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# EFFECT OF FORMULATION VARIABLES ON THE PREPARATION AND IN VITRO - IN VIVO EVALUATION OF CIMETIDINE RELEASE FROM ETHYL CELLULOSE MICROPELLETS

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**ABSTRACT**

Ethyl cellulose embedded prolonged release microparticles containing cimetidine was designed by dispersing the drug-ethyl cellulose mixture in acetone, into a medium of mineral oil and subsequent rigidization of the ethyl cellulose matrix. Significant reproducibility of the manufacturing process was observed. *In vitro-in vivo* correlation revealed the the dissolution process is the rate determining step in drug absorption and the significant *in vivo* efficiency of the dosage form is well expected.

## INTRODUCTION

The design of micropellets as a technique for the preparation of controlled release matrix embedded dosage form has earned importance. Generally, pellets are spherical bodies formed from a mass of finely divided particles by a continuous rolling or tumbling motion[1]. A number of methods for the preparation of gelatin micropellets have been reported. The embedding of drug in hydrophillic gelatin matrix was first reported by Tanaka et al[2]. The process of manufacture was thoroughly mod-

ified and different properties were investigated by Das and Gupta[3].

Cimetidine, a specific $H_2$ - receptor antagonist, has a half life of 123 ±12 min with a much shorter duration of action[4]. The absorption of cimetidine from the gastrointestinal tract is also dissolution rate limited. The prolonged release dosage form of cimetidine is an important therapeutic aspect because it would be able to maintain the steady plasma level of the drug and reduce the frequency of administration. The present investigation envisages the development of a controlled release dosage form of cimetidine in order to maximize the therapeutic benefits and minimize the frequency of administration in case of severe conditions like Zollinger - Ellison syndrom[5].

The development of micropelleted dosage form was achieved by nonaqueous spray congealing technique. Three formulations of micropellets with a drug : ethyl cellulose ratio of 1:1, 1:2 and 1:2.5 were standardized after the preliminary screening. The dosage forms were evaluated both *in vitro* and *in vivo* .

## EXPERIMENTAL

### Materials

Cimetidine - Indian Pharmacopeia, passed through # 100 sieve

Ethyl cellulose - Degree of substitution 2.42 - 2.53, viscosity of a 5% w/w solution in 80 : 20 toluene : ethanol by weight at $25^{o}$ approx. 14 cP

Toluene - Extra pure grade

Liquid paraffin and Light liquid paraffin - Indian Pharmacopeia

Petroleum ether - Boiling range 60 - 80°, wt per ml 0.67 gm

**Methods**

Preparation of Micropellets

A 12% w/v homogeneous solution of ethyl cellulose in acetone was prepared. Powdered cimetidine was dispersed into the solution to form an uniform drug - ethyl cellulose mixture. This mixture was poured at 25°, in a thin steady stream, into 400 gms of mixture of 80% w/w of liquid paraffin and 20% w/w of light liquid paraffin (absolute viscosity 103.10 cP at 25°) while stirring the liquid paraffin mixture at 400 ± 5 r.p.m. After 15 minutes, petroleum ether was added at a rate of 3 ml/min for a period of 30 minutes. During this period, the temperature of the system was very slowly cooled to 5°.

Recovery of the formed micropellets was achieved by decanting the supernatant petroleum ether and successive washing with chilled petroleum ether. It was then dried in open air for 1 hour, followed by 2 hours controlled drying at 60°.

*In vitro* dissolution

The pH profile (pH 1.2 - 7.5) was achieved using the solutions of hydrochloric acid, sodium carbonate and the sodium bicarbonate in double distilled water [6]. Micropellets of cimetidine were placed in the USP XX dissolution basket, covered with 100 mesh nylon cloth to prevent the granules coming out of the basket. Five hundred ml of the dissolution fluid was used. The basket with the granules was rotated at 100 ± 1 r.p.m.

Five ml of the sample aliquots were withdrawn and replenished the same volume. The dissolved drug was assayed spectrophotometrically using Hitachi 200 - 20 UV/Vis spectrophotometer.

*In vivo* Animal Studies.

The *in vivo* dissolution of the drug from the micropelleted dosage form was studied by administering the micropellets to twelve male albino rabbits weighing 2.5 - 3 kgs. On four separate occasions, fast release cimetidine tablets, micropellets of core : coat ratio 1:1, 1:2 and 1:2.5 were orally administered. All dosage contained equivalent to 50 mg of cimetidine. The rabbits were fasted overnight for about 22 hours, while water was allowed ad libitum. At the begining of the experiment, a 0-hour sample of the blood was obtained from the marginal ear vein. Then the micropellets in hard gelatin capsule was placed in the rear pharynx of the rabbit through the hole in wooden gag holding the mouth open. Then by generating air pressure, the capsule was pushed through the pharynx. No water was given and the food was allowed at 4 hrs. Blood samples were withdrawn from the marginal ear vein at fixed interval. After the separarion of the plasma proteins by trichloroacetic acid, the content of drug was determined by HPLC technique[7].

## RESULTS AND DISCUSSIONS

The formation of ethyl cellulose micropellets is a physicochemical phenomenon. The spherical micropellets are formed due to the strong cohesive forces among the molecules of the ethyl cellulose sol, during the continuous rolling motion of the soft microdrops in a viscous medium. The viscosity of the ethyl cellulose sol, stirring speed and the viscosity of the dispersing medium influences the formation of the spherical micropellets.

An important phenomenon was noted during the production of the micropellets. In the present investigation, a soluble drug was dispered into the matrix forming polymer but when the non-solvent petroleum ether was added, the matrix separates as a soft sphere. Some cimetidine may be partitioned into the acetone, which itself is insoluble into the petroleum ether. Thus, the solubility parameter of cimetidine exceeds that of the acetone - petroleum ether mixture. This cimetidine is again adhered to the surface of the newly formed micropellets. Thus preventing the loss of costly drug during the manufacturing steps, as well as incorporating the loading dose. This was supported experimentally by the determination of content of drug at the various stages of the formulation.

The release of cimetidine from the micropellets may either be first order[7] or the diffussion controlled process [8]. The *in vitro* drug release data was plotted according to first order (fig. 1) and Higuchi equation (fig. 2). Drug release appeared to fit both the kinetic models upto certain extent. Deviations from linearity was observed in the plots of Higuchi equation after 110 mins. Therefore, the drug release was followed by diffusion controlled first order dissolution. In the fig. 1, we could observe the dissolution kinetics showing an abrupt inclination in the begining of the plot. This was due to the bursting effect [9] and adherence of the drug particles on the formed micropellets, which would be a highly desirable aspect for the achievement of the loading dose.

The availability of adequate animal models has been desired for estimating the bioavailability of dosage forms in human . Although rabbits are easy to handle, they have not been considered as the ideal animal model because of the difficulty in obtaining the empty stomach[10]. However, control of

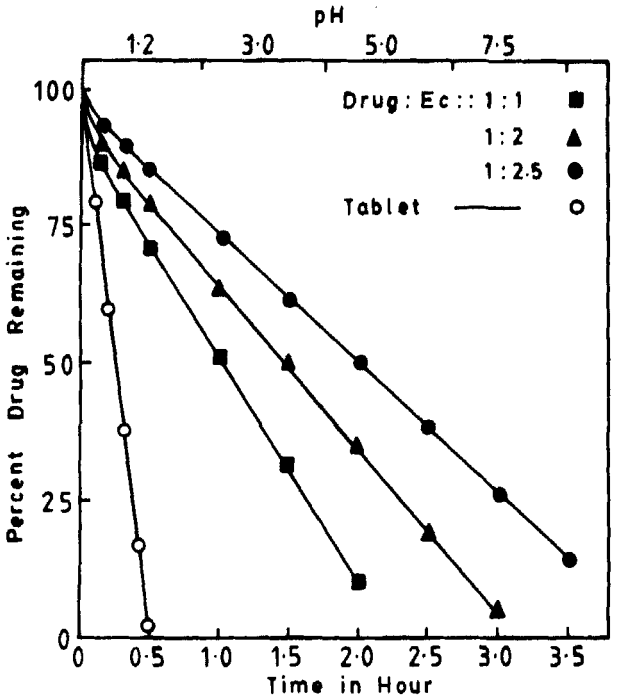


Fig. 1. First order plot of the *in vitro* cimetidine release profile

the stomach emptying rate has increased the usefulness of rabbits in G.I. drug absorption studies and produced good correlation in G. I. drug absorption between rabbits and human[11].

For the *in vivo* study, the use of fasting rabbits showed a great advantage over the retardation of cimetidine absorption from the gastrointestinal tract. The pharmacokinetic parameters were estimated from the serum concentration of cimetidine after administration of either cimetidine powder or cimetidine micropellets (Table). The mean values of the maximum serum level ($C_{max}$) and the time to maximum serum level ($t_{max}$) were not

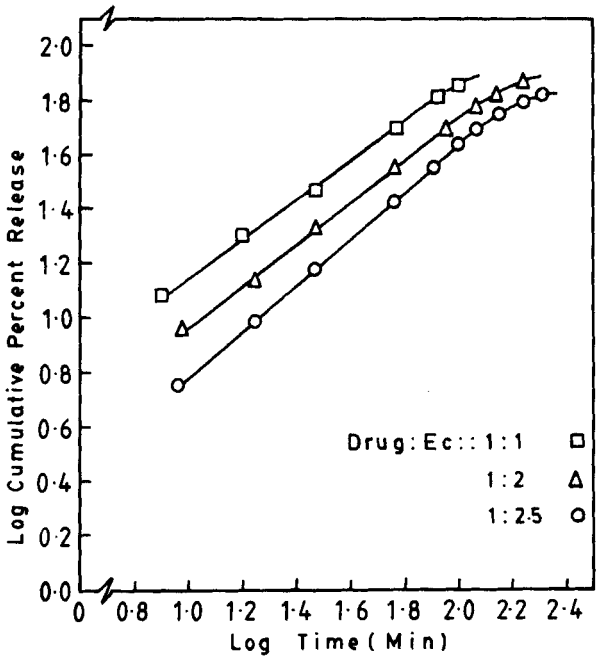


Fig. 2. Higuchi plot of the *in vitro* cimetidine release profile.



significantly different from cimetidine micropellets prepared with lower percentage of ethyl cellulose. The higher $C_{max}$ value is consistent with the shorter $t_{max}$ value. However, a significant difference was obtained for cimetidine microcapsules by using higher concentrations of ethyl cellulose. The plasma $t_{50\%}$ of cimetidine were much longer with the higher concentration of the ethyl cellulose in the formulation. This indicates that cimetidine micropellets prepared by using higher concentration of ethyl cellulose exhibited better controlled release properties.

The relationship between the mean plasma level, $C_m$, and the logarithm of the drug dissolved in 0.5 hr, log $D_{0.5}$, is

**TABLE**

Pharmacokinetic Parameters of Cimetidine Micropellets after Oral Administration in Rabbits

| Concentration of Ethyl Cellulose %w/w | Number of Rabbits | $C_{max}$ µg/ml | $t_{max}$ hour | $AUC_{0-\infty}$ µg.hr/ml | $t_{50\%}$ hour |
|---|---|---|---|---|---|
| 50% | 8 | 0.57 | 2.74 | 6.58 | 4.95 |
| 66% | 8 | 0.45 | 3.52 | 7.95 | 6.51 |
| 71% | 8 | 0.31 | 4.02 | 9.89 | 8.84 |
| Compressed Tablet of Cimetidine | 8 | 0.80 | 1.54 | 3.32 | 2.35 |

Figures are average for eight results; $p < 0.10$

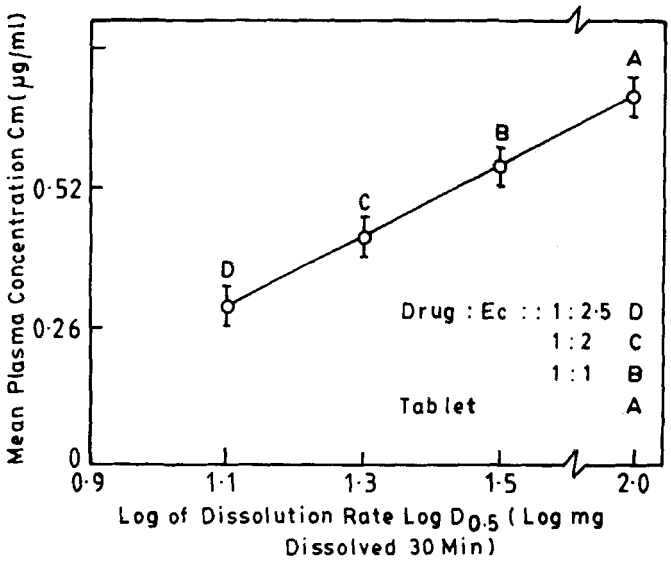


Fig. 3. Correlation of *in vitro* dissolution rate and mean plasma drug concentration, average ± S.E. in nine animals.

shown in figure 3. The regression equation was, $C_m$=0.4212 log $D_{0.5}$-0.1273. Significant correlation between $C_m$ and log $D_{0.5}$ was 0.990 ($P < 0.10$). These results signify that the dissolution process is the rate determining step in the drug absorption. From the correlation coefficient it is well expected that the micropellets of cimetidine would exhibit satisfactory controlled release characteristics.

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