COMPARISON OF ETHYLCELLULOSE MATRIX CHARACTERISTICS PREPARED BY SOLID DISPERSION TECHNIQUE OR PHYSICAL MIXING

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ABSTRACT

The characteristics of ethylcellulose matrices prepared from solid dispersion systems were compared with those prepared from physical mixture of drug and polymer. Sodium diclofenac was used as a model drug and the effect of the drug:polymer ratio and the method of matrix production on tablet crushing strength, friability, drug release profile and drug release mechanism were evaluated. The results showed that increasing the polymer content in matrices increased the crushing strengths of tablets. However the friability of tablets was independent of polymer content. Drug release rate was greatly affected by the amount of polymer in the matrices and considerable decrease in release rate was observed by increasing the polymer content. It was also found that the type of mixture used for matrix production had great influence on the tablet crushing strength and drug release rate. Matrices prepared from physical mixtures of drug and polymer was harder than those prepared from solid dispersion systems, but their release rates were considerably faster. This phenomenon was attributed to the encapsulation of drug particles by polymer in matrices prepared from solid dispersion system which caused a great delay in diffusion of the drug through polymer and made diffusion as a rate retarding process in drug release mechanism.

Keywords: Sustained release, Matrix, Solid dispersion, Ethylcellulose, Release mechanism

INTRODUCTION

In recent years much attention has been paid to the oral sustained release drug delivery systems. Matrices are considered to be the simplest and cheapest method for production of oral sustained delivery systems.

Ethylcellulose has been widely used in production of inert matrices. The factors affecting drug release from these matrices have been extensively investigated (1-3). The application of solid dispersion systems has been evaluated in preparation of prolonged release dosage forms using insoluble polymers. It has been shown that this technique is a valuable method in retarding drug release rate (4-7). Study on the drug release from different size fractions of solid dispersion systems and comparison with corresponding physical mixtures have been the focus of many investigators. However less attention has been paid to properties of tablets prepared from solid dispersion systems.

This study was performed in order to evaluate the properties of tablets prepared from solid dispersion systems in comparison with those prepared from physical mixtures. Ethylcellulose as a polymer and sodium diclofenac as a model drug were used in this study. The effect of drug:polymer ratio and method of matrix production on tablet crushing strength, friability, drug release profile and drug release mechanism were evaluated.

MATERIALS AND METHODS

Materials

Ethylcellulose (Ashacel M-10) was a gift from Colorcon (Italy), Sodium diclofenac was obtained from Darupakhsh (Iran), Potassium dihydrogen phosphate, sodium hydroxide and ethanol were from Merck (Germany).

Preparation of matrices

Mixtures of drug and polymer were prepared either by physical mixing or by solid dispersion technique. To prepare physical mixtures, drug and polymer were passed through 120 µm sieve and mixed in tumbling mixer for 10 minutes to produce mixtures containing 1:1, 1:2 and 1:3 of

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the drug:polymer ratios. To prepare solid dispersion systems, weighed amounts of drug and polymer (in 1:1, 1:2, 1:3 ratios) were dissolved separately in minimum amount of ethanol. Drug solution then was added to the polymer solution and mixed thoroughly. The resulting solution in equal volumes were poured into the petri dishes and oven dried at 50°C to constant weight. The dried films was peeled off and grounded by a porcelain mortar and pestle. Then the samples were passed through 120 µm sieves.

An accurate weight of each mixture was dissolved in the known volumes of ethanol and its drug content was determined by UV spectroscopy at 282 nm through the calibration curve made for the solution of sodium diclofenac in ethanol at this wavelength. Ethylcellulose dose not interfere with diclofenac sodium absorption at this wavelength.

Flat faced tablets, (10 mm in diameter) of the physical mixtures or solid dispersion systems equivalent to 100 mg sodium diclofenac were compressed on an instrumented single punch-tableting machine (Korsch EK-72, Germany) at 10 kN compaction force. The tablet weights were 200, 300 and 400 mg for 1:1, 1:2 and 1:3 drug: polymer ratios, respectively.

Evaluation of matrices

The crushing strengths of the matrices were measured by a hardness tester (Erweka TB24, Germany) 24 h after compaction. Ten tablets were used in each study. Crshing strength of matrices were analysed by one-way analysis of variance and Tukey's multiple comparison test using SPSS statistical software.

The friability of matrices was measured by an Erweka TA3R friablator (Germany). Ten tablets were weighed and tumbled for 4 min at 25 rpm. Tablets were then re-weighed and the percent of friability of tablets was calculated. Student's t-test was used for comparison of friability test between matrices prepared from physical mixtures and those prepared from solid dispersion systems.

Dissolution tests were carried out in a USP dissolution apparatus I (Chemiphan, Iran). The release profiles of matrices containing 100 mg of sodium diclofenac in 1000 ml phosphate buffer of pH 6.8 (prepared according to USP 23, NF 18 instruction) were determined at a rotation speed of 100 rpm, at 37± 0.5°C by the Shimadzu U.V, A-160 double beam spectrophotometer (Japan) at 275 nm wavelength. The mean of three determinations was used to calculate drug release for each formulation.

In order to determine the drug release rates, data were fitted to zero order kinetic (equation1) and Higuchi model (equation2) using statistical software (Minitab, Standard Release 9.1). Regression analysis was used to obtain the release rate constants and correlation coefficients (r). The correlation coefficient for the best statistical fit was used as the principal criteria to evaluate the models.

$$w = w_0 - kt \qquad \text{Equation1}$$

$$w = k\sqrt{t} \qquad \text{Equation2}$$

To analyze the mechanism of drug release, the release data between 5-70% were fitted in the equation 1 (8) by developing a computer program. The value of n was calculated for each formulation. The value of n indicates the mechanism of drug release.

$Q = Kt^n$ Equation 3

Q= the fraction of drug released

K= Release constant

t= Time

n= Release exponent

IR studies

FT.IR (KBr) spectrophotometer (Perkin Elmer Paragon 1000 IR) was used to obtain IR spectra of the pure drug, polymer, physical mixture and solid dispersion (1:3).

RESULTS AND DISCUSSION

The crushing strengths of tablets are given in Table 1. The results of one-way analysis of variance for comparison of crushing strengths of matrices confirmed significant differences. The crushing strengths of matrices increased as the polymer content in tablets increased. For example in tablets made from physical mixtures, the hardness increased from 7.4 kg to 15.1 kg for matrices containing 100 and 300 mg of polymers respectively. The Tukey's test indicated that there are significant differences ($p<0.001$) between crushing strength of matrices containing different amounts of polymer, prepared from physical mixtures. This trend was also observed for tablets made from solid dispersion systems. Increasing the

polymer content. increases the interparticulate bounding during compaction, which results in increase in crushing strength of tablets.

Tukey's test also showed that tablets prepared from physical mixtures were significantly harder than those made from solid dispersion system (table 1). The decreased crushing strength of tablets made from solid dispersion system was probably due to the formation of hard elastic film after solvent evaporation. Particles obtained after film grinding was so hard that resisted deformation under the compaction force.

The results of friability test are shown in table 2. As it can be seen the friability of tablets was independent of the polymer content in tablets. However methods of preparation of drug and polymer mixtures affected the results of friability tests. The tablets made from solid dispersion systems were more friable than those made from physical mixtures (table 2). This effect can be attributed to the decrease in crushing strengths of tablets made from solid dispersion systems. Overall the friability of tablets prepared from physical mixtures and those prepared from solid dispersion system with 1:3 drug: polymer was within reasonable limits according to Marshal (9).

Drug release profiles for tablets made from physical mixtures are seen in Figure 1. All the matrices were disintegrated during dissolution test. The time taken for complete disintegration of matrices was dependent on the polymer content in the matrix. The more polymers present in the matrix, the longer the time for complete disintegration. The drug release from matrices with 1:1 drug:polymer ratio was rapid due to rapid disintegration and all of the drug was released in the first 15 minutes. Increasing the polymer content in matrices resulted in a decrease in drug release in each sampling time. For example the percent of drug release from 1:1 drug polymer mixture was 100% after 15 minutes while the corresponding value for 1:3 mixtures was 13.5%. This relationship between polymer content and drug release has been reported in other investigations (2, 10, 11).

Tables 3 and 4 show the rate constants and correlation coefficients of the fits of release data to different kinetic models for matrices prepared from physical mixture of drug and polymer and those prepared from solid dispersion systems respectively. The correlation coefficient for the best statistical line revealed that Higuchi model was better applicable to the release data. The reduction in release rate by the increase in polymer content was due to the increased thickness of tablets, which resulted in longer diffusional path over which the drug must diffuse and also in production of harder tablets, which retarded the diffusion of water into the matrices and consequently prolonged the time required for disintegration of matrices. Nevertheless in tablets made from physical mixtures, drug release was fast even at drug: polymer ratio of 1:3 and the entire drug was released after 150 minutes. The release profiles for tablets made from solid dispersion systems are shown in Figure 2. The relationship between the polymer content and the drug release was also observed for these matrices. These results are similar to the release profiles of furosemide (5) and diflunisal (7) from Eudragit matrices and also for the release profile of verapamil HCl from ethylcellulose matrices (6), which were prepared from solid dispersion system. The percents of drug release after 15 minutes were 22.5% and 10% for 1:1 and 1:3 drug:polymer ratios respectively.

It has been reported that the crushing strengths of the ethylcellulose matrices has a great influence on drug release rate (2, 3) and the harder tablets have lower release rates. Comparison of release profiles (figure 3) and Higuchi release rates (tables 3 and 4) show that matrices prepared from solid dispersion systems which are softer show considerable slower drug release rate compared to harder matrices prepared from physical mixtures. IR spectra of sodium diclofenac, ethylcellulose and their physical mixtures or solid dispersion systems (data are not shown) indicated that no interaction exists between drug and polymer since all characteristic bands of sodium diclofenac in the IR spectra were also observed in both physical mixtures and solid dispersion systems. Therefore reduction in drug release rate could be attributed to the encapsulation of drug particles by polymer film after solvent evaporation in solid dispersion system which results in slower diffusion of the drug through polymer.

However, the retardation effect of ethylcellulose on drug release from matrices prepared from solid dispersion system was lower than that reported by Dangprasirt and Ritthidej (12).

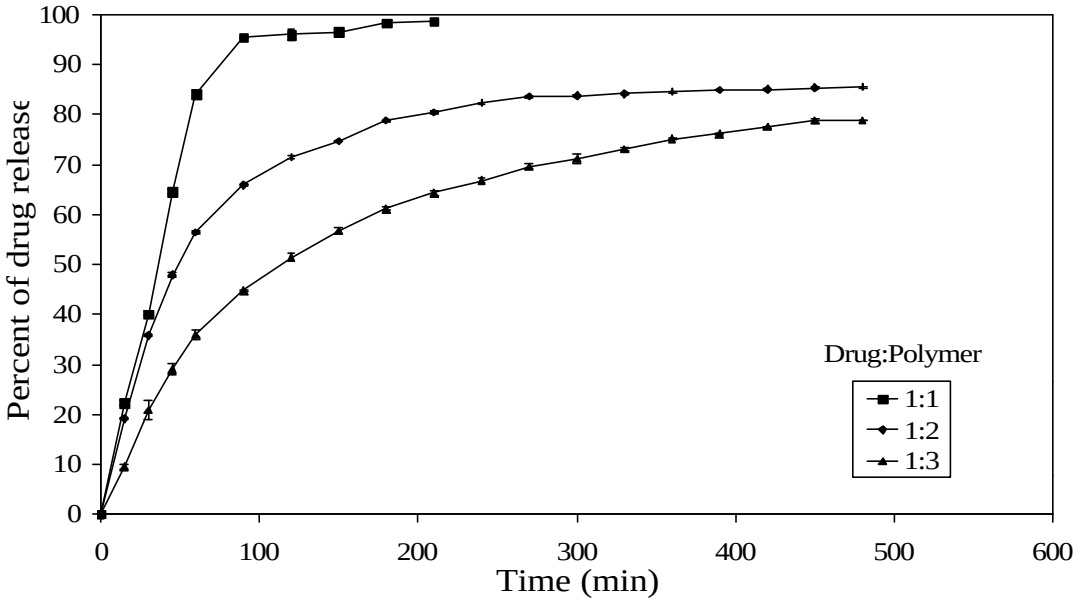

Figure 1. Effect of drug:polymer ratio on sodium diclofenac (100mg) release from matrices prepared from physical mixtures.

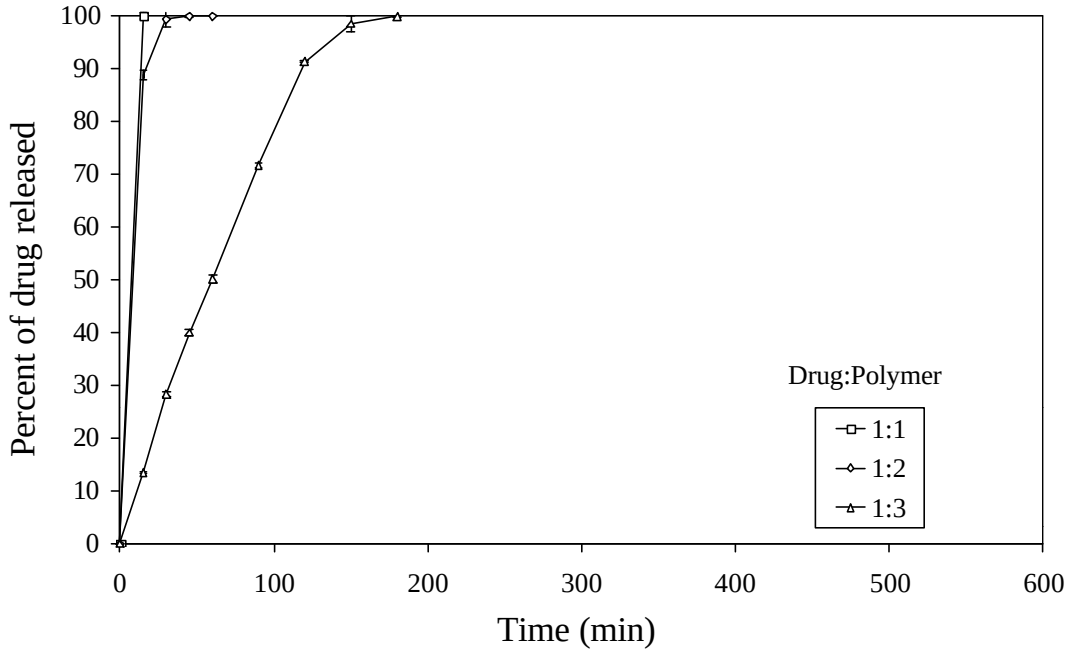

Figure 2. Effect of drug:polymer ratio on sodium diclofenac (100mg) release from matrices prepared from solid dispersion mixtures.

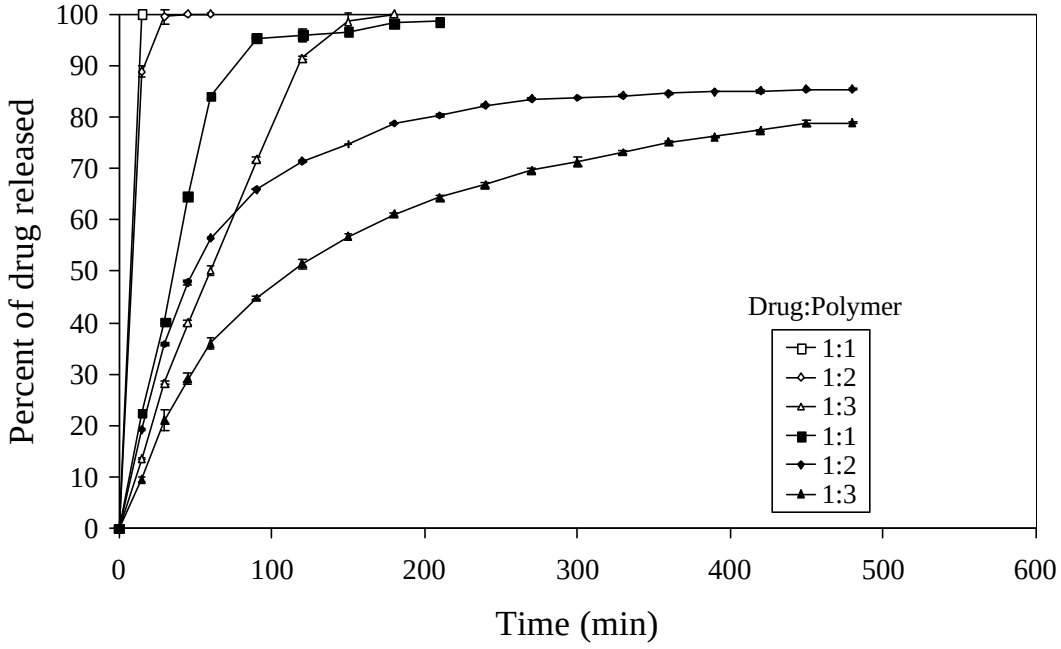

Figure 3. Comparison of sodium diclofenac release from matrices prepared from physical mixtures (open symboles) or solid dispersion mixtures (closed symboles) at different drug:polymer ratios.

Table 1. Crushing strengths of matrices and p value obtained in Tukey test for comparison of crushing strengths in each raw

Drug:Polymer	Crushing strength (kg)		p value
	Physical mixture	Solid dispersion mixture	
1:1	7.4 ± 0.4	4.8 ± 0.3	*** <0.001
1:2	11.2 ± 0.3	8.1 ± 0.5	*** <0.001
1:3	15.1 ± 0.5	13.9 ± 0.3	*** <0.001

*** indicating significant differences between crushing strengths of matrices in each raw.

Table 2. Weight loss after friability testing (%w/w) and the results of t test for comparison of %friability in each raw

Drug:Polymer	Weight loss (% w/w)		The results of t test=p< 0.05
	Physical mixture	Solid dispersion mixture	
1:1	0.60 ± 0.09	1.10 ± 0.10	Significant
1:2	0.30 ± 0.01	1.20 ± 0.09	Significant
1:3	0.50 ± 0.06	0.90 ± 0.08	Significant

Table 3. Values of release rates and the correlation coefficients (r) obtained from fit of release data to different kinetic mo dels for matrices prepared from physical mixture of drug and polymer

Drug:Polymer	Higuchi model		Zero order model	
	Release rate ($\%min^{-1/2}$)	r	Release rate ($\%min^{-1}$)	r
1:1	Not enough data	---	Not enough data	----
1:2	15.8	0.951	2.07	0.830
1:3	9.8	0.990	0.54	0.960

Table 4. Values of release rates and the correlation coefficients (r) obtained from fit of release data to different kinetic models for matrices prepared from solid dispersion systems of drug and polymer

Drug:Polymer	Higuchi model		Zero order model	
	Release rate ($\%min^{-1/2}$)	r	Release rate ($\%min^{-1}$)	r
1:1	7.8	0.903	0.41	0.833
1:2	4.7	0.882	0.08	0.784
1:3	3.4	0.966	0.13	0.904

Table 5. The values of release exponent (n)

Drug:polymer	Matrices prepared from physical mixture	Matrices prepared from solid dispersion system
1:1	Not enough data	0.99
1:2	Not enough data	0.47
1:3	0.87	0.44

These authors prepared 3:1 sodium diclofenac and ethylcellulose solid dispersion system by spray drying and showed this ratio gave continuous release of drug over 12 h period. The observed differences in drug release rate in these studies could be attributed to differences in methods for the preparation of solid dispersion system.

It was also observed that the percent of the drug release reached a plateau for tablets made from solid dispersion systems with 1:2 and 1:3 drug: polymer ratio and not all of the drug was released during the dissolution test. This effect could be attributed to the complete coverage of some of drug particles with impermeable ethylcellulose coating. The barrier effect of ethylcellulose coating in solid dispersion systems is much greater than the barrier effect of ethylcellulose particles surrounding the drug particles in tablets made from physical mixtures.

In fact the drug particles are sealed within a cast film of ethylcellulose in solid dispersion system in such a way that the dissolution medium cannot reach these particles. Increase in polymer content probably increased the thickness of the coating and decreased the percent of the drug release to a high extent. Such incomplete drug release has been reported for release of difunisal from Eudragit RL and RS, which has been attributed to the electrostatic interaction between drug and polymers (7). The values of n for different matrices are listed in Table 5. Due to the rapid drug release it was not possible to obtain enough release data for tablets made from physical mixtures with 1:1 and 1:2 drug: polymer ratios. The value of n for tablets made from physical mixture with 1:3 drugs: polymer ratio indicates that mostly erosion controls drug release from these matrices.

The values of n for tablets made from solid dispersion systems indicated that different mechanisms of release were observed for drug according to the polymer content. While for 1:1 drug:polymer ratio erosion was the predominant mechanism controlling drug release, for 1:2 and 1:3 solid dispersion systems diffusion was the main mechanism. This change in drug release mechanism was due to more effective coating of drug particles with ethylcellulose coating at 1:2 and 1:3 drug: polymer ratios which resulted in delay of drug release and caused slow diffusion as the main mechanism which controlled drug release.

CONCLUSION

The use of solid dispersion technique for preparation of drug and polymer mixtures affected matrix characteristics.

Although tablets, which were prepared from physical mixtures, were harder than those which prepared from solid dispersion systems their release rates were faster. This was attributed to changes in drug release mechanism from erosion to diffusion due to encapsulation of drug particles by polymer in matrices prepared from solid dispersion system. Therefore solid dispersion technique may be a valuable method for preparation of slow release formulation of ethylcellulose matrices and may provides slow release formulation with consumption of less polymer compared to physical mixing of drug and polymer.

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