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Full Length Research Paper

Effect of viscosity grades of ethylcellulose on the sustained release properties of indomethacin from its tablets matrix

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The objective of the present study was to estimate the influence of ethyl cellulose (EC) with different viscosity grades on *in vitro* drug release from EC matrix tablets containing Indomethacin. Four viscosity grades of EC (7, 10, 50 and 100 cp) were studied. The 90 - 125/µm particle size fraction was collected by manual dry sieving and the compression force was varied to produce tablets of equal hardness. The drug release from Indomethacin tablets was determined by dissolution testing as described in the United States Pharmacopoeia (USP). The tablets pore characteristics were studied using helium pycnometry and mercury porosimetry. The release rate constant ranged from 1.25 ± 0.98 for the 7cp viscosity grade tablets to 1.49 ± 1.02 for the 100cp viscosity grade tablets whereas porosity ranged from 5.6% ± 0.3 to 6.8 ± 0.1 when based on gaz pycnometry and from 3.9% ± 0.4 to 5.1 ± 0.2 when based on mercury intrusion. These results indicate that the release rates marginally increased with an increase in viscosity grade. The main explanation for the viscosity grade effect on release rates would be differences in tablet porosity.

Key words: Matrix, ethylcellulose, viscosity grade, indomethacin, dissolution, porosity.

INTRODUCTION

Ethyl cellulose (EC) is a non-toxic, stable, compressible, inert, hydrophobic polymer that has been widely used to prepare pharmaceutical dosage forms. This polymer is often used as a rate-controlling membrane to modulate the drug release from dosage forms with organic or aqueous coating techniques (Shan-Yang Lin et al., 2001; Siepmann et al., 2007; Neau et al., 1999) but few references have focused on the use of EC as directly compressible excipient (Lin et al., 1998; Upadrashta et al., 1993; Upadrashta et al., 1994; Katikaneni et al., 1995; Crowley et al., 2004)).

The present study used EC as the sole direct compression matrix-forming material to deliver Indomethacin, a non steroidal anti-inflammatory drug(NSAID) used in the treatment of rheumatoid. The gastrointestinal adverse effects of NSAIDS led to the search for new delivery systems which can overcome the side effects by controlling the drug release (Elchidana et al., 1999; Wu et al., 2007; Wei et al., 2006)). In this study, Indomethacin Sustained Release Formulation was developed by direct compression technology; which is scientifically and economically appealing. It entails reduced labor, cost, time, operational space, and equipment, and further no heat or moisture is used.

Different EC viscosity grades, (7, 10, 50 and 100 cp), were used. The influence of these viscosity grades, on the matrix porosity and on Indomethacin release rate, was investigated.

MATERIALS AND METHODS

Materials

Indomethacin (Prolabo, France), was micronised and possessed a volume mean diameter of 5µm by laser diffraction. EC 7, 10, 50 and 100 cp viscosity grades (standard grade) were gifts from Hercules (Netherlands) and have an ethoxy content of 44.0 - 51.0%. The term 'viscosity grade' arises from the measurement (ASTM D914) of

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Table 1. Tablets formulation.

Ingredients	Percentage
Micronized Indomethacin	25%
Ethylcellulose	71.8%
Magnesium Stearate	2%
Talc	0.8%
Aérosil®	0.4%

Table 2. Influence of viscosity grade of ethylcellulose on the release rate constant.

EC viscosity grade (cp)	Release rate constant (k)
7	1.25 ± 0.98
10	1.26 ± 0.69
50	1.39 ± 0.54
100	1.49 ± 1.02

the viscosity of a 5% solution of the polymer in 80:20 toluene/ethanol (Porter, 1989). The higher viscosity grade corresponds to a higher polymer molecular weight. Magnesium Stearate and Talc were procured from Prolabo (France). Aerosil was obtained from Degussa (Germany).

Preparation of tablets

Preparation of Indomethacin tablets, by direct compression, was realized according to the formula presented in the Table 1

Required quantities of drug, polymer and lubricants were mixed thoroughly for 15 min at 20 rpm (rotation per minute) in a Turbula T2C mixer (Willy Bachofen, UK). The high polymer level and the use of three lubricants were necessary to reduce the problem of micronized indomethacin flow. The tablets were compressed (11 mm diameter, biconvex punches) using a single-punch tablet compression machine (Korch ECO, Germany). The practical weight of tablets was calculated based on the drug content of the mixture. Each tablet contained 75 mg of indomethacin and other pharmaceutical ingredients as listed in Table1.

To study the effects of the different EC viscosity grades (7, 10, 50 and 100 cp), the 90 - 125 µm particle size fraction was collected by manual dry sieving with laboratory test sieves (RETCH, Germany) and The compression force was varied (Table 2) to produce tablets of equal hardness (12.0 kp) .

Pore structure

The tablet porosity was characterized in two ways. Firstly it was calculated from the apparent density and the dimensions and weight of the tablet, Secondly tablet porosity was obtained from mercury porosimetry measurement (Mattsson et al., 2001; Soren K et al., 2007)

Helium pycnometry

The true density of tablets was determined in triplicate using helium pycnometer (Multivolume pycnometer 1305, micromeritics®).

Twelve tablets were placed in a 12 cm^3 sample cup and purged 20 times at 19.85 psi followed by six analytical runs at 19.85 psi. The equilibration rate was 0.0050 psi/min. An equivalent mass of the powder mixtures was measured in the same manner.

Mercury porosimetry

The tablet pore structure was assessed using mercury porosimetry (AutoPore II 9220, Micromeritics). Incremental volumes of mercury were plotted against pore diameters according to the Washburn Equation (Washburn, 1921), which relates the applied pressure *P*, and the radius, *r*, of the pores intruded with a non-wetting liquid:

$$r = \frac{-2\gamma \cos\theta}{P} \qquad \text{Eq. 1.}$$

The intrusion pressures were between 0.01 and 379 MPa, the pore size corresponding to the intrusion pressure were calculated assuming cylindrical pore and surface tension for mercury of 485 D/cm. The mercury-tablets contact angle was 130°. Twelve tablets were placed in a 5 cc bulb penetrometer. The pressure at each point was allowed to equilibrate for 10 s. Each run was performed in triplicate.

The average pore diameter was defined as the pore diameter at which 50% of the total volume of intruded mercury is intruded.

***In vitro* drug release study**

Drug release from Indomethacin tablets was determined by dissolution testing as described in the United States Pharmacopoeia (USP 24, 2000). Drug release from each tablet was carried out in a USP dissolution paddle assembly (Pharmatest PTWS, France) at 75 rpm and 37 ± 0.5°C. Phosphate buffer (pH 6.8) was used as dissolution medium. Samples (10 ml) were withdrawn at intervals of 60 min and the drug concentration was determined spectrophotometrically at 270 nm (Elchidana et al., 1999).

RESULTS AND DISCUSSION

Result of the dissolution of indomethacin from matrix tablets are shown in Figure 1.

Drug release patterns from EC matrices were characterized using the Higuchi square root of time relationship (Higuchi, 1963).

$$Q = \left(\frac{D\epsilon}{\tau}(2A - \epsilon C_s) C_s t \right)^{1/2} = kt^{1/2} \qquad (2)$$

Where *Q* is the cumulative amount of drug released in time *t* per unit surface area, *D* denotes the drug diffusion coefficient in the matrix phase, *Cs* is the drug solubility in the dissolution medium, A represents the drug concentration in the matrix, is the porosity, denotes the tortuosity of the matrix, and *k* is the dissolution rate constant.

According to the equation, the cumulative amount of drug released is a linear function of the square root of time. In this study, tablets from all viscosity grades followed the

Table 4. Pore structure of tablets.

EC viscosity grade (cp)	Average pore diameter (Å)	Porosity (%)	
		Based on gaz picnometry	Based on Hg intrusion
7	254 ± 24	5.6 ± 0.3	3.9 ± 0.4
10	250 ± 34	5.5 ± 0.2	4.0 ± 0.3
50	367 ± 8	6.1 ± 0.3	4.7 ± 0.3
100	391 ± 11	6.8 ± 0.1	5.1 ± 0.2

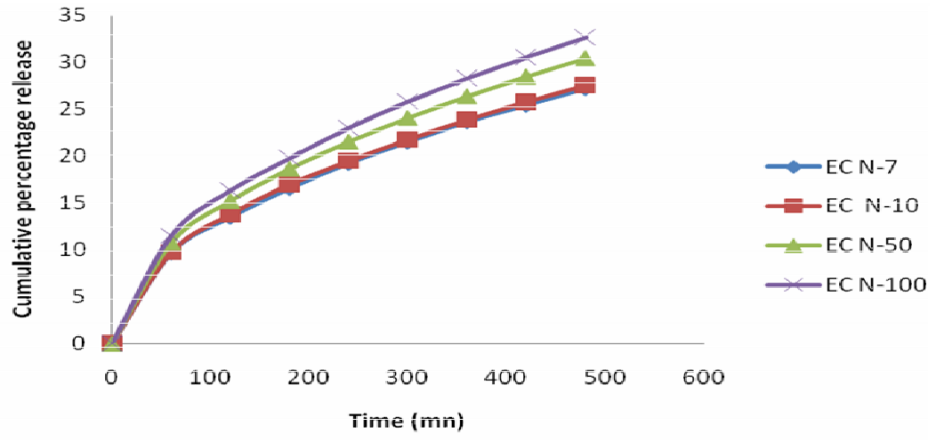

Figure 1. Dissolution profiles of indomethacin tablets prepared with different viscosity grades of EC and compressed to a constant hardness (12.0 kp). The release rates only marginally increased with an increase in viscosity grade.

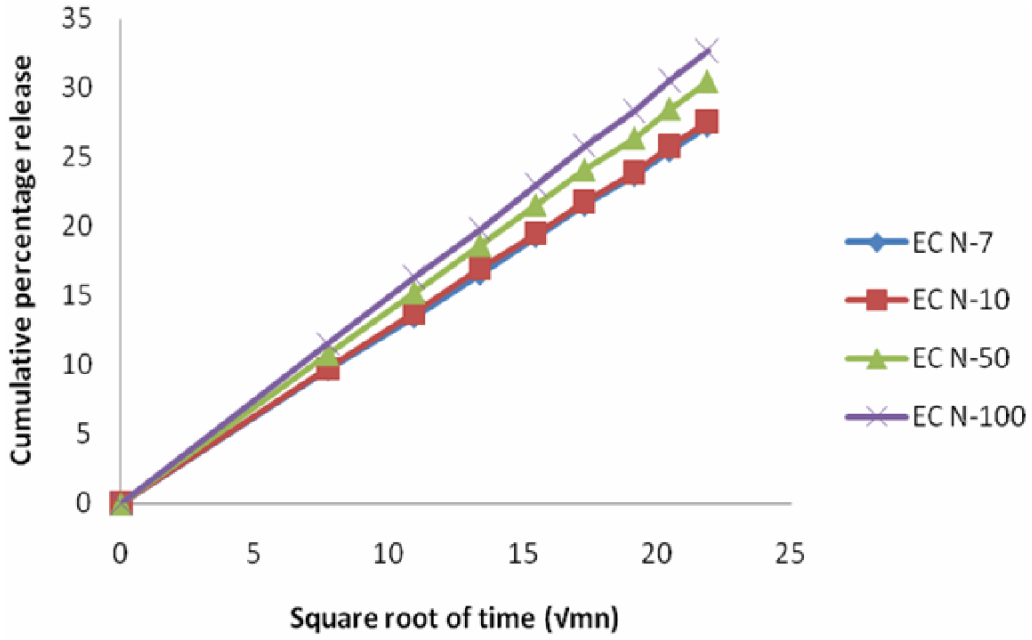

Figure 2. Cumulative amount of drug released as a function of the square root of time for tablets prepared with different viscosity grades of ethylcellulose and compressed to a constant hardness confirm that the linear relationship is expected to be valid up to 30% cumulative drug released. The release of indomethacin from ethylcellulose tablets followed a matrix-controlled diffusion mechanism.

Higuchi model ($r^2 > 0.98$). The linear relationship is valid up to 30% cumulative drug released (Figure 2) (Carstensen, 1993). The release of indomethacin from ethylcellulose tablets followed a matrix-controlled diffusion mechanism.

The use of EC as only polymer and of indomethacin, a poorly soluble model drugs, can explain the slow release rate of tablets (Neau et al., 1999), Raffiee-Tehrani et al. 1988). The level of magnesium stearate, an hydrophobic lubricant, could, also, reduce the drug release rate from an EC matrix (Katikaneni et al., 1995; Shangraw et al., 1993).

The indomethacin release rate from the matrix dependent upon EC viscosity grade employed to prepare the tablet. A marginal increase in the release rate was observed with lower viscosity grade (Table 3)

This relation could be explained by the difference between the viscosity of the permeating aqueous medium and of the dissolution medium, in fact, dissolved EC resulted in differences in viscosity, the higher viscosity grades would yield a lower aqueous viscosity, and a faster drug release rate, because the higher molecular weight polymers are less soluble in water. But, Since EC is essentially insoluble in water; this viscosity difference would be negligibly different.

According to Katikaneni et al. (1995) the more plausible explanation for the viscosity grade effect on release rates would be differences in tablet porosity (Katikaneni et al., 1995).

To confirm this theory, we studied tablets pore characteristics, using helium pycnometry and mercury porosimetry (Table 4). The median pore radius was smaller and the tablets less porous when prepared with low viscosity grade ethylcellulose.

These results explained the difference in the dissolution rate constants, which marginally increased with an increase in viscosity grade. This decrease in drug release rate was due to a reduction in porosity.

According to Upadrashta et al. (1993), tablets prepared using different viscosity grades and a consistent compression force displayed an increase in porosity with an increase in the viscosity grade. In this study, tablets were compressed at constant hardness, however a lower release rates and a reduction in porosity was observed for the 7 and 10 cp grades of EC. An exploration of polymer deformation, at low applied force, may explain this observation. In conclusion, the results of this study demonstrate that the indomethacin release rate was, marginally, dependent upon the viscosity grade of ethyl cellulose.

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