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pH dependent, colon specific, delivery of Ornidazole and Ciprofloxacin Hydrochloride in stomach

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Abstract

This study was carried out to develop an oral colon specific, tablet to achieve site specific release of ornidazole and ciprofloxacin hydrochloride. The basic design consists of coating of ornidazole with eudragit to form microgranules and compressing the ciprofloxacin hydrchloride powder into a tablet to release the ciprofloxacin hydrochloride in the stomach and finally with film coating for stability and esthetic appeal. The ornidazole was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. The ornidazole microgranules were prepared with Eudragit® L-100, by varying drug to polymer ratio and evaluated for the particle size, drug content and in vitro release profile and from the obtained results; one better formulation was selected for further fabrication of tablet. The aim behind developing this formulation was that when any patient suffers from amebiasis, can be treated with conventional ornidazole tablet for instant release but after that the organism resides at the lower GIT(colon) in the dormant phase and many times relapse of the condition occur with the patient. Thus it can be avoided by targeting the drug at the colon after the initial treatment.

Keywords: Ornidazole, Ciprofloxacin HCl, Amebiasis, Eudragit L-100, Extrusion and Spheronisation.

INTRODUCTION

Among modified-release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsatile) and site-specific delivery of drugs. The necessity and advantage of CDDS have been well recognized and reviewed recently [1,2,3] . There were currently few strategies to achieve colonic specificity such as bacterially triggered, pressure controlled, pH dependent and time dependent CDDS [3,4,5] . Recent studies with sensitive and reliable equipment contradict the traditional view and provide evidence of a

decrease in pH at the gastrointestinal region between the ileum and the colon. Apparently the colon has a lower pH value (6.5) than that of the small intestine (7.0–7.8) [6].The basic design consists of coating of ornidazole with Eudragit to form microgranules and compressing the Ciprofloxacin hydrochloride powder into a tablet to release the Ciprofloxacin hydrochloride in the stomach and finally film coating the tablet for stability and esthetic appeal. The ornidazole was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved. The ornidazole microgranules were prepared with Eudragit® L-100, by varying % of coating and evaluated for the particle size, drug content and in vitro release profile and from the obtained results; one better formulation was selected for further fabrication.

MATERIALS AND METHODS

2.1. Materials

Drugs, waxes, polymers, solvents and reagents were sponsored by the VAMA pharmaceuticals, Wadi, Nagpur, Maharashtra, India.

2.2. Microgranules of Ornidazole

Accurately weighed Eudragit L-100 in concentration of 4% was dissolved in mixture of isopropyl alcohol and acetone (1:1) to form a homogenous polymer solution. Core material, i.e. ornidazole sphere of size #30/60 was prepared by mixing Ornidazole, M.C.C., PVPK30 and water followed by extrusion and spheronisation to obtain the sphere of #40/60.These sphere were coated with L-100 to form the10%, 20%, 30%, 40% of coating to yield the sphere of #30/60.

2.2.1. Evaluation of microgranules

Particle size and external morphology Determination of average particle size of ornidazole microgranules was carried out by optical microscopy. The average particle size for the optimized formulation was 425 micron.

Drug content: In a 100 ml volumetric flask, 795.6 mg of crushed microgranules were taken, and volume was made up to mark with pH6.8 phosphate buffer. The flask was sonicated for 1/2 h to dissolve the ornidazole. Then the solution was filtered and from the filtrate appropriate dilutions were made and absorbance was measured at 290 nm by using UV absorption spectroscopy.

Formulation of site specific tablet: Micro granules equivalent to 500 mg of ornidazole were accurately weighed. Finally, the enteric coated sphere of ornidazole was compressed with 11mm punch size, with Ciprofloxacin hydrochloride, M.C.C., and lactose using PVPK30 and cross povidone with magnesium stearate, talc and aerosil. Composition for modified pulsatile device on the basis of design summary is given in Table 1[7, 8, 9]. The finalized formula is as follows,

Table1:- Optimized formula

Sr. No.	Ingredients	Quantity (mg)
1	Ornidazole (500mg) sphere coated with L-100 #30/60 (30% coating)	795.6
2	Ciprofloxacin Hydrochloride	500.0
3	Microcrystalline cellulose	110.72
4	Lactose	27.68
5	PVPK-30	15.0
6	Cross povidone	45.0
7	Magnesium Stearate	2.0
8	Talc	2.0
9	Aerosil	2.0
	Total	1500.0

In vitro release profile of ornidazole & Ciprofloxacin Hydrochloride: - In order to simulate the pH changes along the GI tract, two dissolution media with pH 1.2 and 6.8 were sequentially used referred to as sequential pH change method [10]. When performing experiments, the pH 1.2 medium was first used for 2 h (since the average gastric emptying time is 2 h), then removed and the fresh pH 6.8 phosphate buffer saline (PBS) was added. Nine hundred ml of the dissolution medium was used at each time. Rotation speed was 50 rpm and temperature was maintained at 37±0.5 ◦C. The withdrawn samples were analyzed at 294 nm, by HPLC and percentage release was calculated over the sampling times. The average release of the ornidazole in the 6.8 pH was calculated as 98.5 % and that of ciprofloxacin hydrochloride in the 1.2 pH was about 100 %.

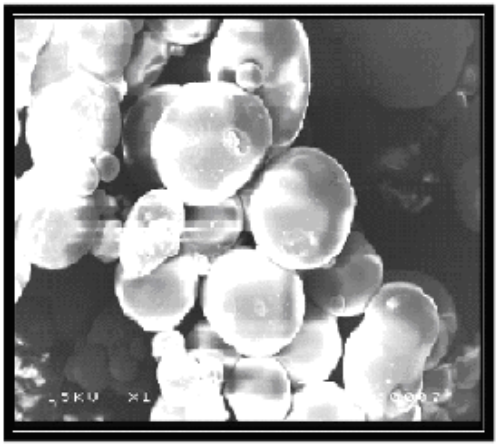
RESULTS AND DISCUSSION

As indicated in introduction, the aim of the work described here was to design a new colonic drug delivery system, for the better treatment of amebiasis. The tablet designed here combines two approaches previously attempted: pH-sensitive delivery and site specific delivery. The system was fabricated into two steps: first, ornidazole was entrapped within pH dependent methacrylic acid copolymers (Eudragit L-100 soluble at pH above 6); second, microgranules were compressed with ciprofloxacin hydrochloride and other excipients.

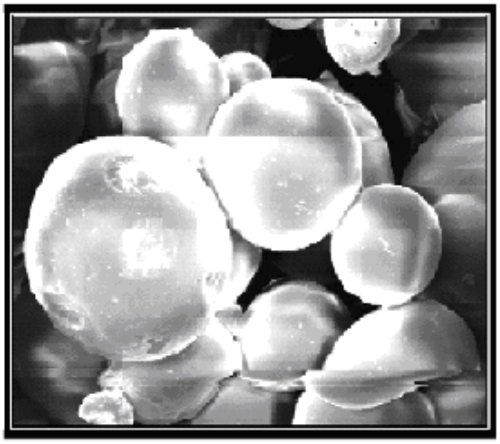
3.1. Preparative aspects and physicochemical properties of eudragit microgranules

To prepare pH dependent microgranules the extrusion and spheronisation technique was used since it yields more uniform particles. The spheres obtained from this process were coated in Fluidized bed coater (FBC).

The mean particle size of the microgranules was determined by the optical microscope fitted with an ocular micrometer and stage micrometer. The average mean particle sizes of the microgranules were found to be 425 micron. The mean particle size of the microgranules significantly increased with increase in % of coating [11]. Scanning electron microscopy was performed to characterize the surface of the formed microcapsules. Particles of 30% and 40% of coating were found to be spherical, smooth and discrete. Scanning electron photomicrographs of 30% and 40% coating formulations are shown in Fig. 1.



Ornidazole microgranules with 30% coating



Ornidazole microgranules with 40% coating

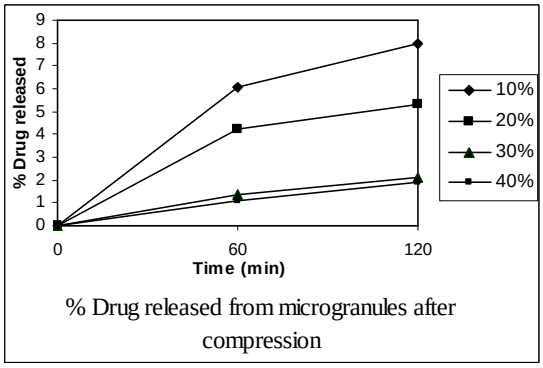
Fig.1. Scanning electron photomicrographs

3.2. In vitro release studies for microgranules

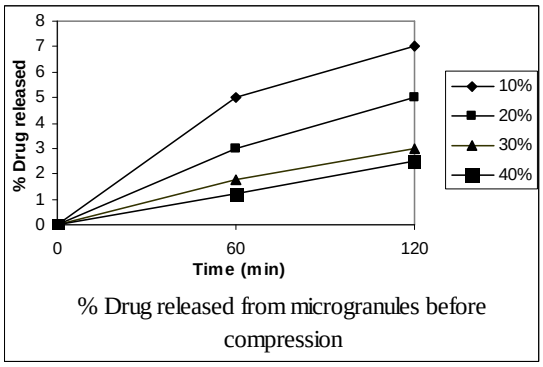
Table2. % Drug released from microgranules

% Coating of L-100	% Release from microgranules			
	before compression		after compression	
	60 min	120 min	60 min	120 min
10 %	5	7	6.1	8
20 %	3	5	4.2	5.3
30 %	1.8	3	1.35	2.1
40 %	1.2	2.5		

In vitro release studies were carried out using USP type II dissolution assembly. The release profile obtained for all the four formulations were shown in table2 and Fig. 2.



% Drug released from microgranules after compression



% Drug released from microgranules before compression

Fig.2. Drug released from microgranules in 0.1N HCl

It was observed that the drug release from the formulations decreased with increase in the % of coating in each formulation before and after compression. The release of drug from polymer matrix takes place after complete swelling Fig. 2. In the first 60 min drug release was 5%, 3%, 1.8% and 1.2% for 10%, 20%, 30% and 40%, respectively before compression. The tablet was subjected to dissolution firstly in the 0.1 N HCl and then in the 6.8 pH phosphate buffer. The average release of the ornidazole in the 6.8 pH was calculated as 98.5 % and that of ciprofloxacin hydrochloride in the 1.2 pH was 100 %.

CONCLUSION

The present study demonstrates that the ornidazole microgranules could be successfully colon targeted by design of time and pH dependent modified formulation. In conclusion, this tablet releases ciprofloxacin hydrochloride in stomach and ornidazole in lower GIT in which microgranules of ornidazole was compressed with suitable excipients. Thus the designed tablet can be considered as one of the promising formulation technique for delivering the multiple drugs at their site of maximum absorption in a single tablet.

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REFERENCES

[1] Watts, P.J., Illum, L., **1997**. *Drug Dev. Ind. Pharm*. 23, 893–913.
[2] Kinget, R., Kalala,W.,Vervoort, L.,Vanden Mooter, G., **1998**. *J. Drug Targeting* 6, 129–149.
[3] Libo, Y., James, S.C., Joseph, A.F., **2002**. *Int. J. Pharm*. 235, 1–15.
[4] Abdul, B., John, B., **2003**. *Pharmatech*, pp. 185–190.
[5] Chourasia, M.K., Jain, S.K., **2003**. *J. Pharm. Pharmaceut. Sci*. 6, 33–66.
[6] Bajpai, S.K., Bajpai, M., Dengree, R., **2003**. *J. Appl. Polym. Sci*. 89, 2277–2282.
[7] Julie, B., Howard, N.E.S., John, M.E., Gillian, P., Fran, M.B., **1996**. *J. Contr. Rel.* 38, 151-158.
[8] Seshasayan, A., Sreenivasa, R.B., Prasanna, R., Ramana Murthy, K.V., **2001**. *Indian J. Pharm. Sci.,* 337–339.
[9] Listair, C.R., Ross, J.M., Mathias, W., Howard, N.E.S., **2002**. *J. Pharm. Pharmacol*. 52, 903–909.
[10] Zahirul Khan, M.I., Zeljko, P., Nevenka, K., **1999**. *J. Contr. Rel*. 58, 215–222.
[11] Morta, R., Jose, L., Vila, J., **1998**. *J. Contr. Rel*. 55, 67–77.