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Research Article

DEVELOPMENT AND EVALUATION OF A NOVEL TIME AND PH-DEPENDENT COLON TARGETED DRUG DELIVERY OF ORNIDAZOLE

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ABSTRACT

Objective: The anti-amoebic drug Ornidazole was developed in this study as a novel colon-specific drug delivery method for the treatment of colonic diseases such as diverticulitis, inflammatory bowel syndrome, and Crohn's disease. Pectin forms a matrix with a pH-sensitive polymeric coating that prevents drug release in the upper gastrointestinal tract, thereby addressing solubility issues. Pectin is sometimes used as an adsorbent, bulk-forming agent.

Methods: Ornidazole-containing core tablets were directly compressed. Ornidazole compression coated tablets were formulated with varying polymer proportions in the coat. All the tablets were studied for weight uniformity, hardness, friability, drug content, and *in vitro* dissolution tests

Results: All formulations demonstrated good Fourier-transform infrared compliance and no interaction between drug, polymer, and other excipients. The study's findings show that the formulation F6 coated with Eudragit RS 100 had a drug release of 99.230.8 for 24 h.

Conclusion: As a result, (F6) is regarded as the optimal formulation. The pH in the colon causes the release of Ornidazole from tablets.

Keywords: Ornidazole, Eudragit RS 100, Hydroxypropyl methylcellulose, Pectin, Time dependent, pH-dependent, Colon drug delivery, Microbial flora.

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INTRODUCTION

Colonic delivery refers to targeted drug delivery into the lower gastrointestinal (GI) tract, which occurs primarily in the large intestine (i.e. colon). Pharmaceutical researchers have spent the past two decades looking for a targeted drug delivery system in the colonic region [1-3]. Many bowel disorders, including ulcerative colitis, Crohn's disease, amoebiasis, and colon cancer, may be treated locally, and for the systemic delivery of protein and peptide drugs, by shielding drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum and releasing them in the ileum and colon, resulting in greater systemic bioavailability [4-7]. Ornidazole is a nitroimidazole with broad-spectrum bactericidal activity against protozoa and some anaerobic bacteria. After passive absorption into the bacterium cell, ferrodoxin type redox systems reduce the nitro group of Ornidazole to the amine group [8-10]. The formation of redox intermediate intracel is thought to be the key component responsible for microorganism destruction. The drug works against anaerobic bacteria such as *Bacteroides fragilis*, as well as protozoa such as Entamoeba histolytica and *Trichomonas vaginalis* [11-14]. The pharmacokinetic profile of Ornidazole, on the other hand, indicates that the drug is fully and easily absorbed after oral administration, about 2 h after a single dose. The traditional tablet form of this medication contains only a small amount of Ornidazole for local action in the colon, but it still relieves amoebiasis [15-18]. Time-dependent, pH-dependent coating systems, carriers, and a pro-drug approach are among the various approaches available for colon-specific drug delivery [15,19]. This study aims to use an abundantly available polymer to deliver Ornidazole to the colon using hydroxypropyl methylcellulose (HPMC) as a carrier.

METHODS

Materials

PM pharma in Tamil Nadu provided ornidazole, and Arati chemicals Ltd in Mumbai provided Eudragit RS 100. Pectin from Mumbai's Research-Lab Fine Chemical Industries. Qualikems fine chem.Pvt.Ltd, Nandesari, Vadodara, Microcrystalline cellulose (MCC), HPMC. Magnesium stearate, Talc from Sd fine-chem limited, Mumbai. And all other chemicals and reagents used are of pharmaceutical grade.

Methods

Fourier-transform infrared (FTIR) studies

The IR spectra of both the drug and the mixture of excipients are analyzed using an FTIR spectrometer. All samples were scanned at a resolution of 4 cm^{-1} over the wavenumber range 4000-400 cm^{1} using the KBr disc method (a binary mixture of 1:1 ratio) [20] to investigate non-thermal analysis of drug-excipient interactions. After that, the mixture was blended in a motor for 3–5 min, and only a small portion of it was uniformly spread and sandwich between the pellets and pressed using KBr pellet press at a pressure of 20,000 psi for 1 min. The pressure was then released and the pellet was placed into the pellet holder and thus scanned in the IR region [21].

Standard curve

Standard stocks were made in 0.1 HCl, 6.8 pH, and 7.4 pH phosphate buffer at 1 mg/ml. The standard solutions were used to make working stock solutions of 100 µg/ml in 0.1 HCl, 6.8 pH, and 7.4 pH phosphate buffer. Different aliquots of the working stock solutions were taken and volume was made up in a volumetric flask with 0.1N HCl, 6.8 pH, and 7.4 pH phosphate buffers.

The absorbance was measured spectrophotometrically at 230 nm for 0.1N HCl and 320 nm for 6.8 pH and 7.4 pH phosphate buffer, respectively, and a calibration curve was constructed [19,22].

Preparation of granules

Accurately weighed amounts of drug, disintegrant, and diluents were mixed in a motor, starch mucilage was added to the above blend to form a wet mass, and granules were made by passing the wet dough mass through sieve no.16 and drying at 500°C for 15 min [23].

Preparation of core tablet

The dried granules were sieved with the number 18 sieve. The granules were thoroughly mixed with the necessary amount of lubricant and glidant. The lubricated granules were compressed to form a core tablet (8 mm) using a Cemach tablet compression device with flat round punches and dies at optimum pressure (Table 1). The average weight of the central tablet was discovered to be 100 mg. The core tablets were tested for hardness, content uniformity, friability, and disintegration. After confirming the compliance with these tests, the core tablets were compression-coated with different coat formulations [17,24].

Preparation of compression coated tablet

The core tablets were coated with the co-polymer Eudragit RS100. Around 35% of the coat formulation was placed in the die cavity, and the Ornidazole core tablet was carefully placed in the die cavity's center before the remaining coat formulation was added. Core tablets were compressed at an applied force using 12 mm punches [10]. The tablet's weight was determined to be 350 mg. The composition of compression coated tablet is given in Table 2

Evaluation of compression coated tablets

Physical characterization of tablet

Official evaluation parameters such as weight variance, hardness, friability, and tablet thickness were measured for all batches [24,25].

Weight variation test

On an analytical balance, twenty tablets from each batch were individually weighed in grams. The average weight and standard deviation were measured, as well as the individual weight of each tablet, using the same and compared with average weight.

Thickness test

Using Vernier calipers, the thickness in mm of 10 pre-weighed tablets was measured individually. The standard deviation and average thickness were recorded.

Hardness test

The hardness of the tablets was determined using a Pfizer hardness tester. The crushing strength of ten tablets of known weight and thickness was measured in kg/cm^2 and the average hardness was calculated, as well as the standard deviation.

Friability test

Twenty tablets were selected from each batch and weighed. In the Roche friabilator, each group of tablets was rotated at 25 rpm for 4 min (100 rotations). To assess the weight loss, the tablets were dedusted and re-weighed. The weight loss from the original tablets was then used to measure friability.

Table 1: Composition of core tablet of Ornidazole

Ingredients	Quantity (mg)
Ornidazole	50
Microcrystalline cellulose	40
Talc	5
Magnesium stearate	5
Average weight	100

Table 2: Composition of core tablet of Ornidazole

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Pectin	50	65	75	95	110	125
HPMC K 100	85	70	60	40	25	10
Talc	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5
Eudragit RS 100	100	100	100	100	100	100
Total (mg)	250	250	250	250	250	250

Drug content

Both the core and coated tablets had their drug content tested. The amount of powder equal to 50 mg of Ornidazole was precisely weighed and transferred to a 100 ml volumetric flask containing 6.8 pH buffer after powdering ten tablets from each formulation. A Ultraviolet (UV)-Visible spectrophotometer set to 320 nm was used to calculate the absorbance of 10 mL of filtrate [26].

Drug release studies of coated tablets in the buffer

For *in vitro* research, the USP type II (paddle) apparatus was used. To simulate GI conditions, the media was changed at different time intervals. The test lasted 24 h, with 0.1 N HCl for the first 2 h (pH 1.2 and up to 2 h in the stomach), pH 6.8 buffer medium for the next 3 h (pH 6.8 and 3 h in the small intestine), and finally pH 7.4 phosphate buffer for the remaining time (pH 7.4 and residence time up to 24 h). The dissolution media were stirred at 50±1 rpm while maintaining a temperature of 37 ± 1^0C. 5 ml of samples were taken periodically and diluted with suitable media before being analyzed at 320 nm with a UV Visible spectrophotometer [22,25].

Drug release kinetics

The suitability of several equations listed in the literature to explain the mechanisms for drug release was evaluated for the release data up to the first 50% drug release. To evaluate the data, the following equations were used: Zero-order model Q=kt; First-order release kinetics In (1-Q) = -kt; Higuchi (Diffusion) equation Q = kt½; Korsmeyer-Peppas kinetics Log Q = log k + n log t [27].

RESULTS AND DISCUSSION

The aim of this study was to develop Ornidazole tablets coated with Eudragit RS 100 for site-specific delivery in the colon for the treatment of ulcerative colitis. The enteric polymer in Eudragit RS 100 Ornidazole tablets allows the drug to be released at a specific pH in the colonic fluid. In the physiological environment of the human body, these tablets are expected to remain intact in the physiological environment of the stomach and small intestine.

However, once they reach the colon, the drug release is activated by the colonic pH, which causes the enteric coat to crack and the embedded drug to be released. The investigational medication (Ornidazole) was delivered to the colon using single-unit systems (tablets) to determine the effectiveness of these formulations for drug delivery to the colon. It is rapidly and completely absorbed from the GI tract with an *in vivo* bioavailability of 90%.

The drug Ornidazole is compatible with the polymers used, according to FTIR research. In the physical mixture, there was no drug-excipient interaction. It also implies that the drug did not undergo any

Table 3: FTIR studies

IR spectra	O-H stretching mode	C-H stretching mode	Asymmetric NO_2 stretching mode	Symmetric NO_2 stretching mode
Ornidazole	3406.53	2976.00	1596.38	1199.10
Optimized FL	3617.30	2967.64	1529.45	1266.15

Table 4: Characterization of tablet blend

Formulation	Angle of repose (°)	Bulk density (g/cc)	Carr's index (%)
F1	23.5	0.462	16.41
F2	21.4	0.479	17.90
F3	24.2	0.482	14.23
F4	25.4	0.467	13.70
F5	22.5	0.461	15.06
F6	22.7	0.470	15.1

Table 5: Characterization of compression coated tablet

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (%)	Friability (%)	%Drug content
F1	0.36	4.99	99.6	0.18	97.13
F2	0.34	5.35	99.5	0.16	98.12
F3	0.43	5.45	99.1	0.13	96.03
F4	0.41	5.2	99.5	0.12	96.40
F5	0.35	5.62	99.7	0.16	97.12
F6	0.31	4.80	99.8	0.14	99.70

All values are expressed as mean±SD, n=3

Table 6: Cumulative percentage of Ornidazole release from different formulations

Time (h)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	3.21±0.2	1.80±2.1	2.60±1.3	6.00±0.9	3.01±1.2	2.0±1.2
2	6.20±1.2	3.01±0.1	6.00±0.6	12.2±1.3	10.1±0.3	6.2±1.6
3	10.10±0.3	4.08±0.8	8.11±0.8	18.1±1.6	24.12±0.6	8.11±0.3
4	12.26±0.4	6.18±1.6	12.08±0.2	22.15±2.0	31.12±1.1	18.45±0.6
5	15.06±1.3	7.96±0.9	17.5±1.51	24.9±1.1	41.6±3.2	26±1.2
6	21.23±2.0	18.23±2.0	22.56±0.2	32.4±0.2	44.3±0.4	32.7±2.0
8	31.06±0.2	29.46±1.2	32.23±2.2	39.23±2.2	48.03±2.4	42.63±0.5
10	40.2±0.6	32.6±1.6	40.9±1.4	42.1±1.2	50.56±2.2	50.2±0.4
12	50.86±2.6	44.63±0.2	53.63±2.9	57±2.2	63.86±0.2	61.6±0.2
18	56.56±1.1	52.73±2.2	65.56±0.4	64.5±1.4	80.56±1.5	87.86±2.4
24	75±0.6	66±1.2	89.23±0.5	83.53±0.6	97.23±0.4	99.23±0.8

Table 7: Drug release kinetics

Formulation	Zero order	First order	Higuchi	Korsmeyer-Peppas	Peppas(n)
F6	0.987	0.684	0.963	0.969	1.748

degradation or chemical interaction during the entire formulation process (Table 3).

Wet granulation and compression were used in this study for tableting, which enabled the granules to have good flow and compacting properties. The optimum value of Carr's index (%) is up to 15%. When the angle of repose (ɵ) is <25, it normally means the material is free-flowing. Through pilot tests, it was discovered that pure Ornidazole had an angle of repose value of 22.71.64, suggesting extremely good flow property (Table 4). Low values of angle of repose (21.41.22–25.41.66) and Carr's index (13.700.08–17.90) suggested that all of the prepared granules had strong flow properties. Since the flow properties of the powder mixture are critical for tablet dose uniformity.

The tablets were successfully made using a mixture of HPMC, Pectin in varying quantities, and Eudragit, Following wet granulation process. All of the tablets were measured and specified for weight variation, thickness, hardness, friability, and drug content (Table 5). The hardness (4.800.29–5.620.11 kg/cm) and thickness (3.120.2–4.30.1) of different batches of tablets varied. The weight variance (345±1.34–351±1.46) and friability (0.12–0.18 %) of various batches of tablets were found to be within the prescribed limits. The drug content was found to be consistent (>98%) within batches of various tablet formulations. As a result, different binder concentrations did not affect the physical characteristics of the tablets.

The evaluation of release profile is recommended as a useful tool in the development and optimization of drug formulations. At a pH of 6.8, the release of core tablets was checked. F6 had a high average drug release (99%) for 24 h, while other formulations had a low average drug release. The second part of the formula was to create a pH-dependent polymeric coating for core tablets. The coat is really good.

At pH 7.0 and 6, the coating polymer Eudragit RS100 dissolves, preventing the drug from releasing the core before it reaches the colonic region. F6 was the core tablet, and it was coated with 2% Eudragit RS100, which gave it a pleasant film luster and elegance. In terms of weight variation, hardness, and drug content, all of the formulations were found to be within the official range. According to the dissolution results, all of the formulations had little to no detectable drug release (i.e. <1% drug release) at pH 1.2 (Tables 6 and 7). The release began in a pH 6.8 buffer for all formulations. This may be due to the fact that Eudragit RS100's dissolution threshold pH is 6.

CONCLUSION

According to the results, a colon-specific drug delivery system is beneficial in the treatment of colon disease. HPMC and Pectin are mucoadhesive polymers with local and systemic benefits that are suitable for colon targeted drug delivery systems. The wet granulation method was used to make Ornidazole. The core tablet is coated with Eudragit RS100, a pH-dependent polymer that dissolves at pH 6.8, and the optimized formulation is F6, which has a drug release rate of 99.25% in 24 h.

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CONFLICTS OF INTEREST

There are no conflicts of interest regarding the publication

AUTHORS CONTRIBUTIONS

All the authors contributed to the preparation of the final manuscript

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