrogel suppositories [128].

Another interesting group of vaginal applications are polymer vaginal pessaries. Although the quantitative bio(muco)adhesiveness of polyethylene glycol was quoted as poor [64], Graham et al. reported a hydrogel prepared from polyethylene glycol 600 providing constant release rates for prostaglandin E2 (PGE2). The polymer was almost colorless, opaque, tough and could be swollen by solvents. Polymer vaginal pessaries containing 10 mg PGE2 released >90% PGE2 during 24 h [129,130].

A further development for such a PGE2 containing system was a crosslinked polymer from PEG 8490, 1,2,6-hexanetriol and dicyclohexylmethane 4,4'-diisocyanate. For in vitro release studies vaginal pessaries were prepared containing trace amounts of radioactive PGE2. Many factors such as the molecular weight of PEG, hydrogel preparation, crystallinity, degree of crosslinking, device geometry and drug solubility affected the diffusion within the gel and across the gel water boundary. Radioimmunoassay showed that PGE2 was stable for >12 months at 4 °C when incorporated into the pessaries [131].

3.3.8. Sulfated polysaccharides

The inhibitory effects of polyanionic substances on the replication of herpes simplex virus (HSV) and other viruses were reported almost four decades ago. However, these observations did not generate much interest, because the antiviral action of the compounds was considered to be largely nonspecific. Shortly after the identification of human immunodeficiency virus (HIV) as the causative agent of the acquired immune deficiency syndrome (AIDS) in 1984, heparin and other sulfated polysaccharides were found to be potent and selective inhibitors of HIV-1 replication in cell culture. Since 1988, the activity spectrum of the sulfated polysaccharides has been shown to extend to various enveloped viruses, including viruses that emerge as opportunistic pathogens (e.g., herpes simplex virus (HSV) and cytomegalovirus (CMV) in immunosuppressed (e.g., AIDS) patients. As potential

anti-HIV drug candidates, sulfated polysaccharides offer a number of promising features. They are able to block HIV replication in cell culture at very low concentrations without toxicity. Furthermore, experiments carried out with dextran sulfate samples of increasing molecular weight and with sulfated cyclodextrins of different degrees of sulfation have shown that antiviral activity increases with increasing molecular weight and degree of sulfation. A sugar backbone is not strictly needed for the anti-HIV activity of polysulfates because sulfated polymers composed of a carbon-carbon backbone have also proved to be highly efficient anti-HIV agents in vitro. Because polysulfates effectively inhibit cell-cell adhesion, polysulfates may be considered as potentially effective in a vaginal formulation to protect against HIV infection. The sulfated polysaccharides have also mucoadhesive properties and therefore these derivatives are very promising candidates for such vaginal systems [132].

3.3.9. Carrageenan

One representative of sulphated polymers is carrageenan. Carrageenan, a compound used in foods from ice cream to soup, is derived from red seaweed. Although the carrageenan-based products are slightly microbicides, they do not actually kill microbes. Rather, they avert infection by binding to the surface of the virus, thus preventing the microbes from adhering to cells and infecting them. Scientists found that products containing both carrageenan and nonoxonyl-9 prevented the vaginal transmission of herpes simplex virus-2 (HSV-2) more effectively than did products with either of these compounds alone. The researchers used HSV-2 because of its similarity to HIV. Like HIV, HSV-2 is an enveloped virus. Some viruses build up in cells until the cells burst and they escape. In contrast, enveloped viruses exit cells by pinching off and inhabiting a small bubble, or envelope, of cell membrane. The researchers speculate that formulations protective against one enveloped virus will be protective against others. When tested vaginally in mice, formulations containing both carrageenan and N-9 effectively prevented infection. Products with carrageenan alone were less effective, and over-the-counter spermicides containing N-9 were least effective. Formulations containing N-9 were much more effective when the virus was introduced into the vagina 5 min after microbicide

treatment, rather than 3 h after treatment. The researchers speculated that N-9 might damage the vagina over the 3-h period, allowing for easier infection. Formulations containing carrageenan alone retained most of their efficacy over 3 h. The carrageenan-based nonoxynol-9 formulation may provide a greater degree of protection from vaginal transmission of both HSV-2 and HIV than currently available nonoxynol-9-containing spermicides [133,134]. Besides being safe, cheap, and widely available, carrageenan is effective over a wide pH range. Carrageenan retains its properties at high temperatures and remains effective for hours within the vagina. Finally, carrageenan is not absorbed by the body, and therefore should cause no systemic side effects.

The findings of Perotti et al. suggest that carrageenan formulations block cell trafficking of macrophages from vagina and that blocking does not result from cytotoxicity. They conclude that blocking cell trafficking may help to prevent sexual transmission of HIV [135].

Results of a Phase I trial of the safety of a formulation containing 2% iota-carrageenan indicate that a 5 mL 2% gel formulation of iota-carrageenan is not associated with significant irritation of the female reproductive tract when administered once daily in the absence of sexual intercourse. Preliminary in vitro results suggest that vaginal formulations of sulfated polysaccharides have the potential to block mucosal HIV transmission [136].

3.3.10. *Na alginate*

The effects of delivery of gel pH and osmolarity on both the mass transport and 'biodiffusion' of the spermicide nonoxynol-9 (N-9) in bovine cervical mucus were evaluated. Delivery gels were alginate crosslinked with calcium chloride containing 3% N-9 and were manufactured over a pH range of 3.4–5.9 and a different osmolarity. Mass transfer parameters (diffusion coefficients and total drug loading) were determined using an UV spectrophotometric technique while biodiffusion (the diffusion distance into mucus at which sperm are killed) was assessed using the Double Ended Test [137]. It was found that delivery gel pH had a significant effect on spermicidal efficacy of the alginate-N-9 system; biodiffusion increased with decreasing pH. Actual N-9 diffusion into mucus was found to be influenced by

both the delivery gel pH and osmolarity. At high N-9 concentration (near the gel/mucus interface) mass transport tended to decrease with decreasing pH at the highest osmolarity. At low concentration, mass transport tended to decrease with increasing osmolarity and decrease with increasing pH at the highest osmolarity. The difference between low and high concentration behavior can be attributed to N-9 micelle formation. These findings are interpreted in the context of the design of intravaginal drug delivery vehicles for spermicides [138].

3.3.11. *Gelatine*

From a historical point of view it can be said, that the old vaginal forms which were based on gelatine can be seen as the first mucoadhesive systems. To date gelatine capsules with different drug loading and additional mucoadhesive polymers inside the capsules have been suggested [139,140].

4. Conclusion

Mucoadhesive polymers are very promising candidates for systemic and local vaginal drug delivery. There is still ongoing research dealing with muco (bio)adhesive vaginal formulations that are capable of delivering the active agent for an extended period at a predictable rate. To date most of the existing dosage forms are based on the synthetic poly(acrylates) but in the near future natural compounds such as chitosan or carrageenan and new derivatives will gain more significance.

Acknowledgements

Figs. 3 and 4 are reprinted from *Biomaterials*, Vol. 22, R.K. Willits, W.M. Saltzman, Synthetic polymers alter the structure of cervical mucus, pp. 449, Copyright (2001) with permission from Elsevier.

Fig. 4 is reprinted from *Vaccine*, Vol. 21, O. Yu-Kyoung, P. Jeong-Sook, Y. Ho, K. Chong-Kook, Enhanced mucosal and systemic immune responses to a vaginal vaccine coadministered with RANTES expressing plasmid DNA using in situ-gelling mucoadhesive delivery system, pp 1985, Copyright (2003) with permission from Elsevier.

Comprimidos bucales y sublinguales. Son pequeños, aplanados y ovales. Los destinados a la administración oral, una vez en la boca se disuelven o se deshacen lentamente; han sido formulados y comprimidos con una presión suficiente, como para que la tableta sea dura. Los comprimidos de progesterona pueden administrarse de este modo. Algunas propuestas modernas utilizan los comprimidos que funden a la temperatura corporal. La matriz de los comprimidos está solidificada, mientras que la droga está en solución. Después de fundirse, la droga queda automáticamente en solución y es disponible para la absorción; se elude así la disolución, un paso limitante de la velocidad de absorción de compuestos poco solubles. Los comprimidos sublinguales, como aquellos que contienen nitroglicerina, clorhidrato de isoproterenol o tetrani-trato de eritritol, se colocan debajo de la lengua. Los comprimidos sublinguales se disuelven rápidamente y las drogas se absorben fácilmente con esta forma de administración.

Comprimidos moldeados o comprimidos triturados (CT)

Los comprimidos triturados se elaboran con material húmedo, utilizando un molde triturador que le otorga la for-

ma de las secciones de corte de un cilindro. Tales comprimidos deben ser completa y rápidamente solubles. El problema más común en la fabricación de estos comprimidos es la dificultad para encontrar un lubricante que sea completamente soluble en agua.

Comprimidos de dispensación (CD). Estos comprimidos proporcionan una cantidad conveniente de droga potente que se puede incorporar con facilidad en los polvos y en los líquidos, evitando así la necesidad de pesar cantidades pequeñas. También han sido convenientes para los compuestos extemporáneos y nunca deben venderse como formas farmacéuticas.

Comprimidos hipodérmicos (CH). Los comprimidos hipodérmicos—blandos y fácilmente solubles—primero fueron utilizados para preparar soluciones inyectables. Dado que en la actualidad se dispone de soluciones parenterales estables para la mayoría de las drogas, no se justifica el uso de comprimidos hipodérmicos para inyectables; además, su uso debería prohibirse ya que las soluciones resultantes no son estériles. Grandes cantidades de estos comprimidos se continúan elaborando, pero para administración oral. Los comprimidos hipodérmicos nunca han sido reconocidos por los compendios oficiales.

Comprimidos

Con el objeto de que las sustancias medicinales, con diluyentes o sin ellos, puedan elaborarse en formas farmacéuticas sólidas con presión, utilizando un equipamiento adecuado, es necesario que el material, ya sea en polvo o en la forma cristalina, posea determinadas características físicas. Estas consisten en capacidad de fluir libremente, cohesividad y lubricación. Los componentes como los desintegradores, destinados a disgregar los comprimidos en los líquidos intestinales, y los polímeros de liberación controlada, que lentifican la liberación de la droga, idealmente deben poseer estas características o no interferir en la acción de los otros excipientes. Dado que la mayoría de los materiales no tienen esas propiedades o a lo sumo poseen una, se han desarrollado métodos de formulación y preparación de comprimidos para impartir estas características desea-

bles a los materiales que van a comprimir para hacer comprimidos.

La unidad mecánica básica de todos los equipos de compresión está constituida por un punzón inferior, que encaja en un molde matriz en el fondo, y un punzón superior, con una cabeza de la misma forma y dimensiones, que entra en la cavidad de la matriz en el tope después que ésta se llenó con el material a comprimir (véase fig. 92-2). El comprimido se forma por la presión aplicada sobre los punzones y después es eyectado de la matriz. El peso del comprimido está determinado por el volumen del material con el que se llena la cavidad de la matriz. Por eso, la capacidad de la granulación para fluir con libertad a la matriz es importante, para asegurar el llenado uniforme y el movimiento continuo de la granulación desde la fuente de alimentación o tolva. Si la granulación del comprimido no posee propiedades cohesivas, después de la compresión éste puede desmenuzarse y deshacerse al manipularlo. Como los punzones pueden moverse libremente dentro de la matriz y el comprimido debe eyectarse con facilidad de las caras del punzón, el material debe tener cierto grado de lubricación que minimice la fricción y permita la remoción de los comprimidos compactados.

Hay tres métodos generales para preparar comprimidos: el de granulación húmeda, el de granulación seca y el de compresión directa. Los métodos de preparación y los componentes agregados se seleccionan para conferir a la fórmula del comprimido las características físicas convenientes para la rápida compresión de éstos. Después de ella, los comprimidos de-

ben tener ciertas propiedades adicionales, como aspecto, dureza, capacidad de desintegración, características de disolución apropiadas y uniformidad, las que también están influidas por el método de preparación y por los materiales agregados a la formulación. En la preparación de los comprimidos compactados, quien los formula debe conocer el efecto que los componentes y los métodos de preparación tienen sobre la disponibilidad de los componentes activos y, por consiguiente, la eficacia terapéutica de la forma farmacéutica. En respuesta a una solicitud de los médicos para cambiar un comprimido de dicumarol por otro pudiera romperse más fácilmente, una compañía de Canadá lo reformuló para hacer un comprimido grande con una ranura. El uso posterior del comprimido, con la misma cantidad de droga que el anterior, dio como resultado demandas en las que se argumentaba que eran necesarias dosis mayores que las habituales para producir la misma respuesta terapéutica. Por otra parte, las comunicaciones bibliográficas indican que la reformulación de un comprimido comercial de digoxina dio como resultado un comprimido que, si bien poseía la misma cantidad de droga, daba la respuesta clínica deseada con la mitad de su dosis original. Los métodos y principios que pueden utilizarse para determinar los efectos de los excipientes y aditivos en la absorción de las drogas han sido revisados.^{2,14,15} Véanse los capítulos 35, 42 y 83.

Componentes de los comprimidos

Además del componente activo o terapéutico, los comprimidos contienen una cantidad de materiales inertes conocidos como aditivos o *excipientes*. Estos pueden clasificarse de acuerdo con su papel en el comprimido terminado. El primer grupo contiene aquellos materiales que contribuyen a impartir características de procesamiento y compresión satisfactorias a la formulación: diluyentes, aglutinantes, deslizantes y lubricantes. El segundo grupo ayuda a brindar las características físicas deseadas a los comprimidos terminados. En este grupo están los desintegrantes, los colorantes; en el caso de los comprimidos masticables, los agentes saborizantes y edulcorantes, y en el de los comprimidos de liberación controlada, los polímeros o ceras, u otros materiales que retardan la disolución.

Aunque el término *inerte* ha sido aplicado a estos materiales, es cada vez más evidente que hay una importante relación entre las propiedades de los excipientes y las formas farmacéuticas que los contienen. Los estudios de preformulación demuestran su influencia sobre la estabilidad, la biodisponibilidad y el proceso de preparación de las formas farmacéuticas. La necesidad de adquirir más información y el uso de patrones para los excipientes fue reconocida en un esfuerzo conjunto de la Academia de Ciencias Farmacéuticas y el Consejo de la Sociedad Farmacéutica de Gran Bretaña (la Academy of Pharmaceutical

Sciences y el Council of the Pharmaceutical Society of Great Britain). El resultado es el denominado *Manual de Excipientes Farmacéuticos*. En la actualidad esta referencia está ampliamente distribuida por el mundo.¹⁶

Diluyentes

Con frecuencia, la dosis única del componente activo es pequeña y la sustancia inerte se agrega para aumentar el volumen, con el propósito de que el comprimido tenga un tamaño práctico para la compresión. Los comprimidos compactados de dexametasona contienen 0.75 mg de esteroide por comprimido; por eso es obvio que debe agregarse otro material para que sea posible su elaboración. Los diluyentes utilizados para este propósito son fosfato dicálcico, sulfato de calcio, lactosa, celulosa, caolín, manitol, cloruro de sodio, almidón seco y azúcar en polvo. Ciertos diluyentes, como manitol, lactosa, sorbitol, sacarosa e inositol, cuando están presentes en cantidad suficiente, pueden impartir a algunos comprimidos compactados propiedades que les permiten desintegrarse en la boca al masticarlos, por lo que se denominan *comprimidos masticables*. Con la masticación, los comprimidos preparados en forma adecuada, se desintegran de manera uniforme en una proporción satisfactoria, con grato sabor y sin dejar después una sensación desagradable en la boca. Los diluyentes utilizados como excipientes para las fórmulas sometidas a compresión directa han sido sujetos a un procesamiento previo para darles fluidez y compresibilidad. Este aspecto se trata bajo el título Compresión directa, página 2487.

La mayoría de los formuladores de comprimidos de liberación inmediata tienden a utilizar en sus formulaciones sólo uno o dos de los diluyentes seleccionados ya mencionados. Por lo general, éstos han sido elegidos sobre la base de una mayor experiencia con alguno y con respecto a sus factores de costo. Sin embargo, en la formulación de nuevos agentes terapéuticos debe considerarse la compatibilidad de los diluyentes con la droga; por ejemplo, las sales de calcio, utilizadas como diluyentes para el antibiótico de amplio espectro tetraciclina, interfieren en la absorción de la droga en el tracto gastrointestinal. Si la droga es poco soluble en agua, se recomienda utilizar diluyentes que sean solubles, para evitar posibles problemas de biodisponibilidad. Las sustancias altamente adsorbentes, por ejemplo la bentonita y el caolín, deben evitarse en la elaboración de comprimidos con drogas utilizadas clínicamente en pequeñas dosis, como los glucósidos cardíacos, los alcaloides y los estrógenos sintéticos, ya que pueden ser adsorbidos después de la administración. La combinación de bases o sales de aminas con lactosa en presencia de un lubricante alcalino da como resultado comprimidos que se decoloran con el tiempo.

La celulosa microcristalina (Avicel) en general es utilizada como excipiente en las fórmulas de compresión

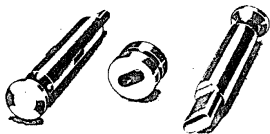


Fig. 92-2. Unidad mecánica básica para la compresión de comprimidos: punzón inferior, matriz y punzón superior. (Cortesía, Vec-tos/Cohlen.)

sión directa. Sin embargo, su presencia en concentraciones del 5 al 15% en las granulaciones húmedas ha demostrado ser beneficiosa en los procesos de granulación y de secado, pues minimiza el endurecimiento de la cubierta de los comprimidos y reduce el proceso de moteado de éstos.

Muchos de los componentes son utilizados para diferentes propósitos, aun dentro de la misma formulación; por ejemplo, el almidón de maíz puede utilizarse en la forma de pasta como un adhesivo. Cuando se agrega la droga como tal o en suspensión es un buen desintegrante. Aun cuando estos dos usos tienen propósitos opuestos, algunas fórmulas de comprimidos utilizan almidón de maíz de ambas maneras. En ciertas fórmulas de liberación controlada se utiliza el polímero de hidroxipropilmetilcelulosa (HPMC), tanto como una ayuda para prolongar la liberación desde el comprimido como también para formar una película en la cubierta de éste. Por esta razón, la mayor parte de los excipientes utilizados en las formulaciones de los comprimidos y de las cápsulas tienen muchas utilidades; ello requiere una comprensión cabal de sus propiedades y limitaciones para emplearlos racionalmente.

Aglutinantes

Los agentes utilizados para impartir cualidades cohesivas a los materiales en polvo se denominan aglutinantes o granuladores. Estas sustancias otorgan a las formulaciones de los comprimidos una cohesividad que asegura que éstos permanezcan intactos después de la compresión, pero también mejoran las cualidades de libre flujo para las formulaciones de gránulos de la dureza y el tamaño deseados. Los materiales más comúnmente utilizados como aglutinantes son almidón, gelatina y azúcares como la sacarosa, la glucosa, la dextrosa, la melaza y la lactosa. Las gomas, naturales y sintéticas, que han sido utilizadas incluyen goma arábiga, alginato de sodio, musgo de Irlanda, goma panwar, goma ghatti, mucilago de vainas de isapol, carboximetilcelulosa, metilcelulosa, polivinilpirrolidona, Veegum y arabogalactano de alerce. Otros agentes que pueden considerarse aglutinantes, en ciertas circunstancias, son el polietilenglicol, la etilcelulosa, las ceras, el agua y el alcohol.

La cantidad de aglutinante utilizado tiene considerable influencia sobre las características de los comprimidos compactados. El uso en demasía de un aglutinante muy fuerte produce un comprimido duro, que no puede desintegrarse fácilmente y es capaz de causar un desgaste excesivo de los punzones y las matrices. Las diferencias de los aglutinantes utilizados para los CR tolbutamida dieron por resultado diferencias en los efectos hipoglucemiantes observados clínicamente. Los materiales que no poseen cohesividad por sí mismos requieren un aglutinante más fuerte que los que sí la poseen. El agua y el alcohol no son aglutinantes en el verdadero sentido de la palabra, aunque por su acción solvente sobre algunos

componentes, como la lactosa, el almidón y la celulosa, cambian el material pulverizado a gránulos y la humedad residual retenida posibilita a los materiales adherirse entre sí cuando se los comprime.

Los aglutinantes son empleados tanto en solución como en forma seca, lo cual depende de los otros componentes de la formulación y del método de preparación. Sin embargo, se intenta agregar diferentes almidones *pregelatinizados* disponibles en la forma seca, de manera que pueda utilizarse sólo agua como solución granulante. La misma cantidad de aglutinante en solución puede ser más efectiva que si estuviera dispersa en forma seca y humedecida con el solvente. Para este último procedimiento, el agente aglutinante no es tan efectivo en la penetración y la humectación de cada una de las partículas dentro de la masa del polvo. Cada una de ellas en la mezcla de polvos tiene una cubierta de aire adsorbida en su superficie, la que debe atravesarse antes de que los polvos puedan ser humedecidos con la solución aglutinante. Después de la humectación, es necesario cierto período para que el aglutinante se disuelva por completo y esté totalmente disponible para su uso. Dado que los polvos difieren en la facilidad con la que pueden humedecerse y en la velocidad de disolución, con esta técnica con frecuencia es posible obtener una adhesión más efectiva con una menor concentración del agente aglutinante.

El método de compresión directa para preparar los comprimidos (véase pág. 2492) requiere un material que no sólo fluya con libertad sino que también sea suficientemente cohesivo como para actuar como aglutinante. Su uso se ha descrito para una cantidad de materiales, como celulosa microcristalina, dextrosa microcristalina, amilosa y polivinilpirrolidona. Se postuló que la celulosa microcristalina es una forma especial de fibrilla de celulosa, en la cual los cristallitos individuales son retenidos muy juntos por uniones de hidrógeno. La desintegración de los comprimidos que contienen celulosa se debe a la ruptura de las uniones entre los cristallitos en un medio desintegrante.

Pasta de almidón. El almidón de maíz se utiliza ampliamente como aglutinante, en concentraciones que varían del 10 al 20%. Por lo común, se prepara tal como se lo ha de usar dispersando el almidón de maíz en suficiente cantidad de agua fría purificada, para obtener una suspensión al 5-10% *p/p*, y se lo entibia en un baño de agua con agitación continua, hasta que se forma una pasta translúcida. Se observó que durante la formación de la pasta no se hidroliza todo el almidón. Por consiguiente, la pasta de almidón no sólo es útil como aglutinante, ya que también se la emplea como método para incorporar algún desintegrador en el interior de los gránulos.

Solución de gelatina. La gelatina generalmente es utilizada en una solución al 10-20%; las soluciones de gelatina deben prepararse en forma fresca según necesidad y utilizarse mientras estén tibias o

puedan solidificar. La gelatina se agrega al agua purificada fría y se deja reposar hasta que esté hidratada. Luego se calienta en un baño de agua para su disolución, y la solución se lleva al volumen final en base al peso para dar la concentración deseada.

Soluciones de celulosas. Diferentes celulosas se han utilizado en forma de soluciones como aglutinantes. Al respecto, la hidroxipropilmetilcelulosa (HPMC) ha sido empleada ampliamente. La HPMC, modelo de una cantidad de celulosas, es más soluble en agua fría que en agua caliente. También es más dispersable en el agua caliente que en la fría. Por esta razón, para obtener un buen gel, liso, que no posea grumos u "ojos de pescado", es necesario agregar la HPMC en agua caliente, casi hirviendo, y enfriar la mezcla con la mayor lentitud mientras se agita lo más rápido que se pueda. Otras celulosas solubles en agua, como la hidroxietilcelulosa (HEC) y la hidroxipropilcelulosa (HPC), han sido utilizadas en soluciones como aglutinantes con buenos resultados.

No todas las celulosas son solubles en agua. La etilcelulosa puede utilizarse efectivamente disuelta en alcohol o como aglutinante seco humedecido luego con alcohol. Se utiliza como aglutinante en los materiales que son sensibles a la humedad.

Polivinilpirrolidona. La PVP puede emplearse como una solución acuosa o alcohólica y su versatilidad ha aumentado su popularidad. Las concentraciones oscilan en torno del 2% y varían en forma considerable.

Debe aclararse que las soluciones aglutinantes son hechas más por el peso que por el volumen. Esto posibilita al formulador determinar el peso de los sólidos que se han agregado a la granulación del comprimido en la solución aglutinante. Ésta constituye parte del peso total de la granulación y debe tenerse en cuenta al tomar el peso del comprimido compactado, el cual deberá contener la cantidad declarada del agente terapéutico.

Como puede verse en el listado de los aglutinantes que figuran en este capítulo, la mayoría de ellos, utilizados en solución, están en forma polimérica. Debido a esto, la fluidez o la capacidad de diseminación de estas soluciones es importante cuando se selecciona el equipo de granulación apropiado. La reología de las soluciones poliméricas es un tema fascinante en sí mismo y debe considerarse para estos materiales.

Lubricantes

Los lubricantes cumplen varias funciones en el proceso de elaboración de los comprimidos. Evitan la adhesión del material de los comprimidos a la superficie de las matrices y los punzones, reducen la fricción entre las partículas, facilitan la eyección de los comprimidos de la cavidad matriz y pueden mejorar la velocidad de flujo de la granulación del comprimido. Los lubricantes utilizados con más frecuencia son talco, estearato de magnesio, estearato de calcio, áci-

do estéarico, aceites vegetales hidrogenados y polietilenglicol (PEG). La mayoría de los lubricantes, excepto el talco, se utilizan en concentraciones menores del 1%. Si se utiliza talco solo, pueden ser necesarias concentraciones de hasta el 5%. En la mayoría de los casos, los lubricantes son materiales hidrófobos. Una selección deficiente o una cantidad excesiva pueden originar la "impermeabilización" de los comprimidos, cuyo resultado es una escasa desintegración del comprimido o una disolución retardada de las drogas medicamentosas, o ambos inconvenientes.

Es muy necesario el agregado del lubricante adecuado si el material a comprimir tiende a adherirse en los punzones y en las matrices. Inmediatamente después de la compresión la mayoría de los comprimidos tienden a expandirse, por lo que pueden unirse y adherirse a los lados de la matriz; pero una elección apropiada del lubricante puede contrarrestar esto.

El método de agregar un lubricante a una granulación es importante, para que el material cumpla su función de manera satisfactoria. El lubricante debe dividirse finamente pasándolo a través de una malla de nailon 60 a 100 sobre la granulación. En producción, esto se denomina *tamizar* el lubricante. Después del agregado del lubricante, se vuelca o se agita suavemente para distribuirlo sin cubrir demasiadas partículas o fragmentarlas aun más. Algunos investigadores han inferido que el orden al mezclar los lubricantes y otros excipientes puede tener un efecto profundo sobre la acción de la forma farmacéutica final. Por lo tanto, el proceso de mezclado en sí mismo es tan importante como la selección del material lubricante.

Estas variables del proceso se pueden ver en la mezcla prolongada de un lubricante en una granulación. La sobregitación puede afectar la dureza, el tiempo de desintegración y la capacidad de disolución de los comprimidos resultantes.

La cantidad de lubricante varía desde tan sólo el 0.1% en algunos casos hasta el 5% en otros. Los lubricantes se agregan a los agentes granulantes en la forma de suspensiones o emulsiones. Esta técnica sirve para reducir la cantidad de procedimientos operacionales y, por consiguiente, el tiempo de procesamiento.

Para la selección de un lubricante debe prestarse atención a su compatibilidad con la droga. Entre éstas quizá la más ampliamente investigada es el ácido acetilsalicílico. Los diferentes talcos varían significativamente la estabilidad de la aspirina. Los que tienen un alto contenido de calcio y una elevada pérdida de la ignición se asociaron con una descomposición aumentada de la aspirina. Desde el punto de vista de la estabilidad, se encontró que la aceptación relativa de los lubricantes de comprimidos combinados con la aspirina disminuye en el siguiente orden: aceites vegetales hidrogenados, ácido estéarico, talco y estearato de aluminio.

El problema fundamental en la preparación de comprimidos solubles en agua es la selección de un

lubricante satisfactorio. Los lubricantes solubles que son efectivos incluyen benzoato de sodio, una mezcla de benzoato de sodio y acetato de sodio, cloruro de sodio, leucina y Carbowax 4000. Sin embargo, se sugirió que las formulaciones utilizadas para preparar comprimidos solubles en agua pueden representar una cantidad de arreglos entre la eficiencia de la compresión y la solubilidad en agua. Mientras que el estearato de magnesio es uno de los lubricantes más ampliamente utilizados, sus propiedades hidrófobas pueden retardar la desintegración y la disolución. Para evitar esta característica impermeabilizante, algunas veces se agrega lauril sulfato de magnesio; que tiene las propiedades lubricantes del estearato de magnesio sin sus desventajas, pero su inocuidad para uso en productos farmacéuticos aún no se ha establecido.

Deslizantes

Un deslizante es una sustancia que mejora las características del flujo de una mezcla de polvos. Estos materiales siempre se agregan en el estado seco justo antes de la compresión (es decir, durante el paso de lubricación). El dióxido de silicio coloidal [Cab-o-sil (Cabor)] es el deslizante de uso más común, en general en bajas concentraciones, del 1% o menos. El talco (libre de asbesto) también se usa y puede desempeñar el doble papel de lubricante/deslizante.

Es especialmente importante optimizar el orden de la adición y el proceso de mezclado de estos materiales con el objeto de maximizar su efecto y asegurar que su influencia sobre el(los) lubricante(s) sea mínima.

Desintegrantes

Un desintegrante es una sustancia, o una mezcla de ellas, agregada a un comprimido para facilitar su ruptura o desintegración después de su administración. Los componentes activos deben liberarse de la matriz del comprimido, tan eficientemente como sea posible, para permitir su rápida disolución. Los materiales que cumplen la función de desintegrantes han sido clasificados químicamente como almidones, arcillas, celulosas, alginas, gomas y polímeros con enlaces cruzados.

Los más antiguos desintegrantes, aun los más populares, son el almidón de maíz y de papa, bien desecados y pulverizados. El almidón tiene una gran afinidad por el agua y se hincha cuando se hidrata, lo que facilita así la ruptura de la matriz del comprimido. Sin embargo, otros autores han sugerido que su acción desintegrante en los comprimidos se debe a la acción capilar más que a la hinchazón; la forma esférica de los granos de almidón aumenta la porosidad del comprimido, lo que promueve la acción capilar. El almidón al 5% es el sugerido, aunque si se desea una desintegración más rápida esta cantidad debe au-

mentarse al 10-15%. Aunque debiera esperarse que el tiempo de desintegración disminuya a medida que se aumenta el porcentaje de almidón en el comprimido, esto no parece ser así en los comprimidos de tolbutamida, en los que parece haber una concentración crítica de almidón para las diferentes granulaciones de la sustancia química. Cuando se desea su efecto desintegrador, se agregan los almidones a las mezclas pulverizadas en el estado seco.

Los materiales conocidos como *superdesintegrantes* han ganado popularidad como desintegrantes. El nombre proviene de los bajos niveles (2-4%) a los que son completamente efectivos. La croscarmelosa, la crospovidona y el glicolato sódico de almidón son ejemplos de una celulosa con enlaces cruzados, un polímero con enlaces entrecruzados y un almidón con enlaces cruzados, respectivamente.

El desarrollo de estos desintegrantes fomentó nuevas teorías acerca de los diferentes mecanismos por los que actúan los desintegrantes. El glicolato de almidón sódico se hincha 7 a 12 veces en menos de 30 segundos. La croscarmelosa lo hace 4 a 8 veces en menos de 10 segundos. El almidón se hincha igualmente en las tres dimensiones y la celulosa sólo en dos direcciones, dejando esencialmente igual la longitud de la fibra. Dado que la croscarmelosa es el agente desintegrante más efectivo, se postuló que la velocidad, la fuerza y la extensión de la hinchazón desempeñan un papel importante en aquellos desintegrantes que actúan por hinchazón.

La PVP de enlaces cruzados se hincha poco, aunque retorna con rapidez a su estado original después de la compresión. Se ha postulado también que el factor principal para el funcionamiento de la PVP de enlaces cruzados se debe a las fibras o a la acción capilar.¹²⁻¹⁹

Además de los almidones, se ha usado una gran variedad de materiales considerados efectivos como desintegrantes. Entre ellos se incluye al Veegum HV, la metilcelulosa, el agar, la bentonita, la celulosa y productos de la madera, la esponja natural, las resinas de intercambio catiónico, el ácido alginico, la goma guar, la pulpa de citrus y la carboximetilcelulosa.²⁰ El lauril sulfato de sodio en combinación con el almidón también se ha comportado como un desintegrante efectivo. En ciertos casos se postuló que la aparente efectividad de los tensioactivos para mejorar la desintegración de los comprimidos se debe a un aumento de la velocidad de humedecimiento.

El desintegrante por lo general se mezcla con los ingredientes activos y los diluyentes previamente a la granulación. En algunos casos puede ser ventajoso dividir el almidón en dos porciones: una parte se agrega a la fórmula pulverizada antes de la granulación y el remanente se mezcla con el lubricante y se agrega antes de la compresión. Incorporado de esta manera, el almidón cumple un doble propósito: la porción agregada al lubricante desintegra rápidamente el comprimido a gránulos, y el almidón mezclado con los componentes activos desintegra éstos a parti-

culas más pequeñas. Se ha visto que el Veegum es más efectivo para desintegrar los comprimidos de sulfatiazol cuando la mayor parte se agrega después de la granulación y sólo una pequeña parte antes de este proceso. También se observó que, de manera similar, las arcillas del tipo de la montmorillonita son buenos desintegrantes cuando se agregan a las granulaciones preparadas como polvos. Son mucho menos desintegrantes cuando se los incorpora dentro de los gránulos.

Además de la presencia de los desintegrantes, otros factores también pueden afectar el tiempo de desintegración de los comprimidos compactados. El aglutinante, la dureza del comprimido y el lubricante pueden influir en el tiempo de desintegración. Por lo tanto, cuando el formulador se enfrenta a un problema relacionado con la desintegración de un comprimido compactado, puede ser que la solución no sólo dependa de la selección y de la cantidad del agente desintegrante.

La evolución del dióxido de carbono es también una manera efectiva de producir la desintegración de los comprimidos compactados. Los comprimidos que contienen una mezcla de bicarbonato de sodio y un acidulante, como ácido tartárico o ácido cítrico, pueden generar efervescencia cuando se les agrega agua. Se añade una cantidad suficiente de ácido como para producir una reacción neutra o levemente ácida cuando la desintegración en agua es rápida y completa. Una desventaja para el uso de desintegradores de tipo efervescente es que los comprimidos deben conservarse en atmósfera seca durante todo el tiempo que duran la elaboración, el almacenamiento y el empaque. Los comprimidos efervescentes solubles constituyen la forma preferida de distribuir aspirina y agentes edulcorantes no calóricos.

Colorantes

Los colorantes en los comprimidos compactados no tienen otra función que mejorar la apariencia estética de la forma farmacéutica. El color ayuda al fabricante a controlar el producto durante su preparación y también es de utilidad para el usuario como modo de reconocer. La amplia diversidad en el uso de colorantes en las formas farmacéuticas sólidas posibilita que el color sea una categoría importante en el código de identificación desarrollado por la AMA para reconocer un comprimido en casos de envenenamiento.

Todos los colorantes utilizados en los productos farmacéuticos deben ser aprobados y certificados por la FDA. Durante varias décadas estuvieron sometidos a rígidas normas de toxicidad y, como resultado de ello, muchos han sido eliminados de la lista de colorantes de la FD&C o "deslistados", y muchos otros se han incluido como buenos. Los colorantes actualmente aprobados en los EE.UU. figuran en el cuadro 92-1. Cada país tiene su propia lista de colorantes aprobados y los formuladores deben tomarlos en con-

sideración cuando diseñan sus productos para el mercado internacional.²¹

Cualquiera de los colorantes solubles en agua aprobados y certificados por la FD&C, las mezclas de ellos o sus lacas correspondientes pueden utilizarse para colorear comprimidos. Una laca coloreada es la combinación por adsorción de un colorante soluble en agua al óxido hidratado de un metal pesado, con el resultado de una forma insoluble del colorante. En algunos casos se utilizan varios colorantes, para dar intencionalmente al comprimido una coloración heterogénea con aspecto moteado. No todos los colorantes disponibles satisfacen todos los criterios requeridos como colorantes ideales para productos farmacéuticos. Se ha investigado la fotosensibilidad de muchos de los usados con mayor frecuencia y de las lacas correspondientes, así como la protección brindada por numerosos vidrios empleados para elaborar los envases de los comprimidos.

Otra propuesta para mejorar la fotoestabilidad de los colorantes ha sido el uso de sustancias químicas que absorben la luz ultravioleta en las formulaciones de comprimidos con colorantes. La línea Di-Pac (Am star) es una serie de azúcares coloreados para compresión directa disponibles en el comercio.

El método más común para agregar un colorante a la formulación de un comprimido es disolverlo en la solución aglutinante antes del proceso de granulación. Otra propuesta es adsorberlo en el almidón o en el sulfato de calcio proveniente de su solución acuosa; el polvo resultante se seca y aglutina con los otros componentes. Si se utilizan lacas insolubles, pueden aglutinarse con el resto de los componentes secos. Con frecuencia, durante el secado los colorantes en las granulaciones húmedas se difunden, de lo que resulta una distribución despareja del color en la granulación. Después de la compresión, los comprimidos podrán tener una apariencia moteada debido a la distribución despareja del colorante. La difusión de los colorantes puede reducirse mediante el secado lento de la granulación a baja temperatura y su agitación mientras se está secando. Se ha demostrado la afinidad de varios colorantes aniónicos hidrosolubles certificados para varios almidones naturales; la afinidad en estos casos colabora para prevenir la difusión del color.

Otros aditivos han actuado como inhibidores de la difusión de los colorantes. El tragacanto (1%), la goma arábiga (3%), la atapulgit (5%) y el talco (7%) han sido efectivos para inhibir la difusión del FD&C Azul N° 1 en lactosa. Utilizando lacas coloreadas, el problema de la difusión del color se evita, ya que las lacas son insolubles. La prevención del moteado puede reforzarse usando lubricantes y otros aditivos, que antes se han coloreado de manera similar a la granulación. El problema del moteado se agudiza a medida que aumenta la concentración del colorante y es una característica indeseable de muchos comprimidos comerciales.

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