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Ethylcellulose matrix controlled release tablets of a water-soluble drug

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Abstract

Pseudoephedrine hydrochloride was used as a model drug to prepare direct compression sustained release tablets with ethylcellulose (EC). Initially, different viscosity grades of EC were studied. An increase in viscosity grade resulted in a marginal to moderate increase in the release rate. However, lower viscosity grades produced harder tablets. The highly compressible 10 cp grade was used to study the effect of drug loading, particle size, compression force, and magnesium stearate concentration on release properties. The rate of drug release decreased with a decrease in the drug concentration in the matrix. Except for tablets prepared with EC having a particle size fraction 250–420 and 177–250 μm, drug release up to 80% exhibited a square root of time dependency and tablets remained intact during dissolution. Tablets prepared with either the EC 250–420 or 177–250 μm particle size fraction eroded. The square of the release rate is proportional to drug concentration in the matrix, indicating that the release of pseudoephedrine hydrochloride from EC matrices is primarily matrix-controlled.

Keywords: Ethylcellulose; Pseudoephedrine HCl; Release rate; Direct compression; Viscosity grade; Particle size

1. Introduction

Ethylcellulose (EC) is an inert, hydrophobic polymer that has been widely used in a number of dosage forms. It has been used as a binder (Chowhan, 1980), in preparing microcapsules and microspheres (Jalsenjak et al., 1976; Bodmeier and Chen, 1989) and as film-forming and matrix-forming material for sustained release dosage forms (Shaikh et al., 1987; Porter, 1989). Most of these processes require solubilization of all or part of the EC using organic solvents.

Direct compression technology is scientifically and economically appealing. It entails reduced labor, cost, time, operational space, and equipment, and further no heat or moisture is used. It is the preferred method of manufacture for producing immediate or sustained release tablets. Fassihi (1987) used EC with polyethylene glycol, Eudragit RS, stearyl alcohol, and dicalcium phos-

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phate to prepare direct compression tablets for retarding theophylline release. Stamm and Tritsch (1986) studied the release of metoclopramide HCl from direct compression tablets of EC (20 cp) and lactose. Caffeine loading was varied in ethylcellulose controlled release matrix tablets and percolation effects in non-swellable matrices were examined (Bonny and Leuenberger, 1993).

Our interest in EC resulted from its successful use as a direct compression controlled release vehicle for poorly soluble model drugs (Upadrashta et al., 1993). The compressibility and compactibility properties of EC have recently been reported (Upadrashta et al., 1994). The present study used EC as the sole direct compression matrix-forming material to deliver a water-soluble drug. In the continuing effort to define the characteristics of this system, the effects of the viscosity grade and particle size of EC, drug loading, the applied force, and magnesium stearate concentration on pseudoephedrine hydrochloride release were investigated.

2. Materials and methods

EC 10, 20, 45 and 100 cp viscosity grades (standard grade) were gifts from Dow Chemical Co. (Midland, MI) and have an ethoxy content of 48.0–49.5%. The term 'viscosity grade' arises from the measurement (ASTM D914) of 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. Pseudoephedrine HCl was a gift from Sandoz Research Institute (Lincoln, NE) and magnesium stearate was obtained from Mallinckrodt Corp. (Chicago, IL).

Compression studies were conducted using a 7/16 inch standard concave punch and die set on an automated Carver press (Model C-12, Fred S. Carver Co., Menomonee Falls, WI). The compression rate was 31 mm/s and dwell time was 0.1 s. Tablet weights were fixed at 482.5 mg. Drug, EC, and 0.5% magnesium stearate were physically mixed and compressed at 22.24 kN.

To study the effects of the different EC viscosity grades (10, 20, 45 and 100 cp), the 105–149 μm particle size fraction was collected by manual dry sieving with laboratory test sieves (USA Standard Testing Sieves). The drug concentration in the matrix was 16.67%.

Subsequently, the highly compressible 10 cp grade was employed to study the effect of the particle size of EC, drug loading, compression force, and magnesium stearate concentration. Drug loadings were 12.5, 16.7, and 25%, and tablets were compressed using the 74–105 μm particle size fraction of EC. To examine the EC particle size effect, five size fractions (74–105, 105–149, 149–177, 177–250 and 250–420 μm) were collected using the test sieves as above, and the drug loading was maintained at 25% of the formulation dry weight.

The effect of the applied force on drug release was evaluated by preparing tablets using 4.45, 8.90, 13.34, 17.79 or 22.24 kN as the compression force. To study the effect of lubricant concentration on release rates, five different concentrations of magnesium stearate ranging from 0.5 to 3.0% of the formulation were employed. For the compressional force and lubricant concentration studies, the 74–105 μm fraction of EC was employed with 25% drug.

Tablet hardness was measured using a Schleuniger hardness tester (Model 2E, Vector Corp., Marion, IA) and five determinations were averaged. Dissolution studies were performed at 37° C using the USP method II with the stirring speed

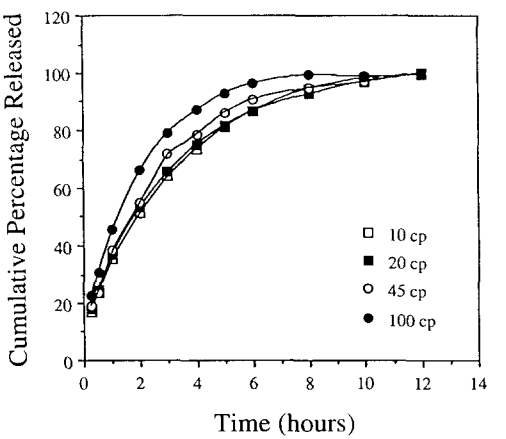

Fig. 1. Dissolution profiles of pseudoephedrine HCl tablets compressed at a constant force of 22.24 kN.

maintained at 100 rpm. Distilled water was used as the dissolution medium. Samples (10 ml) were withdrawn at specified intervals and the drug concentration was determined spectrophotometrically at 206 nm.

3. Results and discussion

Dissolution profiles of pseudoephedrine HCl tablets prepared with different viscosity grades of EC are shown in Fig. 1. Drug release patterns from EC matrices were characterized using the Higuchi square root of time relationship (Higuchi, 1963):

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

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, C_s is the drug solubility in the dissolution medium, A represents the drug concentration in the matrix, ϵ is the porosity, τ 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.

Tablets from all viscosity grades remained intact during dissolution and drug release up to 80% followed the above model ($r^2 > 0.987$). The immediate release of drug present at the surface of the tablets resulted in a non-zero y-intercept. The data, as presented in Fig. 2, confirm that the linear relationship is expected to be valid up to 75% cumulative drug released (Carstensen, 1993). Deviations from this linear relation were seen for data beyond 80% cumulative amount released, indicating that a release mechanism different from strict Fickian diffusion was then in effect.

The release rates and tablet hardness are presented in Table 1. Since EC is essentially insoluble in water, the viscosity of the permeating aqueous medium should be only negligibly different from that of the dissolution medium. If indeed dissolved EC resulted in differences in viscosity, the higher viscosity grades would yield a lower

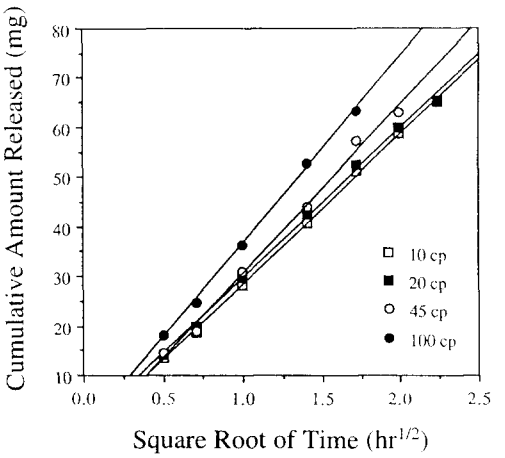

Fig. 2. Cumulative amount of drug released as a function of the square root of time for tablets prepared with different viscosity grades of ethylcellulose compressed at constant force (22.24 kN).

aqueous viscosity, and a faster drug release rate as seen here, because the higher molecular weight polymers are less soluble in water. A more plausible explanation for the viscosity grade effect on release rates would be differences in tablet porosity.

Tablets prepared using these different viscosity grades and a consistent compression force displayed an increase in porosity with an increase in the viscosity grade (Upadrashta et al., 1994). The reported differences in porosities became more profound as the compression force was increased. In the present study with drug-loaded tablets, the maximum achievable hardness was associated with the 10 cp grade and the minimum with the 100 cp grade, indicating that higher viscosity grades were less compressible. Harder tablets were associated with lower dissolution rates.

Table 1
Influence of viscosity grade of ethylcellulose on tablet hardness and release rate constant for tablets compressed at a constant applied force

Viscosity grade (cp)	Hardness (kp)	Release rate constant (mg/h$^{1/2}$)
10	23.3 ± 0.4	30.23 ± 0.41
20	21.5 ± 0.4	30.17 ± 0.38
45	14.1 ± 0.4	33.86 ± 0.32
100	12.0 ± 0.3	37.69 ± 0.45

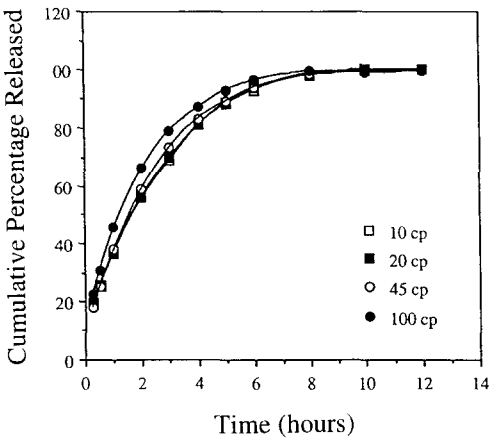

Fig. 3. Dissolution profiles of pseudoephedrine HCl tablets compressed to a constant hardness of 12.0 kp.

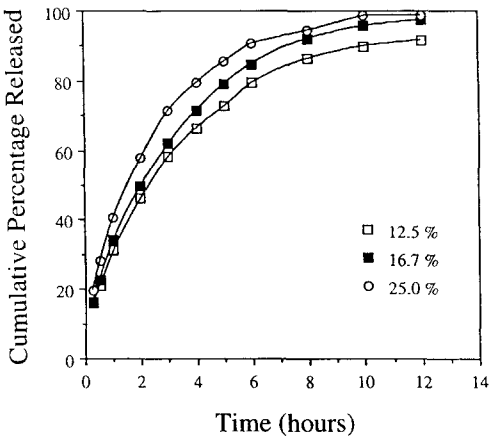

Fig. 4. Effect of pseudoephedrine HCl loading on dissolution profiles of ethylcellulose tablets.

To separate the hardness effects from constituent effects, tablets of each EC viscosity grade were compressed to a constant hardness (12.0 kp) by varying the compression force. Fig. 3 presents the dissolution profiles of these tablets. The differences between the dissolution profiles were reduced when compared to results from the constant force study. The dissolution rate constants from the square root of time relationship are presented in Table 2. The release rates only marginally increased with an increase in viscosity grade when tablets were compressed to the same hardness. The lower release rates of the 10 and 20 cp grades of EC at constant hardness may be due to extensive deformation of EC even at low applied forces. The force required to compress tablets to constant hardness (Table 2) is linearly related to the polymer viscosity grade ($r^2 = 0.989$).

The dissolution profiles of tablets with 12.5, 16.7, and 25.5% drug compressed at 22.25 kN are shown in Fig. 4. A significant increase in the release rate and a slight decrease in tablet hardness were observed with an increase in the drug concentration (Table 3). The decrease in tablet hardness may be due to a decrease in the compressibility of the matrix resulting from the higher drug proportion. The increase in release rate is attributed to the increase in drug concentration, resulting in an increase in porosity and a concomitant decrease in the tortuosity of the matrix (Desai et al., 1966; Foster and Parrott, 1990a). The data were further analyzed by plotting the square of the release rate as a function of drug concentration in the matrix (Fig. 5). A linear relationship between the square of the release rate and drug concentration ($r^2 = 0.989$) indicates that drug release from EC matrices is primarily by matrix-controlled diffusion.

The effect of the particle size range of EC on drug release from the tablets compressed with

Table 2
Required applied force and release rate constant for tablets compressed to a constant hardness

Viscosity grade (cp)	Applied force (kN)	Release rate constant ($mg/h^{1/2}$)
10	3.56	33.73 ± 0.40
20	4.45	33.57 ± 0.38
45	8.90	36.75 ± 0.36
100	22.24	37.69 ± 0.45

Table 3
Influence of drug content on tablet hardness and release rate constant for pseudoephedrine HCl tablets prepared with ethylcellulose

Drug loading (%)	Hardness (kp)	Release rate constant ($mg/h^{1/2}$)
12.5	25.5 ± 0.4	20.08 ± 0.52
16.7	23.3 ± 0.4	29.41 ± 0.48
25.0	20.8 ± 0.5	48.63 ± 0.49

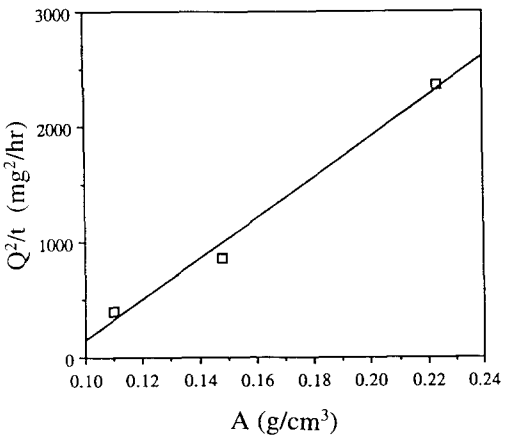

Fig. 5. Plot of square of release rate as a function of drug concentration.

25% pseudoephedrine HCl at 22.25 kN is shown in Fig. 6. Tablets prepared with 74–105, 105–149 and 149–177 μm particle size fractions remained intact during the dissolution study, whereas tablets prepared with particle size fractions 177–250 and 250–420 μm eroded.

Table 4 lists the drug release rate and hardness for tablets prepared with different particle size fractions of EC. Using a constant compression force, increasing the particle size caused a decrease in tablet hardness and an increase in the release rate. Since a decrease in particle size increases the theoretical number of contact points

Table 4
Influence of particle size of ethylcellulose on tablet hardness and release rate constant for pseudoephedrine HCl tablets

Particle size fraction (μm)	Hardness (kp)	Release rate constant (mg/h$^{1/2}$)
240–420	10.1 ± 0.5	–
177–240	12.6 ± 0.4	–
149–177	21.5 ± 0.5	48.63 ± 0.49
105–149	26.2 ± 0.5	46.03 ± 0.46
74–105	28.9 ± 0.4	40.98 ± 0.41

in the powder, it is reasonable to conclude that the number of interaction points or the bonding surface area governs the tablet hardness. The erosion of tablets prepared with particle size fractions 177–250 or 250–420 μm provides further evidence that the interparticle forces were reduced with an increase in particle size. Characterization of tablets prepared using different particle sizes of EC and consistent compression forces revealed that the porosity increased with an increase in particle size (Katikaneni et al., 1995). This increase in porosity would result in a faster drug release.

The dissolution profiles of 25% pseudoephedrine HCl tablets compressed using applied forces from 4.45 to 22.25 kN are shown in Fig. 7. The release rate constants from the square root of time relationship and the respective tablet hardness are presented in Table 5. Tablet hard-

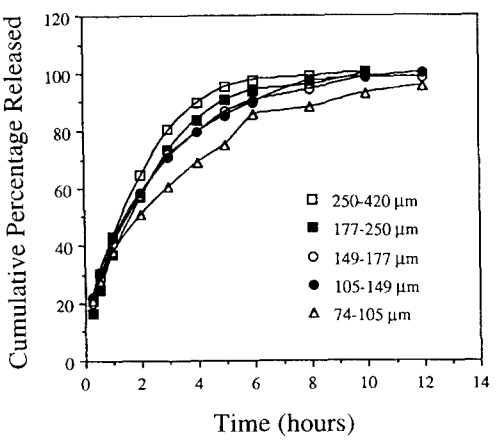

Fig. 6. Effect of particle size of ethylcellulose on the dissolution profiles of pseudoephedrine HCl tablets.

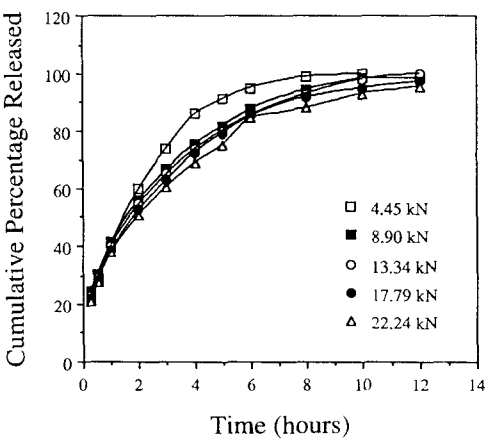

Fig. 7. Effect of applied force on the dissolution profiles of pseudoephedrine HCl tablets.

Table 5
Influence of applied force on tablet hardness and release rate constant for pseudoephedrine HCl tablets prepared with ethylcellulose

Applied force (kN)	Hardness (kp)	Release rate constant ($mg/h^{1/2}$)
4.45	12.5 ± 0.3	46.87 ± 0.49
8.90	20.3 ± 0.4	45.06 ± 0.34
13.34	22.7 ± 0.4	41.91 ± 0.38
17.79	26.5 ± 0.4	41.25 ± 0.42
22.24	28.9 ± 0.4	40.67 ± 0.37

Table 6
Influence of magnesium stearate content on tablet hardness and release rate constant for pseudoephedrine HCl tablets prepared with ethylcellulose

Lubricant concentration (%)	Hardness (kp)	Release rate constant ($mg/h^{1/2}$)
0.5	28.9 ± 0.4	39.52 ± 0.41
1.0	26.7 ± 0.4	39.37 ± 0.38
1.5	23.3 ± 0.5	39.31 ± 0.42
2.0	22.1 ± 0.4	39.13 ± 0.48
3.0	17.2 ± 0.4	37.63 ± 0.46

ness increased 2.3-fold when applied force was increased from 4.45 to 22.25 kN, while the release rate decreased by only 15%. The decrease in the release rate may be due to a decrease in porosity and a simultaneous increase in matrix tortuosity owing to the formation of a continuous matrix at high applied forces (Foster and Parrott, 1990b).

An increase in the level of magnesium stearate, a hydrophobic lubricant, could further reduce the drug release rate from an EC matrix (Fig. 8). The release rates and hardness of these tablets are given in Table 6. At the 3% level, a slight decrease in the release rate was observed and the tablet hardness substantially decreased over the 0.5–3% magnesium stearate concentration range. Lubricants reduce the tablet hardness for plastic materials due to a decrease in interparticle interactions in the presence of lubricant, which prevents bond formation (Jarosz and Parrott, 1984).

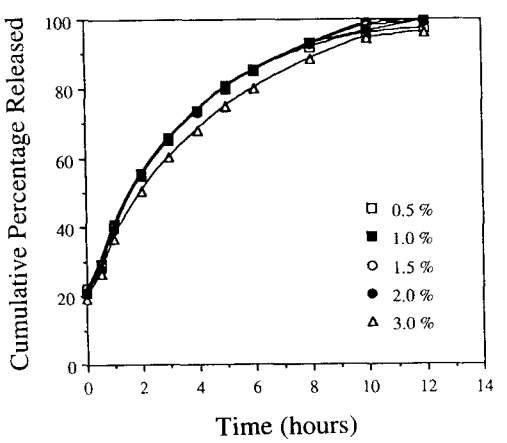

Fig. 8. Effect of magnesium stearate concentration on the dissolution profiles of pseudoephedrine HCl tablets.

A negligible decrease in the release rate from tablets containing 0.5–2.0% magnesium stearate was observed. This could be explained by the counteraction of two effects. The decrease in the tablet hardness, which is consistent with an increase in porosity and a decrease in tortuosity, will increase the release rate. The counter effect is the retarding influence of the hydrophobicity of the matrix due to the presence of magnesium stearate. At 3.0% lubricant concentration, the retarding influence of hydrophobicity exceeds the increase due to porosity, leading to the observed decrease in the drug release rate.

4. Conclusions

Direct compression tablets prepared with pseudoephedrine HCl in EC matrices showed sustained drug release over a period of 10 h. The lower viscosity grades of EC are more compressible than the higher viscosity grades, resulting in harder tablets and slower release rates. Drug release up to 80% from the EC matrices followed the Higuchi model. An increase in the drug concentration resulted in an increased release rate. Magnesium stearate did not decrease the release rate but decreased tablet hardness. The release of pseudoephedrine HCl from ethylcellulose tablets followed a matrix-controlled diffusion mechanism. Thus, different release rates can be achieved by modifying the parameters considered in this study.

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