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CONTROLLED-RELEASE MATRIX OF ACETAMINOPHEN-ETHYLCELLULOSE SOLID DISPERSION

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ABSTRACT

In this study ethylcellulose was evaluated as a carrier for preparation of prolonged release acetaminophen tablets. Solid dispersions containing three levels of ethylcellulose and acetaminophen (1:3; 1:1; 3:1) were prepared by the solvent method. Also physical mixtures at the same level of ethylcellulose and acetaminophen were prepared. Systems composed of solid dispersion or physical mixture containing the equivalent weight of 50 mg acetaminophen, Lactose fast-flo as diluent and 1% magnesium stearate as

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lubricant were compressed into tablets and tested for dissolution. The dissolution data showed that the drug release decreased as the level of ethylcellulose increased in the solid dispersion formulations. The drug release from tablets prepared with solid dispersion followed the diffusion controlled model for inert porous matrix, while the drug release from tablets prepared with physical mixture followed the first-order kinetic model.

INTRODUCTION

The term solid dispersion has been defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting, solvent or melting-solvent method (1). The technique of solid dispersion in which a drug is incorporated in an inert carrier or matrix has been extensively used to enhance the dissolution of poorly water soluble drugs (1-5). Drug release can either be accelerated or retarded, depending on the nature of the carrier whether hydrophylic or hydrophobic (6). Thus incorporation of a water soluble drug as acetaminophen with an inert hydrophobic carrier as ethylcellulose polymer can possibly prolong drug release due to association of drug particle with carrier.

In this work attention were directed toward the study of controlled release systems of acetaminophen

and ethylcellulose using the solid dispersion technique versus physical mixture. The influence of ethylcellulose level and methods of preparation on the properties of the resulting tablets were investigated. Also the dissolution data were analyzed in order to explain the mechanism of drug release.

MATERIALS

Acetaminophen, (Supplied by Warner Lambert Co., PR); Ethylcellulose, (Supplied by Searle Co., PR); Lactose fast-flo (Foremost, Wisconsin, USA); Magnesium stearate, (Ruger Chemical Co., Inc.).

METHODS

Solid Dispersion Systems

Solid dispersions containing three levels of ethylcellulose and acetaminophen (1:3; 1:1; 3:1) were prepared by the solvent method. Ethylcellulose polymer was added very slowly and dissolved in ethanol 95% with magnetic stirrer under constant stirring. After complete solubilization of ethylcellulose polymer, acetaminophen was added to the stirred polymer solution and stirring continue until the drug was completely dissolved. After complete solubilization of acetaminophen, all the alcohol was evaporated on a Rotavapor at 80-90°C, until a dry and white mass was observed (solid dispersion). The

solidified solid dispersion was removed and stored in a desiccator over night. The solid dispersion was passed through US Standard Sieve No.20 and fraction size of 20/100 was separated.

Physical Mixture Systems

Physical mixtures containing three levels of ethylcellulose and acetaminophen (1:3; 1:1; 3:1) were prepared. The powder mixture was added in order to Turbula Mixer and mixed for 5 minutes.

Blending

Lactose fast-flo was added to both physical mixture or solid dispersion systems. The materials for each formulation were mixed in Turbula Mixer by order mixing for 10 minutes. Magnesium stearate was passed through screen #30 and was added to the mixture and mixed for further 5 minutes.

Compaction

The blended formulations were tableted on a Rotary Manesty B3-B tablets press. A set of 12/32 inches round flat-faced punches and a die were selected. Weight and hardness of the tablets were monitored during the tabletting operation using an analytical balance and Schleuniger hardness tester. Target hardness was 7-9 kp and target weight was 450 mg in all formulations.

Control Preparation

Tablets as control were obtained by mixing acetaminophen with Lactose fast-flo by order mixing for 10

minutes in Turbula Mixer. Magnesium stearate was passed through screen #30 and added to the mixture and mixed for further 5 minutes. Finally, the blended formulations were compressed into tablets.

Dissolution Test

The USP/NF Basket method (Apparatus #1) was used for testing dissolution of all formulations. The rotational speed was held constant at 50 rpm. and the medium was 900 ml distilled water at 37°C. Samples of 10 ml were withdrawn from the dissolution kettles at each time interval and measured for absorbances by U.V./Visible spectrophotometer at wavelength of 249 nm. Sample volumes were replaced with an equal volume of distilled water at ambient temperature.

RESULTS AND DISCUSSION

Effect of Methods of Preparation on Acetaminophen Release

Tablets from physical mixture systems, solid dispersion systems were prepared as well the control, using Lactose fast-flo as diluent and magnesium stearate as lubricant.

Figure 1 show that the methods of preparation used has a significant effect on drug release from tablets prepared from a ratio of acetaminophen:ethylcellulose (1:3). As indicated in Figure 1, the dissolution data

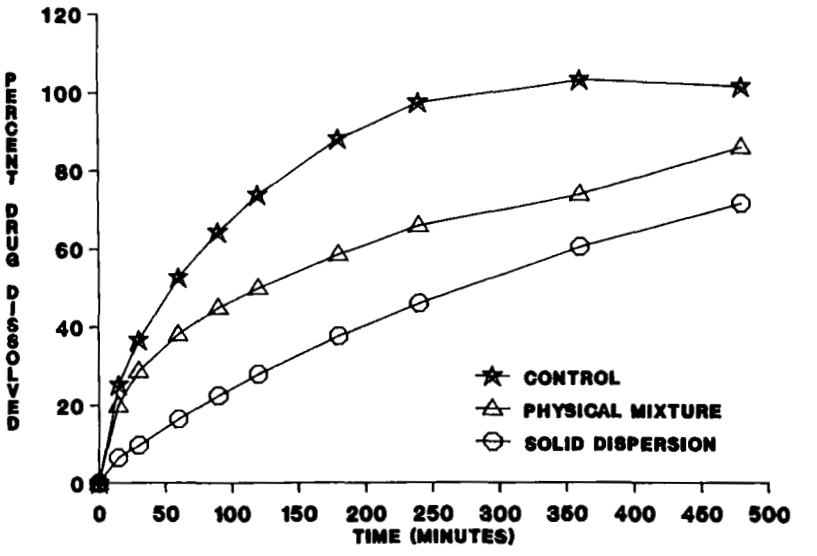

Figure 1
Effect of methods of preparation on acetaminophen (APAP) release from tablets with APAP:E.C. (1:3).

for tablets prepared from acetaminophen:ethylcellulose (1:3) ratio using solid dispersion method showed significant decrease in acetaminophen release. However tablets prepared from ratios of acetaminophen:ethylcellulose (1:1) and (3:1), the methods of preparation showed no significant effect on acetaminophen release. The drug release was approximately similar from all methods of preparation as shown in Figure 2 for tablets prepared from acetaminophen:ethylcellulose (3:1).

Effect of Ethylcellulose Levels on Acetaminophen Release

The release rate of acetaminophen was decreased by the incorporation of acetaminophen in three different

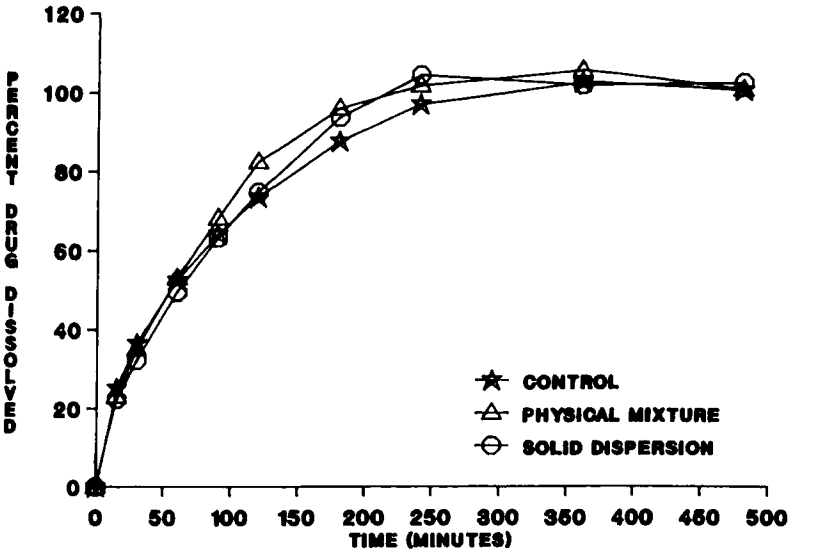

Figure 2
Effect of methods of preparation on acetaminophen (APAP) release from tablets with APAP:E.C. (3:1).

levels of ethylcellulose, using the solid dispersion technique.

The drug release from tablets prepared with physical mixture system of acetaminophen:ethylcellulose (3:1) and (1:1) were not slower than control tablets, while tablets prepared with physical mixture system of acetaminophen: ethylcellulose (1:3) showed significant decrease in acetaminophen release over 6 hours. Only 65.6% drug was released, while 97.0% drug was released from the control tablets after 4 hours of testing dissolution as shown in Figure 3.

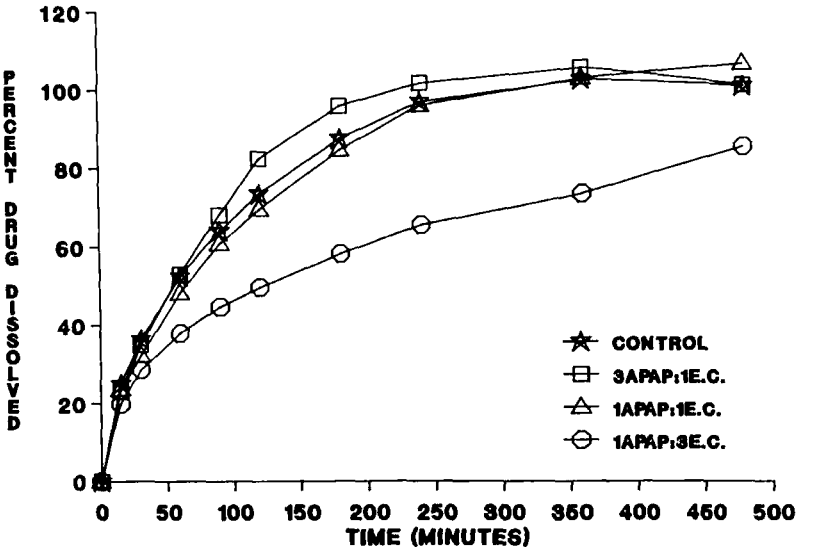

Figure 3
Effect of ethylcellulose levels on acetaminophen (APAP) release from tablets prepared with physical mixture.

The drug release from tablets prepared with solid dispersion system of acetaminophen:ethylcellulose (3:1) showed the same release profile as the control, while tablets prepared with solid dispersion of acetaminophen:ethylcellulose (1:3) showed the slowest drug release profile. The percent of drug release from tablets prepared with solid dispersion of acetaminophen: ethylcellulose (1:3) was 45.7%, while the percent of drug release from tablets prepared with solid dispersion of acetaminophen:ethylcellulose (1:1) is 84.1% and from control tablets was 97.0% after 4 hours of testing

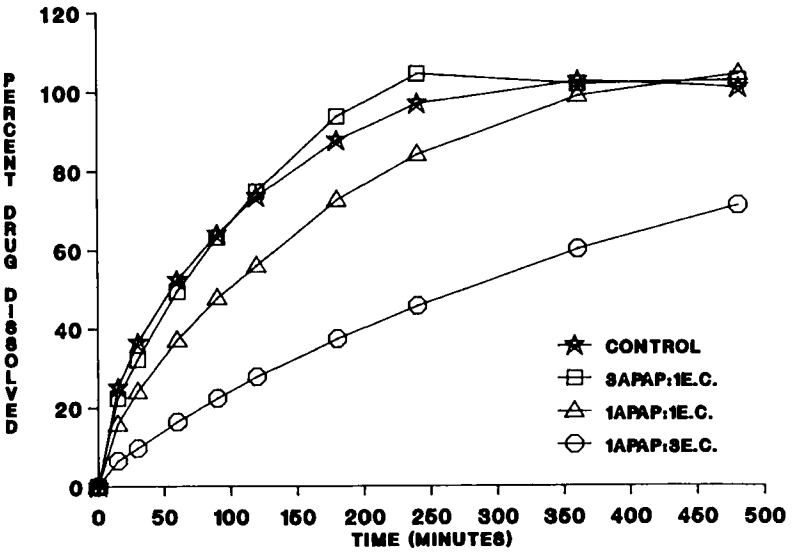

Figure 4
Effect of ethylcellulose levels on acetaminophen (APAP) release from tablets prepared with solid dispersion.

dissolution as shown in Figure 4. As the percent of ethylcellulose increased in the solid dispersion system, the percent of acetaminophen released from tablets containing solid dispersion system and Lactose fast-flo decreased.

Mechanism of Drug Release

Several publications (7-10) have dealt with the mechanism by which a drug would be released from a dosage form. From the dissolution data it was found that tablets compacted from physical mixture systems and

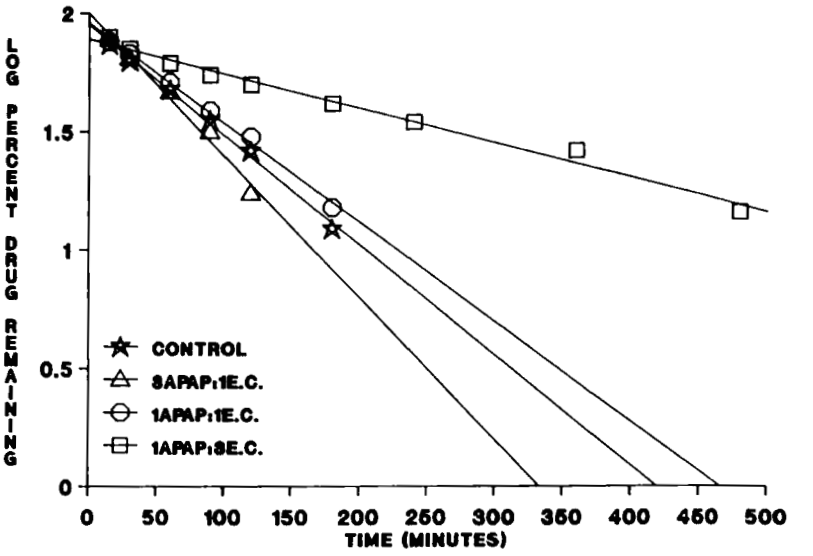

Figure 5
First—order plot for acetaminophen (APAP) release from tablets prepared with physical mixture.

Lactose fast-flo fit the first-order kinetic model as shown in Figure 5

$$\log A = \frac{kt}{2.303} + \log Ao$$

where, A is the amount of drug left in tablet; Ao is the initial amount of drug in tablet; k is the firstorder release rate constant and t is the time.

From the dissolution data as shown in Figure 6 it was found that tablets compacted from solid dispersion systems and Lactose fast-flo fit a square root of time relationship. Higuchi stated that the amount of total

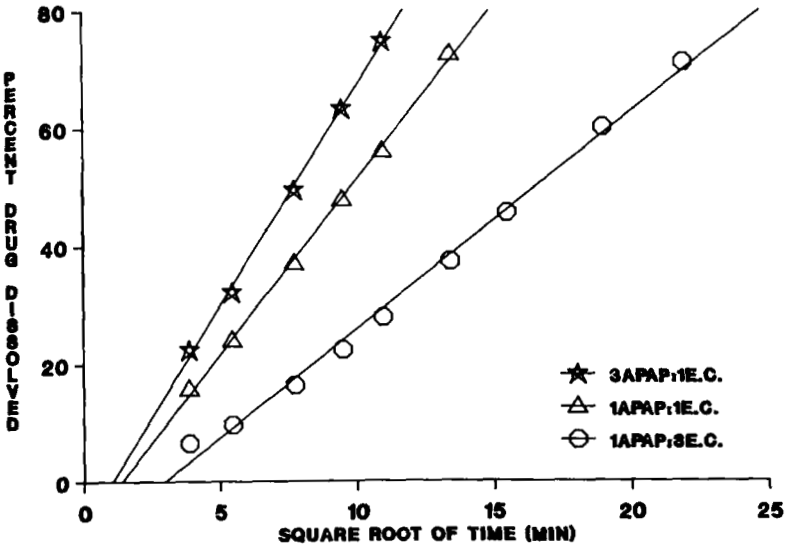

Figure 6

Square root of time plots for acetaminophen (APAP) release from tablets prepared with solid dispersion. physical mixture.

drug released from a planar system having a heterogeneous matrix, would be determined by the following relationship,

$$Q = \left[\frac{D\,\epsilon}{\tau}\,(2A - \epsilon\,Cs)\,Cs\,t\right]^{\frac{1}{2}}$$

where, Q is the amount of drug released after time t per unit area; D is the diffusitivity of the drug; ϵ is the porosity in the matrix; τ is the tortuosity factor; A is the total amount of drug present in the matrix; Cs is the solubility of the drug present in the matrix and t is the time.

CONCLUSIONS

The process of solid dispersion of acetaminophen with ethylcellulose is applicable to the controlled release system, but different levels of ethylcellulose produced different results. The ethylcellulose imparted controlled release characteristics in solid dispersion formulations but the effectiveness and the mechanism of drug release was dependant on the polymer level. Ethylcellulose polymer can effectively produced a sustained release formulations of the water soluble drug acetaminophen using the solid dispersion technique.

REFERENCES

1. W.L.Chiou, S.Riegelman, J. Pharm. Sci., 58, 1281, 1505 (1969).
2. J.Akbuga, A.Gursoy, F.Yetimoglu, Drug Dev. Ind. Pharm., 14, 2091 (1988).
3. R.Jachowicz, Int. J. Pharm., 35, 1, 7 (1987).
4. Y.E.Hamza, Pharm. Ind., 52, 363 (1990).
5. A.T.Serajuddin, P.C.Sheen, M.A.Augustine, J. Pharm. Sci., 79, 463 (1990).
6. N.A.Shaikh, S.E.Abidi, L.H.Block, Drug Dev. Ind. Pharm., 13, 1345, 2495 (1987).
7. T.Higuchi, J. Pharm. Sci., 52, 1145 (1963).
8. J.B.Schwartz, A.P.Simonelli, W.I.Higuchi, J. Pharm. Sci., 57, 274 (1968).

9. P.Singh, S.J.Desai, A.P.Simonelli, W.I.Higuchi, J. Pharm. Sci., 56, 1542, 1548 (1967).

10. F.Sjuib, A.P.Simonelli, W.I.Higuchi, J. Pharm. Sci., 61, 1374, 1381 (1972).