

**FORMULATION AND DEVELOPMENT OF ENTERIC COATED ORNIDAZOLE TABLET FOR COLON TARGETED DRUG DELIVERY SYSTEM**

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ABSTRACT

Lactose-based placebo tablets were prepared and coated using various combinations of Eudragit L100 and Eudragit S100, by spraying from aqueous systems. The Eudragit L100 Eudragit S100 combinations (w/w) studied were 1:0, 4:1, 3:2, 1:1, 2:3, 1:4, 1:5 and 0:1. The coated tablets were tested in vitro for their suitability for pH dependent colon targeted oral drug delivery. The same coating formulations were then applied on tablets containing ornidazole as a model drug and evaluated for in vitro dissolution rates under various conditions. The disintegration data obtained from the placebo tablets demonstrate that disintegration rate of the studied tablets is dependent on: (i) the polymers combination used to coat the tablets, (ii) pH of the disintegration media, and (iii) the coating level of the tablets. Dissolution studies performed on the ornidazole tablets further confirmed that the release profiles of the drug could be manipulated by changing the Eudragit L100 and Eudragit S100 ratios within the pH range of 6.0 to 7.0 in which the individual polymers are soluble respectively, and a coating formulation consisting of a combination of the two copolymers can overcome the issue of high gastrointestinal (GI) pH variability among individuals. The results also demonstrated that a combination of Eudragit L100 and Eudragit S100 can be successfully used from aqueous system to coat tablets for colon targeted delivery of drugs. For colon targeted delivery of drugs the proposed combination system is superior to tablets coated with either Eudragit L100 or Eudragit S100 alone.

Keywords: Aqueous film coating; Colon targeted drug delivery; Enteric coated tablet; Ornidazole; pH-dependent delivery system.

INTRODUCTION:

The oral aspect is considered to be most convenient for administration of drugs to Patients. Normally dissolves in stomach field as intestinal fluid and absorb from these regions of GIT. It is a serious drawback in conditions when localized delivery of drugs into the colon is required as drugs needs to be protected from the hostile environment of upper GIT. Targeted drug delivery into the colon is highly desirable for local treatment of variety of bowl diseases such as ulcerative colitis, cirrhosis disease, amoebiasis, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs^[1]. Formulations for colonic delivery are also suitable for delivery of drugs, which are polar and / or susceptible to chemical and enzymatic degradation in upper GIT; in particular, therapeutic proteins and peptides are suitable for colonic deliveries^[2-4]. A colonic targeted approach found to be effected in minimizing uncertain side effects^[5]. So, the colon, as a site for drug delivery, offers distinct advantages on account of near neutral pH, a much longer

transit time, relatively low proteolytic enzymatic activity and offers a much greater responsiveness to absorption enhances. There are various methods or techniques through which colon drug targeting can be achieved, for example, formation of prodrug, coating with pH sensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure-controlled drug delivery systems, osmotic pressure controlled systems^[6]. Coating of the drugs with pH-sensitive polymers provides simple approach for colon-specific drug delivery. Taking advantage of the highest pH value of the colon content, the dosage form containing the active drug in a core is coated with pH-dependent material which dissolves at the pH of the colon. But recent studies using sensitive and reliable equipments contradict the traditional view and provide evidence of a fall in pH at the GI region between ileum and colon. Apparently, the colon has a lower pH value (6.5) than the small intestine (7.0–7.8), and the jejunal region of some individuals has a higher pH (range 6.1–7.2) than the small

intestine or colon of other individuals. Accordingly, high individual variability in physiological pH of the GI tract is a matter for concern. In fact, in a recent in vitro study, Ashford et al. Demonstrated that coating with a pH-dependent polymer (Eudragit S100) would result in either delivery of the drug at the duodenum, or not at all, depending on individual pH variability of the GI tract. Most commonly used pH-dependent coating polymers are methacrylic acid copolymers – Eudragit L100-55, Eudragit L100 and Eudragit S100 which dissolve at pH 5.5, 6.0 and 7.0 respectively and hence, none of these polymers are suitable to be used alone for coating of dosage forms that would start releasing the drug at pH 6.5 although this has been generally accepted as the desired pH for colon - targeted delivery. Since Eudragit S100 dissolves at the highest pH within the range, our hypothesis was that it would be possible to combine Eudragit S100 with either Eudragit L100-55 or Eudragit L100 at various ratios to manipulate the drug release within the colon the pH range of 5.5–7.0 or 6.0–7.0 respectively. Therefore, the main objective of our study was to develop a single coating system for colon targeted oral delivery of drugs that would allow the dosage form to pass the jejunum (pH 6.1–7.2, residence time 1 h) intact, start disintegrating at the lower small intestine (pH 7.0–7.8, residence time 2 h) and slowly release the drug either at the small intestine or to the colon (pH 6.5, residence time 2 h) depending upon the pH profile of the GI tract of particular individuals. We aimed to develop an aqueous based system rather than the currently used organic based system for most of these polymers. The studied formulations have been designated as Eudragit L100 and Eudragit S100 ratios (w/w) throughout the text.

2. MATERIALS:

Ornidazole was obtained as a gift sample from Aarti Drugs Ltd. Mumbai (India). Eudragit L100 and Eudragit S100 were obtained From Research lab Fine chem. (India). Opacifer titanium dioxide; Plasticizer Triethyl citrate (TEC) obtained from Lobachemie Pvt.Ltd. Mumbai(India).Other excipients used to prepare the tablets were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

3. METHODS:

3.1. Preparation of core tablets:

The placebo tablets were prepared using a direct compression method of manufacture using lactose monohydrate as the main filler and other excipients were mixed and then compressed into tablets on a single rotary tablet press (Shree Bhagwati Machtech India Pvt. Ltd.)

using 10 mm size (diameter), round and shallow concave punches. The target tablet weight was set at 400 mg. The ornidazole tablets also had lactose monohydrate as the main filler, but required wet granulation. The granules prepared using a suitable binder (aqueous) and dried in a hot air oven at 45°C for 2h were screened through a 24 mesh sieve, blended with some external excipients and then compressed into tablets under similar conditions as for the placebo tablets, but the tablet contain 100.0 mg of ornidazole. Both the placebo and ornidazole tablets (cores) were evaluated for appearance, uniformity of weight, hardness, friability and disintegration time to meet predetermined criteria suitable for coating.

3.2. Preparation of the spraying dispersion for coating:

Eudragit S100 and Eudragit L100 have different film forming properties, Initially, a coating formula was optimised for each polymer separately; polymer dispersions prepared and then combined at various proportions to obtain the desired combination-ratio of Eudragit L100 S100. Trials were conducted using Eudragit L100 and Eudragit S100 ratio (w/w) of 1:0, 4:1, 3:2, 1:1, 2:3, 1:4, 1:5 and 0:1. Apart from the polymer(s) the coating formula contained Tri ethyl citrate (TEC) as plasticiser, talc as glidant and titanium dioxide. A dispersion of the coating-aid materials was prepared separately and then combined with the polymer dispersion(s). For Eudragit S100, the TEC was added directly to the polymer dispersion.

3.3. Coating of the tablets

The tablets were coated at three levels (about 10, 12 and 14%, w/w total solid applied) using a R & D Coater (Ideal curve Pvt. Ltd. India) by spraying the coating dispersion continuously from the spraying gun (up to 40–45° C outlet temperature) The flow-rate (usually, 16 mg/min/kg of tablets) of the spraying dispersion atomised air pressure used required adjustments depending on the polymer ratio used in the formulation. After coating, the tablets were dried in an oven at 45°C.

3.4. Disintegration test

Disintegration testing (disintegration Tester, Electrolab, India.) was carried out according to the British Pharmacopeial (BP) 1993 method for enteric coated tablets using phosphate buffer media of various pH (5.5, 6.0, 6.5, 6.8, 7.0 and 7.5) at the buffer stage following 2 h in 0.1N HCl. Each coating formulation was tested in 3 to 4 different pH media as shown in Table1. The effect of coating level (total solid applied) on disintegration time was also checked for each formulation.

Table 1: Disintegration time of the tablets (coated at various levels) tested at various buffer (pH) media: six tablets were tested in each case, and the disintegration time (min) is shown as a range for the time taken by all six tablets to disintegrate.

| Formulations | Coating level (%, w/w) | pH of the disintegration medium | | | | | |
|--------------|---------------------------|---------------------------------|-------|--------|---------|-------|-------|
| | | 5.5 | 6 | 6.5 | 6.8 | 7 | 7.5 |
| 1:0 | 10 | <120 | 40-50 | 13-15 | – | – | – |
| | 12.3 | <120 | 55-63 | 14-18 | – | – | – |
| | 13.8 | <120 | 52-68 | 20-22 | – | – | – |
| 4:1 | 10.7 | – | 53-69 | 15-18 | 13-15 | – | – |
| | 12.4 | – | 62-76 | 15-21 | 14-17 | – | – |
| | 14.5 | – | 61-67 | 17-28 | 15-20 | – | – |
| 3:2 | 10.6 | – | 62-67 | 20-24 | 16-23 | 14-18 | – |
| | 11.6 | – | 66-72 | 22-27 | 22-35 | 17-22 | – |
| | 13.7 | – | 78-84 | 30-32 | 25-28 | 22-26 | – |
| 1:1 | 9.8 | – | – | 20-25 | 16-22 | 13-18 | 13-16 |
| | 12.1 | – | – | 23-27 | 19-24 | 16-22 | 13-18 |
| | 14.2 | – | – | 28-34 | 26-31 | 18-26 | 17-21 |
| 2:3 | 12.4 | – | – | 33-41 | 17-23 | 18-21 | 20 |
| | 13.6 | – | – | 38-43 | 24-28 | 20-27 | 16-26 |
| 1:4 | 13.6 | – | – | 98-106 | 59-66 | 33-43 | 24-26 |
| 1:5 | 14.8 | – | – | >120 | 88-106 | 49-51 | 22-24 |
| | 16.5 | – | – | >120 | 113-124 | 48-66 | 24-28 |
| 0:1 | 14.3 | – | – | – | <120 | <120 | 32-40 |

3.5. Dissolution test:

In vitro drug release studies were carried out using USP apparatus (Paddle type TDT-06N, Electrolab India.) at 50 rpm, $37 \pm 0.5^\circ\text{C}$ and 900 ml dissolution medium by buffer change technique. Tablet bearing Ornidazole were suspended in simulated gastric fluid pH 1.2 (900 ml), for 2hr. The dissolution media was then replaced with mixture of simulated gastric fluid and simulated intestinal fluid pH 4.5 (900 ml) for next 2hrs, then for next 2 hrs simulated intestinal fluid pH 6.8 (900ml) and the release study was carried out further in simulated intestinal fluid (900ml) pH 7.4. Samples were withdrawn periodically and compensated with an equal amount of fresh dissolution media. The samples were analyzed for drug content by measuring absorbance at corresponding λ_{max} of the dissolution medium, using UV- spectrophotometer (UV-1800, Shimadzu, Japan). The percentage cumulative release for Ornidazole was calculated over the sampling times using Beer Lambert's curve generated in the respective medium. Studies were performed in triplicate and the mean cumulative percentage of drug calculated (\pm SD) and plotted against time.

4. RESULT:

4.1. Disintegration test:

At the highest level of coating (i.e., about 14% w/w) all the formulations met Pharmacopeial (BP/ USP) requirements for the enteric performance test in the 0.1N HCl. Also at the lower levels (i.e., about 10% and 12% w/w) almost all the formulations passed the test in 0.1N HCl, but the tablets coated only with Eudragit S100 (formulation 0:1) failed the enteric performance test at both the lower levels (i.e., about 11% and 12% w/w).

Formulations with Eudragit L100 disintegrated at lower pH buffer media at faster rates than formulations with Eudragit S100, and the higher the pH of the buffer medium the lower was the disintegration time for a particular formulation. Also, the tablets coated at higher levels had longer disintegration times than those coated at lower levels at the same medium.

4.2. Dissolution test:

All the coating formulations of ornidazole tablets coated at 10–14% levels met the USP criteria for the enteric performance test in 0.1N HCl (for 2 h) except tablets

coated with only Eudragit S100 which passed the enteric test at a higher level (17.6%) of coating. The dissolution profiles of tested formulations in pH 7.4 buffer are presented in Fig. 1. The tablets coated with only Eudragit L100 (formulation 1:0) started releasing the drug after 20 min and released about 80% of the drug within 60 min. A

direct relationship is apparent between the decrease in the dissolution rates and increase in the Eudragit S100 contents in the formulations. Linear regression analyses of the data demonstrated a good correlation ($r^2 = 0.99$) between the Eudragit S100 content in the formulations and $t_{50\%}$ in the tested medium.

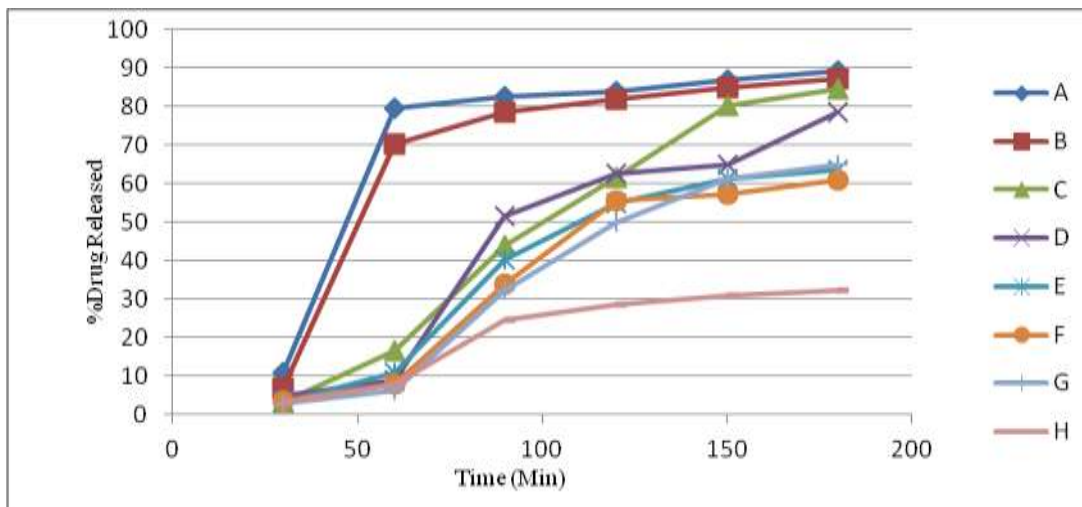


Figure 1: Dissolution profiles of ornidazole tablets in pH 7.4 phosphate buffer. The ornidazole core tablets were coated with Eudragit L100 Eudragit S100 combinations of 1:0 (A), 4:1(B), 3:2 (C), 1:1 (D), 2:3 (E), 1:4 (F), 1:5 (G) and 0:1 (H) ratios (w/w), and tested in 0.1N HCl for 120 min prior to the buffer stage.

Tablets coated with only Eudragit S100 (formulation 0:1) had the slowest dissolution rate. Although tablets of this formulation released about 33% of the drug on average after 180 min. Combination formulations containing only 16–19% of Eudragit L100 (i.e., formulations 1:4 and 1:5) released about 60–65% of the drug within 180 min.

5. DISCUSSION:

The disintegration and dissolution data obtained from all the tested formulations clearly demonstrate that the solubility of the films obtained from various combinations of the two polymers, Eudragit L100 and Eudragit S 100, and the dissolution profiles of the coated tablets in various pH media could be manipulated by changing the combination ratios of the two polymers. The increased disintegration/dissolution time obtained for almost all the formulations under all testing conditions for tablets with the higher levels of coating than those with lower levels demonstrated the effect of coating thickness on the disintegration /dissolution rate. The superiority of the combination formulations is further demonstrated by the results obtained from prolonged dissolution studies of the tablets of 1:4 formulation under extreme conditions. However, the formulators should take into consideration that other factors like coating thickness, total polymer applied, physico-chemical properties of the active drug, loading dose, variable intestinal transit time of the dosage

form under fed and fasting conditions and some pathophysiological factors would also influence the effectiveness of the coating system and thus the release process.

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