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Gastro-intestinal diffusion tablet: influence of polyoxyethyleneglycol 400

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Abstract

The influence of the incorporation of PEG 400 in a cellulose acetate film to control the release of indomethacin or aminophylline was studied. The aminophylline tablets coated with 20% of PEG 400 and 10 or 20% of diethylphthalate were resistant in purified water if the membrane amount was higher than 13 mg per tablet. The dissolution rate of indomethacin was very low, 1.3–6.0%. Without PEG in the membrane the dissolution rate of aminophylline tablets was slow (6% in 18 h). The increase of the membrane weight (28–41 mg) resulted in a decrease of the dissolution rate with 10 and 20% of diethylphthalate. There was a correlation between the $T_{20\%}$ and the coating amount for aminophylline. The solubility of the drug had a large influence on its dissolution rate. With indomethacin which is poorly soluble, it was difficult to obtain efficient dissolution with a GDS system using PEG 400.

Keywords: Gastro-intestinal diffusion system; GDS-indomethacin-aminophylline; PEG 400-controlled release

1. Introduction

The aim of sustained release formulation optimization is often to obtain a zero-order dissolution kinetic. The coating agents are water non-soluble polymers such as ethylcellulose, cellulose acetate, acrylic and methacrylic acids. A gastro-intestinal diffusion system (GDS) consists in a soluble core (Janicki and Jedras, 1990) including the drug (metoprolol, dilthiazem, lithium acetate, disopyramide) and tablet excipients. The porous membrane covering the core controls the diffusion rate of the drug. The coating membrane is made by pulverization of a dispersion of an hydrophilic agent (arabic gum 35–75% w/w (Janicki and Jedras, 1987; Janicki and Jedras, 1990; Jedras and Janicki, 1987; Jedras et al., 1989), dextran 40 000 75% w/w (Jedras and Janicki, 1987), sodium chloride 38.5–48.4% w/w (Janicki and Jedras, 1990), PEG, sucrose 60–75% w/w (Kallstrand and Ekman, 1983)) dispersed in a non-soluble polymer (cellulose acetate). In contact with the gastro-intestinal fluid, the hydrophilic agent is solubilized

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and pores are created. The liquid passes through the porous membrane and dissolves the drug. The dissolution rate is constant during the diffusion process. A zero order controlled release is observed after a lag time (20 min to 2 h). Several parameters influence the dissolution rate: the weight of the membrane, the amount of hydrophilic agent, the hydrophilic agent granulometry and the hydrophilic agent viscosity in solution. GDS tablets have at least two main advantages: they avoid pore obstruction by non-soluble particles and they cause less local irritation because the diffusion occurs on a larger area. The aim of this study was to estimate the influence of different concentrations of PEG 400 and diethylphthalate on the resistance of the membrane in water and on the dissolution rate of two types of tablet: tablets containing indomethacin (poorly soluble drug) or aminophylline (freely soluble drug). We tried to explain the mechanism of the dissolution (diffusion or osmotic pressure) using a urea dissolution medium.

2. Materials and methods

Indomethacin is poorly soluble in water. The water solubility of aminophylline is 1 g in 5 ml. Cellulose acetates (Eastman chemical, Paris, France) are not soluble in purified water and are freely soluble in methylene chloride/isopropylic alcohol mixtures (Eastman Chemical International, 1990). Cellulose acetate CA 398-10 and CA 320S have different substitution degrees (acetyl, hydroxyl and combined acetic acid). Tablet formulae are summarized in Table 1. Tablets (10 mm diameter and 10 mm curve radius) were manufactured using a wet granulation process. The hardness was 80–120 N. The coating solution composition is shown in Table 2. The coating operation was carried out in a coating pan (Millinox, Paris, France). Different weights of membrane were compared: from 10 to 59 mg/tablet. The membrane weight was calculated with 50 tablets taken at different times during the coating operation. The PEG 400 content was expressed in percentage of the dry coating weight.

Table 1
Formulae of tablets for GDS systems

Indomethacin	85.0 mg	Aminophylline	75.0 mg
NaCl	249.5 mg	NaCl	259.5 mg
PVP 90	21.5 mg	PVP	21.5 mg
Magnesium stearate	2.0 mg	Magnesium stearate	2.0 mg
Total weight	358 mg		358 mg

Table 2
Coating solution composition to obtain GDS systems

Cellulose acetate E 398	20 g
Cellulose acetate E 320	20 g
PEG 400	0–94 g
Diethylphthalate	0–10.5 g
Ethanol 95%v/v	480 ml
Methylene chloride	700 ml

2.1. Assays

The integrity of the coating was evaluated by the resistance of the membrane in purified water during 1 h. The dissolution rate was studied with a USP XXIII apparatus II (paddle) using 900 ml of dissolution medium over 18 h. For indomethacin, we used a pH 6.2 $\pm$ 0.1 phosphate buffer with a 75 rpm stirring rate and a spectrophotometric measurement at 318 nm. For aminophylline, purified water (pH 5.8 $\pm$ 0.2) was used with a 50-rpm stirring rate and a spectrophotometric measurement at 269 nm. Dissolution rate of aminophylline was also assessed in 900 ml of a urea solution 366 g/l (7 Osm/kg) in purified water, with a stirring rate of 50 rpm over 18 h. This dissolution medium was used to avoid a possible mechanism of osmotic release.

3. Results and discussion

The aspect of indomethacin tablets coated with 20% of PEG 400 was not modified after 1 h in water (Table 3). With 5% of PEG 400, the percentage of diethylphthalate (4%) was not sufficient and a lower resistance of the film appeared on the sharp-edged of the tablet. With 70% of PEG 400,

Table 3
Resistance of different GDS systems in purified water without stirring

	PEG 400 (% w/w)	Diethylphthalate (% w/w)	Membrane mass (mg)	Resistance
Indomethacin	5	4	10 ± 1	bad
	20	4	10 ± 1	good
	70	0	10 ± 1	good
Aminophylline	0	20	28 ± 1	good
	20	0	33 ± 2	bad
	20	10	13 ± 1	bad
	20	10	28 ± 2	good
	20	10	31 ± 2	good
	20	10	41 ± 2	good
	20	20	12 ± 1	bad
	20	20	28 ± 1	good
	20	20	41 ± 2	good
	20	20	59 ± 3	good

the film was not really regular. The film formation could be modified by the high viscosity of the solution. Aminophylline tablets coated with 20% of PEG 400 and 10 or 20% of diethylphthalate were resistant if the membrane weight was higher than 13 ± 2 mg per tablet. The coating operation was easier with indomethacin than with aminophylline because indomethacin tablets had a lower wettability and their surface was not very wetted during the coating process. Because of their high wettability and solubility, aminophylline tablets needed more diethylphthalate as plasticizer to improve the spreading and the elasticity of the film. $T_{50\%}$ of indomethacin tablets without coating was 21 min. By increasing the PEG 400 content from 20 to 70% the dissolution rate of indomethacin increased from 1.3 ± 0.8 to 6.0 ± 2.5% (Table 4). This rate was very low without any influence of the amount of diethylphthalate. $T_{50\%}$ of non-coated aminophylline tablets was 8 min. Without PEG in the membrane the dissolution rate was slow (6% after 18 h) (Table 4). With sodium chloride and methylene blue tablets, Ozdemir (1990) showed that only 10% were released at 7 h with 40% of PEG 400, and less than 12% with 50% of PEG 400. PEG 400 was necessary to allow the release of aminophylline. For lithium acetate tablets (Janicki and Jedras, 1990), 6% were released with 33% of arabic gum, and 48% with 75% of arabic gum after 6 h. By increasing the hydrophilic agent particle size (arabic gum) the dissolution kinetic increased: 63% at 8 h for particles < 63 μm, and 73% for 160-μm particles (Jedras and Janicki, 1987; Jedras and Janicki, 1990). The increase of the membrane weight (28 ± 2 to 41 ± 2 mg) resulted in a decrease of the dissolution rate with 10% of diethylphthalate. The same thing was observed with 20% of diethylphthalate. There was no influence of the amount of plasticizer for a same coating weight on the aminophylline release. There was a correlation between the $T_{20\%}$ of aminophylline and the coating weight ($T_{20\%} = -1897.3 + 1685.7 \log m$, $r = 0.9899$). It was possible to make a controlled release dosage form by increasing the membrane weight. Using diisopyramide phosphate, the amount released after 8 h was: 147 mg with 15–18 mg membrane, 101.8 mg with 23–26 mg, 87.5 mg with 32–35 mg (Jedras and Janicki, 1987, 1989, 1990). The viscosity of the hydrophilic agent is important. Arabic gum coating (high viscosity) had a lower dissolution kinetic at 60 min (6%) than sodium chloride (14%) (Janicki and Jedras, 1990). In urea dissolution medium the 20% PEG 400, 10% diethylphthalate aminophylline formulation had a 5-h 36 ± 0.2 $T_{20\%}$ and an 11-h 36 ± 0.5 $T_{50\%}$. The release was similar with and without urea showing a diffusion mechanism (Fick law). If osmotic pressure would occur the dissolution profile would be lower. The solubility of the drug had a great influence on the drug dissolution rate.

Table 4
Influence of the percentages of PEG 400, diethylphthalate and the membrane weight on the dissolution parameters of indomethacin and aminophylline GDS tablets

	PEG 400 (% w/w)	Diethylphthalate (% w/w)	Membrane weight (mg)	$T_{20\%}$	$T_{50\%}$	release (%)
Indomethacin	20	4	10 ± 1			1.3 ± 0.8 at 640 min
	70	0	10 ± 1			6.0 ± 2.9 at 640 min
Aminophylline	0	20	28 ± 1	>18 h		6.0 ± 2.0 at 18 h
	20	10	28 ± 2	8 h 38 ± 0.5	13 h 45 ± 0.7	
	20	10	31 ± 2	11 h 08 ± 0.4	17 h 16 ± 0.6	
	20	10	41 ± 2	13 h 45 ± 0.6	>18 h	
	20	20	28 ± 2	7 h 40 ± 0.2	10 h 50 ± 0.5	
	20	20	41 ± 2	12 h 52 ± 0.7	>18 h	
	20	20	59 ± 3	>18 h		

With a poorly soluble drug like indomethacin it was not easy to obtain an efficient dissolution using a GDS system with PEG 400. Similar observations (Theeuwes, 1983) were reported with osmotic tablets (Oros™) and the necessity of push-pull formulations. The dissolution mechanism was the diffusion even with a high sodium chloride content. Zero order kinetics were observed (Janicki and Jedras, 1990) with GDS containing lithium and 48% of hydrophilic agent. A 20-min lag time appeared with a 20–29 mg coating weight and 30 min with 37–39 mg. A 20–30-min lag time (Janicki and Jedras, 1990) appeared when the amount of hydrophilic substances was low. The introduction of a low quantity of drug (< 5 mg) increased the dissolution rate without any lag-time.

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