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Formulation Design and Optimization of an Enteric Coated Sustained Release Mucoadhesive Tablet of Metronidazole

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ABSTRACT: Metronidazole is an antibacterial, widely recommended in the treatment of amoebiasis infections, diarrhoea, trichomoniasis infections, and giardiasis infections. The drawback of this drug is its taken three times daily for 5 to 7 days, which may give poor patients compliance In the present study, an attempt was made to decrease dosing frequency by prepare a mucoadhesive tablets. Various hydrophilic polymers such as HPMC, Sodium alginate, Tragacanth, Sodium CMC and hydrophobic polymer EC are used to prepare mucoadhesive tablets and EC is use for enteric coating were subjected to friability, content uniformity, surface pH, wash-off test and dissolution study. The results of friability tests carried out for all the formulations are with in the official limit and acceptable. According to *in vitro* drug release study the formulation containing HPMC (81.17897%) before coating and (68.93494% after coating with ethyl cellulose), ethyl cellulose (83.91042% before coating and 51.06213% after coating with ethyl cellulose) and tragacanth (83.75215% before coating and 73.24184% after coating with ethyl cellulose) gives better result than the other formulation. Among these three formulations, the formulation containing ethyl cellulose gives better result. According to surface pH study all the formulations showed satisfactory result. According to wash-off test the formulation containing HPMC, ethyl cellulose, tragacanth and the formulation containing HPMC and SCMC both have showed better result. Among these four formulations, the formulation containing HPMC gives better mucoadhesive property.
Key words: - Mucoadhesive, enteric coating, metronidazole.

INTRODUCTION

All over the world the pharmaceutical industry has developed interest in novel routes of drug delivery. This is because discovering new molecules are expensive and hence novel routes of drug delivery can enhance pharmacokinetics of existing drug molecules. Controlled drug delivery system gives a major contribution in the pharmaceutical field, not only in the formulation of drug product but also designing of drug product by incorporating several advance polymer systems. These polymer systems maintain the release rate as well as the concentration in the biological system, characterize the permeation through the appropriate biological membrane and any first-pass metabolic effects prior to entry of the drug into the systemic circulation.[1]

Bioadhesion is an interfacial phenomenon in which two materials at least one of which is of biological nature are held together with the other (bioadhesive material) by means of interfacial forces for extended period of time. When the biological substrate is mucosal coat of surface tissues then the phenomenon is called mucoadhesion. Simple coating of the tablet

by the polymers can control the dissolution rate of drug from the tablets. Various polymers such as hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC) and eudragit have been used for the polymeric film coating of the tablets. These polymer coatings act as diffusion controlling membrane. The selection of the coating material is very important; the coating material will decide the dissolution rate of the drug molecules[2]

Enteric coating is meant to protect the drug from the gastric acidic environment, to prevent or reduce the side effect of the drug by protecting the gastric mucosa from some drugs, to deliver some drugs intended for local action in the intestine, to provide a delayed-release component for repeat-action tablets and to deliver drugs, which are primarily absorbed in intestine.

The enteric coating of the tablets utilizes the pH differences of gastric pH 1-3 and intestinal pH 6-8. The materials used for enteric coating are acid impermeable polymers. Therefore an ideal enteric coating should dissolve at a pH slightly lower than [3].

Metronidazole is an antibacterial, widely recommended in the treatment of amoebiasis infections, diarrhoea, trichomoniasis infections, and giardiasis infections. The drawback of this drug is its taken three times daily for 5 to 7 days, which may give poor patients compliace In the present study, an attempt was made to decrease dosing frequency by prepare a mucoadhesive tablets using hydrophilic polymers such as HPMC, Sodium alginate, Tragacanth, Sodium CMC and hydrophobic polymer EC.[4]

MATERIALS AND METHODS

Metronodazole was obtained as gift sample from diamond drugs Pvt. Ltd, Howrah, W.B. HPMC and Na alginate were purchased from Loba Chemicals Ltd, Mumbai. SCMC, EC and tragacanth were purchased from S. D. Fine Chemical, Mumbai. Methanol and talc used were of analytical grades and purchased from S. D. Fine Chemical, Mumbai. Sodium hydroxide pellets, Hydrochloric acid and potassium dihydrogen ortho phosphate used were of analytical grades and purchased from E.Merck (India) Limited, Mumbai

1. Method of preparation of metronidazole mucoadhesive tablet: -

Mucoadhesive tablets each containing 100 mg and 200 mg of metronidazole were prepared by conventional wet granulation method employing HPMC, SCMC, Na alginate, EC and tragacanth as mucoadhesive materials as shown in the formulae given in table (6) and table (7). A batch of 100 tablets was prepared in each case a blend of 20 gm of metronidazole with required amount of polymers which were then granulated along with a solvent blend of water and ethyl alcohol (1:1). At first the required quantity of drug and polymer taken in a motor and pestle for trituration. Then the solvent is added drop wise with continuous stirring until the wet mass is formed. Then the wet masses were passed through 12 mesh sieve and wet granules were dried at 60º C for 4 hours. The dried granules (20 mesh) after blending with talc (0.5 gm) and magnesium stearate (0.5 gm) in a laboratory cube blender for 5 mins were compressed into 400 mg tablets of hardness 5-6 kg/sq.cm on a tablet compression machine using 12 mm biconcave shaped punches. The tablets were then considered for further study.[6]

2. Coating procedure of mucoadhesive tablet: -

a. Preparation of film coating solution:-

A basic film coating solution as shown in table (8) was prepared. In a 500 ml clean beaker about 125 ml of methanol was measured and the required amount of polymer ethyl cellulose was added and allowed to soak overnight. Next day morning it was kept under a stirrer for 5 mins to get a uniform dispersion of the polymer solution. Other ingredients such as plasticizers, opacifier etc were added by mixing to get the coating liquid.[7]

b. Coating procedure:-

20 tablets of metronidazole taken in a perforated tray. The coating solution was filled into the spray gun. Then the coating solution was sprayed over the tablets from certain distance by controlling the spray rate. Constant temperature was maintained, while the tray was shaken manually. The solution was sprayed intermittently allowing the solvent to evaporate. The process was continued until the uniform coating was formed. In order to get uniform coating, the process variables including gun distance, temperature, spray pressure etc. were adjusted, to balance and control the addition of solution and the drying rate.[8]

3. Evaluation of enteric coated mucoadhesive tablets of metronidazole

a. Friability: -

The friability test was done using Roche's friabilator. Ten tablets were selected and weighed individually. Then the friability test was carried out at 25 rpm for 4 mins. These tablets were then again weighed and percentage loss in weight was calculated.[9]

b. Content uniformity: -

The tablet was kept in 100 ml volumetric flask containing phosphate buffer pH 7.4 for 24 hours. After the tablet was completely dissolved the solution was centrifuged. After centrifuged the supernatant was taken and the absorbance was measured by spectrophotometrically at 319 nm. Dilution was done by phosphate buffer pH 7.4 when required[9].

c. Surface pH: -

The surface pH of the formulation was determined in order to investigate their possible side effects *in vivo*. An acidic or alkaline formulation will cause irritation of the mucosal membrane and hence this is an important parameter in developing a mucoadhesive dosage form.

A combined glass electrode was used for determination of surface pH. The tablets were first allowed to swell by keeping them in contact with 5 ml distilled water pH 6.5 ± 0.5 for two hours in 10 ml beakers. pH was then noted by bringing the electrode near the surface of the formulation and allowing to equilibrate for 1 min[10].

d. Wash-off test: -

The mucoadhesive properties of the tablets were evaluated by an *in vitro* adhesion testing method known as wash-off method. Pieces of intestinal mucosa were mounted on to glass slides were connected with suitable support. About 2 tablets attached on to the slide and the support was hung on to the arm of a USP tablet disintegrating test machine. By operating the disintegrating test machine was given a slow regular up and down movement in the test fluid (phosphate buffer pH 7.4) at 37° C temperatures. At the time of detachment of both tablets was noted down[11]

e. In vitro drug release study from the formulated tablet: -

The *in vitro* drug release studies were performed using USP dissolution rate test apparatus, paddle type. Dissolution study was carried out for 12 hours. Apparatus used

USP Dissolution Apparatus-Paddle type, temperature maintained 37 ± 0.1º C, rpm of the instrument used 100 rpm, duration of dissolution study 12 hours, dissolution media Phosphate buffer pH 7.4, volume of the dissolution media 900 ml. Samples 5 ml each were withdrawn after every 1 hour for 12 hours. To maintain the volume in dissolution vessel, 5 ml of fresh buffer was replaced in each case after withdrawal of the sample. The samples were collected in test tubes after filtration through watt man filter paper. The amount of the drug in the aliquots was quantified by taking the absorbance of the sample at 319 nm spectrophotometrically, using phosphate buffer pH 7.4 (dissolution media) as the blank.

RESULTS AND DISCUSSION

1. Evaluation of enteric coated mucoadhesive tablets of metronidazole

a. *Friability: -*

As per the obtained result, it can be summarized that the average percentage loss in weight of the formulations FH, FE, FS, FA, FT, FHS, FEA and FHT was found to be in the range of 0.051% to 0.065%. The percentage loss in weight is permissible for all the formulated tablets. (table 1)

b. Content uniformity: -

The percentage drug content of the formulations FH, FE, FS, FA, FT, FHS, FEA and FHT was found to be in the range of 87.50071% to 97.86319%. In all the prepared tablets the specified amount of metronidazole were found, which indicates the uniformity in drug content. (table 2)

c. Surface pH: -

The tabulated data shows that the surface pH of the formulations FH, FE, FS, FA, FT, FHS, FEA and FHT was found to be in the range of 7.0 to 7.5. it seems that the surface pH of all the formulations were with in the satisfactory limit. (the official limit is 6.5-7.5) (table 3)

d. Wash-off test: -

The detachment time of the formulations FH, FE, FS, FA, FT, FHS, FEA and FHT was found to be in the range of 361 mins to 473 mins. It indicates that all the formulations have more or less mucoadhesive properties. (table 4)

e. In vitro drug release study from the formulated tablet: -

The formulation FH containing 200 mg metronidazole has shown a better drug release of 81.178% before coating in comparisons to formulations FE, FS, FT, FA, FHT, FHS and FEA with in 12 hours. The formulation FH shows sustained drug release may be due to the higher mucoadhesive property of the polymer. (table 5)

The formulation FE containing 200 mg metronidazole has shows a better drug release of 51.062% after coating in comparisons to formulations FH, FS, FT, FA, FHT, FHS and FEA with in 12 hours. The formulation FH shown sustained drug release may be due to double coating by the polymer ethyl cellulose. (table 6).

Table 1. Average percentage loss in weight of the formulated tablets

Formulation code	Average % loss in weight
FH	0.054
FS	0.057
FE	0.058
FA	0.065
FT	0.051
FHS	0.058
FEA	0.053
FHT	0.055

Table 2. Drug content of the formulated Tablets

Formulation code	Drug content (mg/tablet)	%Drug content
FH	194.43850	97.21925
FS	175.00142	87.50071
FE	193.74280	96.87140
FA	181.72638	90.64801
FT	195.72638	97.86319
FHS	178.09516	89.04758
FEA	192.09276	96.04638
FHT	194.91262	97.45631

Table 3. Surface pH profile of the tablets

Formulation code	Surface pH
FH	7.0
FS	7.5
FE	7.1
FA	7.3
FT	7.1
FHS	7.2
FEA	7.2
FHT	7.1

Table 4. Detachment time exhibited by the formulated tablets

Formulation code	Sl no. of tablet	Detachment time (min)	Average (min)
FH	1	486	473
	2	460	
FE	1	408	404
	2	400	
FS	1	357	361
	2	365	
FT	1	435	433
	2	431	
FA	1	380	370
	2	360	
FHS	1	415	418
	2	421	
FEA	1	374	366
	2	359	
FHT	1	370	370

Table 5. Comparative dissolution profiles of uncoated FH_1, FE_1, FS_1, FA_1, FT_1, FHS_1, FEA_1, and FHT_1 formulations

FORMULATION CODES	% CUMULATIVE DRUG RELEASE
FH	81.17897
FE	83.91042
FA	92.16141
FS	92.40482
FT	83.75215
FHS	89.45734
FEA	83.17366
FHT	84.74817

Table 6. Comparative dissolution profiles of FH_1, FE_1, FS_1, FA_1, FT_1, FHS_1, FEA_1, and FHT_1 formulations after coating with EC

FORMULATION CODES	% CUMULATIVE DRUG RELEASE
FH+EC	68.93494
FE+EC	51.06213
FA+EC	88.31467
FS+EC	84.3239
FT	73.24184
FHS	79.49799
FEA	77.53169
FHT	78.21295

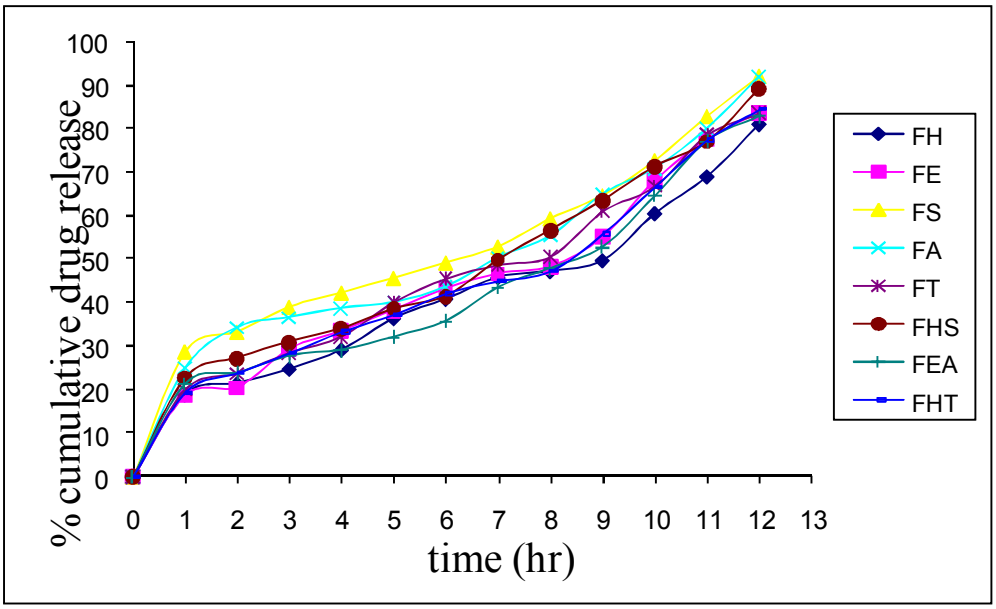

Figure 1. Comparative dissolution profiles of uncoated FH, FE, FS, FA, FT, FHS, FEA, and FHT formulations

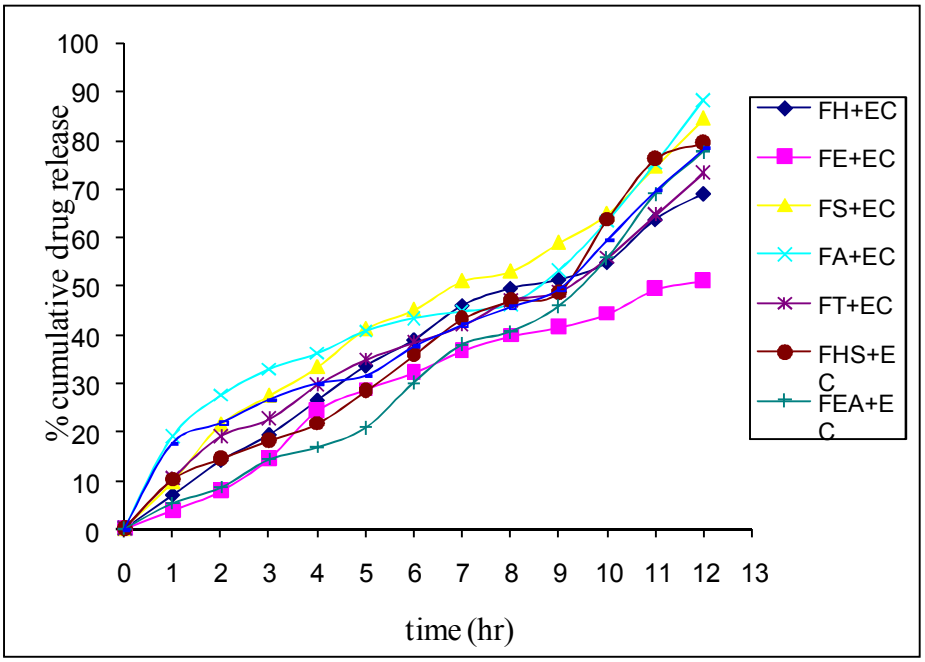

Figure 2. Comparative dissolution profiles of FH, FE, FS, FA, FT, FHS, FEA, and FHT formulations after coating with EC

CONCLUSION

The present study carried out on the formulation and development of mucoadhesive metronidazole tablets by taking HPMC, SCMC, Sodium alginate, ethyl cellulose, and tragacanth as mucoadhesive polymers by the method of wet granulation. The coating was done by spraying method using ethyl cellulose as a polymer. The proposed mucoadhesive formulation found to be successful with respect to parameters evaluated such as friability, content uniformity, surface pH, wash-off test and dissolution study. The results of friability tests carried out for all the formulations are with in the official limit and acceptable.

According to *in vitro* drug release study the formulation containing HPMC (81.17897%) before coating and (68.93494% after coating with ethyl cellulose), ethyl cellulose (83.91042% before coating and 51.06213% after coating with ethyl cellulose) and tragacanth (83.75215% before coating and 73.24184% after coating with ethyl cellulose) gives better result than the other formulation. Among these three formulations, the formulation containing ethyl cellulose gives better result. According to surface pH study all the formulations showed satisfactory result. According to wash-off test the formulation containing HPMC, ethyl cellulose, tragacanth and the formulation containing HPMC and SCMC both have showed better result. Among these four formulations, the formulation containing HPMC gives better mucoadhesive property.

Further research can be planned using other mucoadhesive polymers. *In vivo* studies of the formulation can also be carried out.

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