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Studies on enteric coated sustained timed-release tablets of Metronidazole

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Abstract

The present article deals with an oral dosage form proposed for the attainment of timed release drug delivery of metronidazole. Metronidazole containing matrix tablets coated with 3,4,5 & 6% w/v cellulose acetate phthalate in acetone were examined for applicability as timed release tablets with a predetermined lag time of 4-5 hrs. Different types of enteric coated tablets were prepared and there drug dissolution profile was studied in 0.1 N HCl (0 to 2hr) and PBS 6.8 (2-24 hr) as dissolution media at 37±0.5 ºC,100 rpm by USP Apparatus-1(Basket assembly). The result indicated that the tablets with timed release functions could be prepared and,that the lag time were increased as the coat concentrations increased (3% to 6%w/v).The different kinds of timed release enteric coated tablets that showed lag time of 2 to 5.4 hrs in in- vitro dissolution in 2% w/v rat caecal content in 6.8 PBS(Phosphate buffer saline). The lag time showed a good agreement between the in- vitro test in PBS 6.8 and in -vitro test in 2% w/v rat caecal content. However the lag times were 4.5 hrs in in-vitro test in 2%w/v rat caecal content medium.

Key words: Cellulose acetate phthalate, Enteric coated, Metronidazole, lag time, 2%w/v rat caecal content.

Introduction

This study deals with an oral dosage form proposed for sustained timed- release drug delivery of metronidazole[1]. Metronidazole is the preferred drug for the treatment of intestinal amoebiasis. The administration of this drug in the conventional tablet dosage form provides minimal amount of metronidazole for local action in the colon, still resulting in the relief of amoebiasis[2-3, but with unwanted systemic effects. Timed release may therefore be a better alternative to overcome

the limitations of the conventional tablet dosage form. The present work was aimed at the preparation of timed release[4-6] tablets of metronidazole by enteric coating the matrix tablets of the drug to obtain the drug release after a lag time of about 4-5 hrs[7-9]. Enteric coated dosage forms of cellulose acetate phthalate[10] are designed to provide protection in the stomach. Application of a thick coat causes a delay in the drug release in small intestine and delays the drug release. This time controlled drug release may be retarded up to 5 hrs this targets the drug to the colon. Cellulose acetate phthalate is widely used as enteric film coating material or as a matrix binder for tablets and capsules. These enteric coating resists prolonged contact with the strongly acidic gastric fluids. The present investigation was carried out to evaluate to the ability of cellulose acetate phthalate based timed release tablets to target the drug to human colon such that these novel tablet formulations could be used for an effective and safe therapy of amoebiasis.

Materials and methods

Metronidazole I.P. (Nestor Pharmaceuticals Limited, Delhi) was used as a model drug. Cellulose acetate phthalate , Ethyl cellulose (Ethocel 50 cps), Hydroxy propyl methyl cellulose (HPMC E50 LV), Potassium dihydrogen orthophosphate, Magnesium stearate, Talc (s.d. fine-chem Limited , Mumbai) were used .

Preparation of core matrix tablets

The formula for matrix tablets containing 200 mg of Metronidazole is shown in table -1. The tablets were prepared by wet granulation method. HPMC was used as a diluent and a mixture of talc and Magnesium Stearate (2:1) was used as a lubricant. Each tablet was compressed to a theoretical weight 400 mg. All the process variables, like mixing time, compaction force etc were kept constant. Metronidazole, HPMC[12], Ethylcellulose were sieved through #60 to get uniform particle size. Weighed quantity of drug and polymer with diluent were blended together. Sufficient quantity of starch paste (10%w/v) was added to the powder mixture and mixed to get a wet mass. The wet mass was passed through sieve#10 and dried at 50 ºC for 2 hrs. The dried granules were then passed through sieve#20 and then weighed. The dried granules were lubricated with a mixture of talc and magnesium stearate (2:1) .The granules were compressed in to airtight container until evaluation.

Table-1: Composition of the core matrix tablets

Ingredient	Amount (mg)*
Metronidazole	200
HPMC E50 LV	128
Ethyl cellulose	20
Starch 10% w/v added as paste	40
Talc	8
Magnesium Stearate	4

* The amount in mg is given for a single tablet.

Tablet coating

The four batches of tablets CAP-I,II,III,IV were prepared by coating[17] with different conc. of cellulose acetate phthalate (3,4,5 & 6% w/v) in Acetone , polyethylene glycol-400 (1.5%w/v) was used as a plasticizer[11]. The desired volume of coating solution was poured on the prewarmed tablets (batch size of 40 gm) bed in a pan coater. The coating process was repeated till the desired level of coating was accomplished. The % mass increase of the tablets upon coating was taken to be indicative of the coat thickness[11].

Analytical procedure to determine metronidazole in tablets and dissolution media

The drug content of metronidazole was determined by HPLC (Shimadzu HPLC class VP), UV-VIS detector VP, with two LC-10 AT VP pumps, CTO-10AS VP column oven (Shimadzu), SCL-10A VP system controller (Shimadzu) and RP C-18 column (250×4.6 mm^2 ID, particle size 5µm) was used. The software class-VP series version 5.03 (Shimadzu) was attached with the HPLC system. The water TD (made up of 0.4 % triethylamine and pH adjusted to3.7 with 5% Orthophosphoric acid) and Acetonitrile was used as a mobile phase. The column temp. was maintained at 40ºC. The mobile phase was pumped at a flow rate of 0.7ml/min in the ratio of 44:56 (Acetonitrile and TD water.)

The eluent was detected by UV detector at 254nm. The standard curve for metronidazole was constructed in the conc. range of 0.1 to 50µ g/ml using mebendazole (2µg/ml) as an internal standard. The correlation coefficient was found to be (r=0.999).

Determination of drug content

20 tablets of metronidazole were taken and powdered in pestle and mortar. Powder equivalent to 100mg of drug was transferred to a 100ml vol. flask containing 40 ml of methanol. The content was allowed to stand overnight to ensure complete solubility of the drug and finally the volume was made up. 1 ml of internal standard (Mebendazole) after a suitable dilutions was estimated for drug at 254nm by reverse phase HPLC method.

In-vitro dissolution test

Drug release studies were carried out by using USP XXXIII dissolution apparatus (type 1 basket, 100 rpm, 37±0.5ºC) For 2 hrs in 0.1 N HCl (900ml). Then the dissolution medium[13-15] was replaced with PBS 6.8 for 22 hrs. The susceptibility of matrix tablets to enzymatic action of colonic bacteria was also assessed by continuing the release studies in rat caecal medium (2%w/v rat caecal content in pH 6.8 PBS) obtained after 7 days of enzymatic induction with 1 ml of guar gum dispersion .

DSC studies

Differential Scanning Calorimetry (DSC) was employed to detect any possible chemical interactions between the drug and polymers (HPMC E50 LV, Ethocel,) and other excipient employed in tablet formulations. DSC studies for the pure Drug, and the prepared tablets were carried out in order to study the polymorphic changes in the drug as well as its interaction with the excipients. Samples of pure Drug and powdered tablets were weighed directly in pierced aluminium pans (5 mg) and scanned between 20°C to 200°C at a heating rate of 10ºK min^{-1} under static N_2 gas at a pressure of 20 p.s.i.g. and 50ml/ min flow rate.

Stability studies

Stability testing forms an integral part of the formulation development process as the stability[16] of the active components is a major criterion in determining its acceptance or rejection .To assess the long term stability (2 years), the optimized formulations CAP-III were stored at 40º C /75% RH for 6 months and were observed. It provides evidence on how the quality of a drug substance/drug product varies with time under the influence of environmental factors such as temperature and humidity and ensures the safety and efficiency of a formulation. In order to achieve this goal, a preliminary aging study was conducted for the optimized batches of the formulated Timed–release tablets.

Results and discussion

The present study was aimed at developing timed-sustained release tablets of metronidazole to treat amoebiasis. In case of timed release drug delivery system it was observed that as we increased the coat thickness of Cellulose acetate phthalate, there was a proportionate increase in the lag phase.

***In-vitro* dissolution test**

The release profile of metronidazole from the timed -sustained release tablets of different batches (CAP-I to CAP-IV) are given in the following fig 1 and 2. All the tablets were subjected to in vitro dissolution with 0.1 NHCl for 2 hrs[13]. No drug release was seen during this time period. Then the same formulations were subjected to in vitro dissolution with 6.8 PBS for next 22 hrs. It was observed that CAP-I min lag phase (2.4 hrs) with maximum drug release (98%) and CAP-IV showed the maximum lag phase (5.4 hrs) with total percent drug release (78%). But the CAP-III showed appropriate combination of lag phase (5.2 hrs) with total percent drug release (90%) as shown in fig:1.

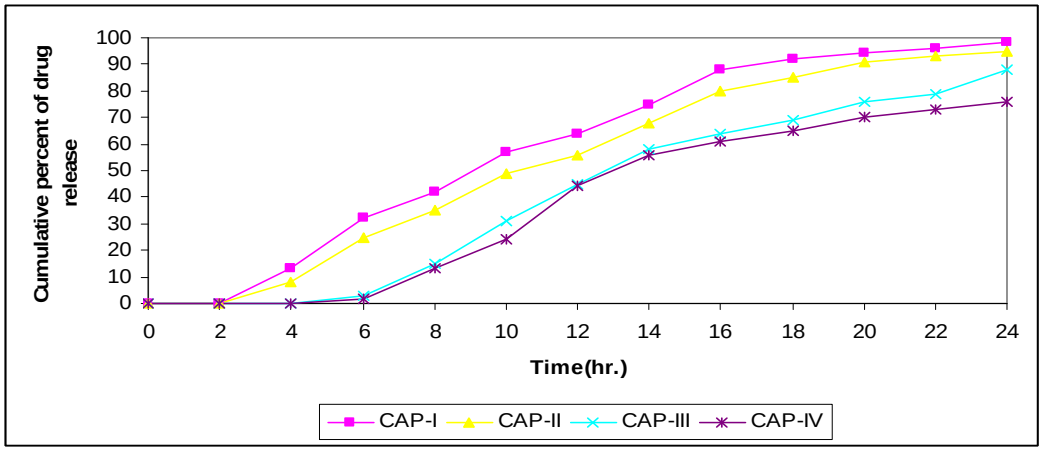

Fig 1: Comparative drug release profile of CAP-I, II, III and CAP-IV

Note: 0-2 hrs: in vitro dissolution with 0.1 N HCl; 2 -24 hrs: in vitro dissolution with pH 6.8 phosphate buffer saline.

In -vitro dissolution study was also conducted with pH 6.8 PBS containing 2% w/v rat caecal content for 22 hrs (as shown in fig:2). There were slight difference in in-vitro dissolution study results as the Cellulose acetate phthalate is not degraded by the rat caecal contents[18-20]. The

results of dissolution studies with and without rat caecal content were almost identical with minor differences.

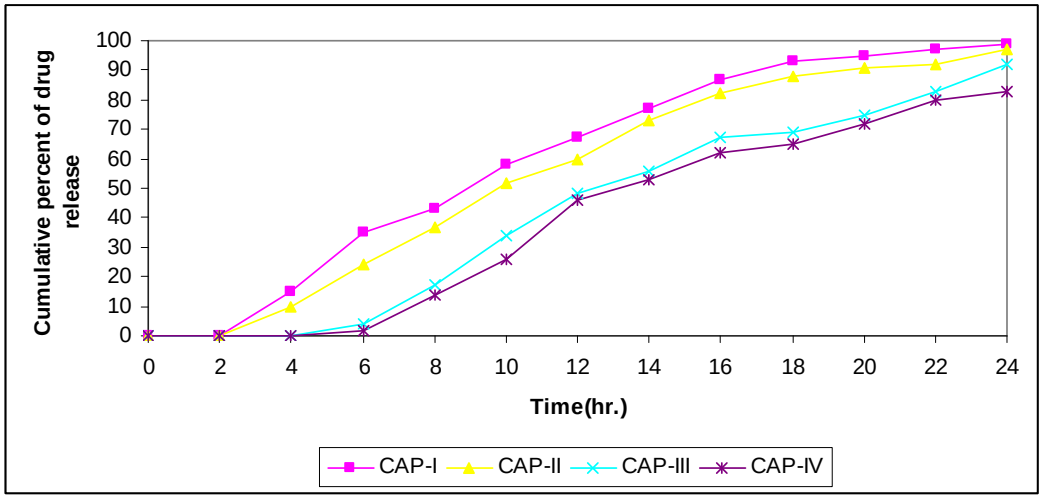

Fig 2: Comparative drug release profile of CAP-I, II, III and CAP-IV *

*0-2 hrs: in vitro dissolution with 0.1 N HCl; 2 -24 hrs; in vitro dissolution with 2%w/v rat caecal content in pH 6.8 phosphate buffer saline.

Effect of cellulose acetate phthalate coat conc. on the lag phase

At a coat conc. of 5%w/v Cellulose acetate phthalate provided the most appropriate timed – release formulations with a lag phase of (5.4 hrs) with less than 4% total drug release after 5 hr of dissolution study. It was seen that as we increase the coat conc. from 3% to 6%, consequently there was increase in lag phase from 2.2 hr to 5.4 hr respectively.

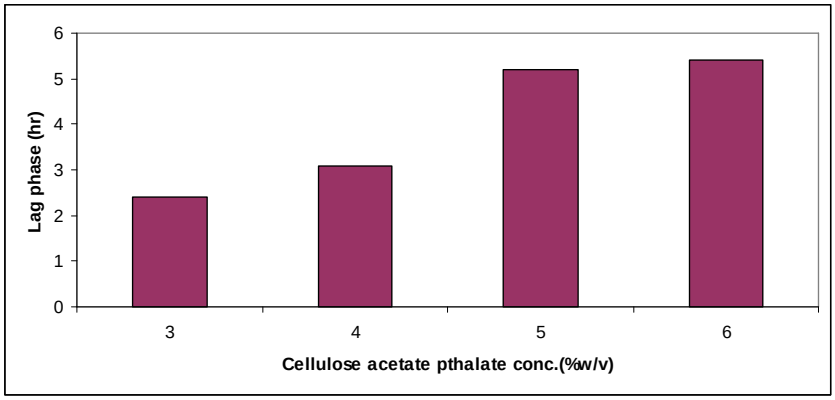

Fig 3: Effects of coat conc. on the lag phase of different timed-release formulations

DSC analysis results

The possibility of occurrence of any drug –excipients interactions in the tablets was predicted by conducting DSC studies (fig: 4). A sharp endothermic peak corresponding to the melting point of pure drug metronidazole was found at 166ºC. For drug sample and powdered optimized formulations. Even after storing the formulations at 40ºC/75% R.H. for 6 months, the thermograms did not show any significant shift in endothermic peaks. Based on the thermograms

of DSC, there appears to be no possibility of interactions between metronidazole and excipients, Cellulose acetate phthalate used in the tablets.

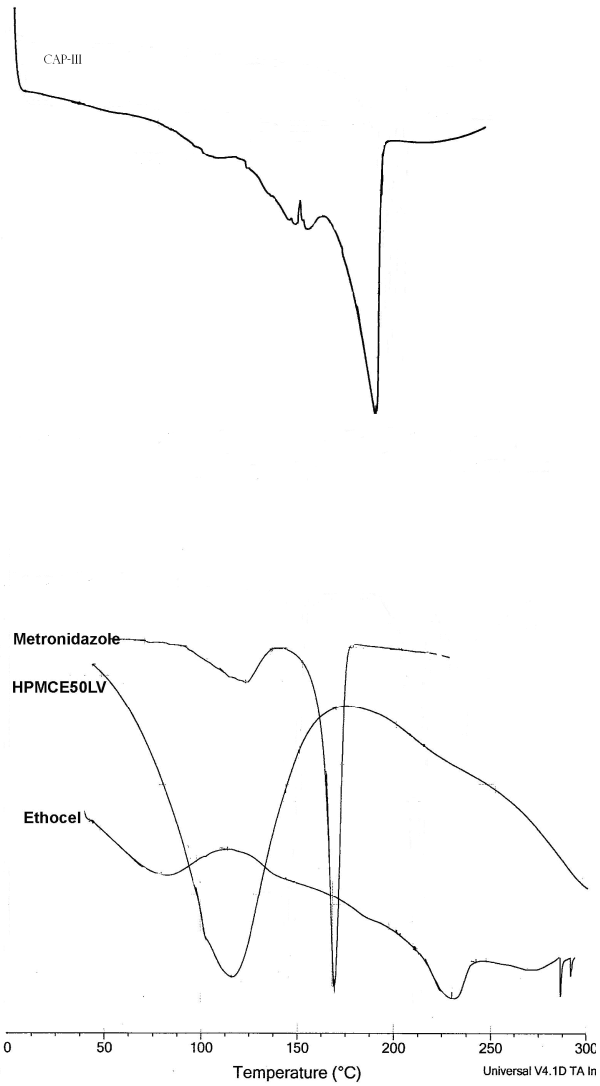

Fig 4: Differential scanning calorimetric thermograms of optimized tablet sample (CAP-III), metronidazole, HPMC, Ethyl cellulose

Stability study

Stability study was carried out for 6 month on the optimized formulations of the Metronidazole (CAP-III). For stability study, ten tablets of optimized formulations were placed in humidity chamber at 75% R.H., 45°C .The formulations were evaluated for physical appearance, weight variation, hardness, and friability and percent drug release. No change in the physical appearance of the tablets was found. The observed results of the optimized formulations after 6 months indicate that formulations could provide a shelf life of 2 years.

Conclusion

Enteric coated tablets utilizing Cellulose acetate phthalate displayed a timed-release function i.e. a lag phase was observed in the dissolution profile and drug was released after the lag time. Also there were similarity in the dissolution test results of the formulations with pH 6.8 PBS and pH 6.8 PBS containing 2% w/v rat caecal content. CAP-III was selected as the optimized formulation (having 5% w/v coat conc. of Cellulose acetate phthalate) with lag phase (5.2 hrs) with total percent drug release (90%).

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