Pharmaceutical studies on polysaccharides formulation for colonic drug delivery

A Thesis
Submitted in Partial Fulfillment of the Requirements for Master Degree of Pharmaceutical Sciences

In
Drug Technology
By

Ahmed Mamdouh Coucha
Bachelor of Pharmaceutical Sciences, May 2000

Under Supervision of

Prof. Dr. Seham El-Sayed Abd El-Hady
Professor of Pharmaceutics and Industrial Pharmacy,
Department of Drug Technology
Faculty of Pharmacy, Ain Shams University

Prof. Dr. Laila Khairi
Head of the National Organization of Drug Control and Research

Dr. Nahed Daoud Mortada
Associate Professor and Head of Department of Pharmaceutics
Faculty of Pharmacy, Ain Shams University

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جامعة عين شمس
كلية الصيدلة
قسم تكنولوجيا الأدوية

دراسات صيدلانية على صياغات عديدى السكريات لنظم إيتاء دوائية للقولون

رسالة مقدمة لنيل درجة الماجستير في تكنولوجيا الأدوية

إعداد

أحمد ممدوح قوشة

تحت إشراف السادة

الأستاذة الدكتورة / سهام عبد الهادي
أستاذ الصيدلانيات والصيدلة الصناعي
كلية الصيدلة – جامعة عين شمس

الأستاذة الدكتورة / ليلي خيرى
رئيس الهيئة القومية للرقابة علي الأدوية والبحوث

الدكتورة / ناهد داوود مرتضى
أستاذ مساعد الصيدلانيات
كلية الصيدلة – جامعة عين شمس

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First and foremost thank **God** for helping me to fulfill this work.

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Words are not enough to express my profound gratitude to ***Prof. Dr. Abdelhameed El-Shamy*** for the endless effort that he exerts for helping, guiding and assisting us in the drug technology department.

Finally, I would like to dedicate this work to my family, my father, my mother, my uncle, my wife and my two sisters, that without their great support this thesis wouldn’t have appeared. Thank you.

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Abstract

Inflammatory bowel disease (IBD) is a spectrum of chronic, idiopathic inflammatory intestinal conditions. It is characterized by periods of remissions and relapsing exacerbations. No curative treatment is available and the therapeutic goal is to bring the patient into a long lasting remission and to prevent any relapses. For induction and maintenance of remission, various drugs can be used among which dexamethasone is one of the choices. Dexamethasone is a highly potent and long acting glucocorticoid with strong topical and systemic anti-inflammatory effect and negligible sodium-retaining properties. High doses of dexamethasone and long duration of therapy exposes the IBD patient to serious complications. In order to achieve an effective therapy with lower side effects dexamethasone was targeted to the colon using pectin (P) and alginic acid (A) either alone or in combination with chitosan (C) as a tool for site specific delivery beneficing from the specific biodegradation of such polymers by the colonic microflora. Such targeting could decrease the systemic side effects and produce an effective therapy.

First, dexamethasone was embedded into matrix tablets using different P: C and A: C ratios (1:0, 10:1, 6:1 and 2:1) beneficing from the polyelectrolyte complex formation between these polymers. The prepared tablets were subjected to *in vitro* release studies in pHs 1.2, 5.5, 7.4 and 6.8 mimicking mouth to colon pH gradient and using the pH shift method. In our effort to interpret the release mechanism, each matrix was subjected to further investigations by studying the percent matrix erosion, the normalized water uptake the unconstrained swelling behavior and analyzing the front movement profiles. *In vivo* evaluation was carried out in the cecum of conscious male rats with and without antibiotic treatment. Matrices prepared with pectin and alginic acid only failed to retain the drug enough period to reach the colon as 100 % of the drug was released after 4 and 3.5 hrs from each matrix respectively. On the other hand the addition of chitosan retarded the drug release. An inverse relationship was found between the % drug released and % chitosan incorporated in the tablet with the 2:1 P: C and A: C ratio producing the highest drug release retardation. Only 17.5 and 21 % of dexamethasone load was released after 5 hours

(the estimated time a dosage form takes to reach the colon) from the P: C and A: C matrices respectively. The release of dexamethasone involved different mechanisms depending on the composition of the matrix. In the P and A matrices release was by surface erosion while in the matrices containing chitosan release involved matrix relaxation and diffusion. The contribution of each mechanism depended on the P: C and A: C ratio. As the amount of chitosan increased the relative contribution of the diffusion component increased which was computed through the Peppas and Sahlin equation and was confirmed by measuring the percent matrix erosion, the normalized water uptake, the unconstrained swelling behavior and analyzing the front movement profiles of each matrix.

Second, compression-coated tablets containing dexamethasone in the core were prepared by dry coating with either pectin or alginic acid alone or in combination with chitosan in the same aforementioned ratios at three different coating levels: 1:1, 2:1 and 3:1 coat: core (ct:cr) ratio. The *in vitro* release was done according to the same previously mentioned conditions**.** Pectin and alginic acid alone were unable to protect the core tablet from premature release at the chosen coating levels. The addition of chitosan lowered the coat solubility and a better tablet protection was achieved at lower coating levels. The dexamethasone release from each formula exhibited an initial lag period that was dependent on the coating level and the composition of the coat. Following this lag period a stage of controlled drug release was observed. The order of drug release from the 2:1 P:C and A:C coat mixtures was by diffusion at all coating levels, indicating that the level of coat had no effect on the mechanism of drug release at this ratio. For the other ratios the order of drug release varied according to the coating level.

The 2:1 P:C and A:C matrices and the tablets coated with 2:1 P:C and A:C compression coating at 2:1 and 3:1 ct:cr ratio were chosen to be tested for the release under the effect of colonic microflora in cecum of curious rats as these formulae gave the best drug release retardation. A significant increase of drug release was observed that proves the potential ability of such polysaccharides based system to be used in colon targeting. The compression coating was superior to the matrix as the

former ensured a complete silent period before reaching the colon and a rapid enzymatic biodegradation in the colon.

Key word: Colon targeting, pectin, alginic acid, chitosan, matrix tablet, compression coating, dexamethasone, microflora activated systems.

Introduction

Almost all of the oral solid controlled release products are based on the designs of matrix, membrane-controlled and osmotic systems. The release mechanisms from these dosage forms generally involve: ***(Korsmeyer et al., 1983)***

1. Drug diffusion through a viscous gel layer, tortuous channels, or a barrier.
2. Drug dissolution via system erosion.
3. Drug solution or suspension forced out of the device by osmotic pressure.

A matrix can be defined as a dispersion of a drug into a polymer; this dispersion may be either in a particulate or a molecular form. The former is simply a suspension of drug particles homogenously distributed in the polymer matrix, whereas the latter is a matrix with drug molecules dissolved in the polymer ***(Velasco et al., 1999; During and Fassihi, 2000; Qiu and Zhang, 2000; Sako et al., 2002).*** The matrix system is one of the most popularly used controlled drug delivery systems because of its versatility, effectiveness and the low cost of manufacturing. In addition to its broad FDA acceptance, it has got a favorable *in vivo* performance and is widely used in controlling the release of drugs that have a wide range of physico-chemical properties. The manufacturing process of a matrix system involves a few number of steps and is done using conventional equipments ***(During and Fassihi, 2002; Williams III et al., 2002).***

Based on the type of the polymer used, a matrix system can be classified into a **hydrophilic matrix** and a **hydrophobic one**. The commonly available **hydrophilic polymers** used include hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, xanthan gum, sodium alginate, polyethylene oxide, and cross linked homopolymers and copolymers of acrylic acid.

Hydrophobic matrix systems usually use waxes and water insoluble polymers in their formulation. Natural and synthetic waxes of different melting points have been used; examples include carnauba wax, paraffin waxes and low molecular weight polyethylenes. Insoluble polymers such as fine powders of

ammoniomethacrylate copolymers (Eudragit RL 100, RS 100,), ethylcellulose, cellulose acetate , cellulose acetate butyrate (CAB), cellulose acetate propionate and latex dispersion of methacrylic ester copolymers (Eudragit NE 3OD) are also being used in hydrophobic matrix systems ***(Qiu and Zhang, 2000).***

When the **hydrophilic matrix** is placed in water, steep water concentration gradients are formed at the polymer water interface resulting in water imbibition into the matrix. Water acts as a plasticizer and reduces the glass transition temperature of the system, until it reaches the temperature of the surrounding; at that point the polymer undergoes transition from the glassy to the rubbery state forming a gel layer. At the formed gel layer the mobility of the polymer chains are enhanced leading to polymer relaxation with more water imbibition resulting in a dramatic decrease in the concentration of both the polymer and the drug and an increase in the dimensions of the system i.e. swelling. The polymer concentration decreases until it reaches a critical concentration below which polymer chains detach off the matrix and approach the bulk phase, such concentration is known as the disentanglement concentration ***(Ju et al., 1995; Brazel and Peppas, 1999a, 1999b; Sipmann and Peppas, 2001).***

This dynamic system is described in the literature by different synonyms, such as swelling – controlled release system ***(Korsmeyer and Peppas, 1983)***, hydrogel matrices or polymeric matrices exhibiting moving boundaries ***(Lee, 1985)***. The physicochemical definition of hydrocolloid matrices was adopted by ***Mockel and Lippold,(1993)*** whereas ***Ford, (1994)*** proposed the pharmaceutical term hydrophilic matrix tablets. Generally it is convenient that such systems are referred to as a swellable matrix tablets ***(Colombo et al., 2000a).***

In **hydrophilic matrices**, there are two contributing mechanisms involved in the drug release: the **Fickian diffusional release** and the **relaxational release**. Diffusion is not the only pathway by which a drug is released from the matrix. The

erosion of the matrix following the polymer relaxation also contributes to the overall release. The contribution of each component to the overall release is dependent on the properties of the drug and the matrix ***(Peppas and Sahlin, 1989a; Narasimhan, 2000; Qiu and Zhang, 2000).***

In non swelling matrices or in cases where the relaxation time of the polymer is very small compared to the solvent diffusion time i.e. once solvated these polymers establish an equilibrium state almost immediately thus keeping the dimensions constant throughout the release process. In these systems Fickian diffusion is observed, the drug molecules diffuse through the constant gel layer into the bulk, creating a receding zone. This zone is responsible for the $t^{1/2}$ dependence of the release rate. In swelling systems, those systems where the polymer relaxation rate is the rate limiting step compared to the penetrant diffusion rate, Case II transport (time independent diffusion) is observed. The drug is convected (carried) by the relaxing polymer to the bulk resulting in a constant release rate (zero order).

According to ***Alfrey et al., (1966)*** a system present in a thermodynamically compatible solvent swells and rearranges to accommodate the advancing solvent, creating a sharp penetrant front moving in a constant velocity. This swelling process results in a stress that can cause anomalous or case II transport, whereas poor solvents will be restricted to diffusion in the pore space inside the polymer leading to Fickian transport.

In these systems (hydrophilic matrices), a gel layer may be formed on the tablet surface. The thickness of the formed gel layer, through which the drug diffuses to the bulk, controls the drug release kinetics. The gel layer thickness depends on the relative contributions of water penetration, chain disentanglement and mass transfer in water (polymer erosion) ***(Lee, 1981).*** The gel strength depends on the concentration, viscosity and chemical structure of the rubbery polymer ***(Colombo et***

al., 2000b). This gel layer is a dynamic layer that is sandwiched between the swelling front; which is the boundary between the glassy polymer and the rubbery phase and that is associated with the rate of water uptake; and the erosion front, which is the boundary between the rubbery phase and the dissolution medium, from which the matrix erodes into the bulk and is associated with the matrix erosion rate ***(Colombo et al., 1995; Colombo et al., 2000a).*** The balance between the rate of erosion and the rate of water penetration is the main factor that determines the gel layer thickness, which shows three distinct regimes: it increases when the penetration of water is the fastest phenomenon, stays constant when the erosion rate is similar to the penetration rate and decrease when all of the polymer is in the rubbery phase ***(Harland et al., 1988).***

As the drug release kinetic is deeply associated with the complicated dynamics of the gel layer, it shows a complex profile that ranges initially from Fickian to anomalous (non Fickian) and subsequently from quasi-constant to constant, becoming first order at the end of release ***(Colombo et al., 2000a).***

A simple semi empirical equation termed the power-law model was introduced to describe the drug release behavior from a hydrophilic matrix system ***(Korsmeyer et al., 1983; Davidson and Peppas, 1986; Riteger and Peppas, 1987; Sipmann and Peppas, 2001) .***

$$Q=Kt^n \qquad (1)$$

Where,

K: rate constant

n: diffusional exponent

Q: M_t/M_∞ Fraction of drug released or fractional uptake of solvent at time t

K is related to the rate constant incorporating characteristics of the macromolecular network system and the drug, while n is related to the specific transport mechanism. For n= 0.5, the drug release follows the fickian diffusion

mechanism that is driven by a chemical potential gradient. For n=1 drug release follows a zero order mechanism which occurs via the viscoelastic relaxational transport that is associated with stresses and phase transition in hydrated polymers. For 1>n>0.5, a balance between both mechanisms is observed ***(Brazel and Peppas, 1999b; Sipmann and Peppas, 2001).***

Another model was developed by ***Peppas and Sahlin, (1989b)*** that considered the contribution of the diffusional and the relaxational (erosion) mechanisms in the release of the drug from a hydrophilic matrix and is represented by the following equation.

$$M_t / M_\infty = k,t^m + k_2 t^{2m} \qquad (2)$$

Where,

k_1: Diffusional rate constant.

k_2: Relaxational rate constant.

m: the diffusional exponent.

Equation (2) allows the quantitative estimation of the involved mechanism of release by means of calculating the ratio between the relaxational contribution, R and the diffusional contribution, F according to the following equation: ***(Colombo et al., 2000a)***

$$\frac{R}{F} = \frac{K_d}{K_r} t^m \qquad (3)$$

The work in this chapter will be concerned with the formulation of dexamethasone matrix tablets intended for colon targeting using pectin and alginic acid either alone or in combination with chitosan. The prepared tablets will be