ORIGINAL ARTICLE

CODES™ drug delivery: Design and evaluation of metronidazole tablets

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Abstract

Aim: The present study aimed to develop and demonstrate the study of combined effects of biodegradable polymer coated with different pH-sensitive polymers in the formulation of Metronidazole tablets for colon targeted drug delivery. **Materials and Methods:** Metronidazole Hydrochloride is cored with various proportions of biodegradable polymers such as xanthan gum and chitosan. Then, the double-layered system was designed based on pH-sensitive eudragit S100 and eudragit L100 as an inner layer and outer layer, respectively. To evaluate the *in-vitro* dissolution profile of CODES™ tablets in gastrointestinal fluids, the test was performed using three consecutive media and drug release kinetics are performed. The drug excipient interaction of CODES™ formulation was characterized by Fourier transform infrared (FT-IR). **Results and Discussion:** From the *in-vitro* drug release studies, F6 tablets were considered as the optimized formulation, which retard the drug release in the stomach (pH 1.2) and small intestine (pH 7.4) and progressively increase the release of 75.75% in the colon (pH 6.8) due to mucoadhesive properties of chitosan. The FT-IR analysis shows that there is no interaction between drug and excipient. The drug release kinetics followed supercase – II transport with erosion mechanism. **Conclusion:** Briefly to conclude that CODES™ technology is a promising method for approach to deliver drug to colon due to the controlled release of biodegradable polysaccharides and gastric resistance polymer.

Key words: Biodegradable polymer, CODES™ technology, Eudragit S100, Gastric resistance polymer, Metronidazole hydrochloride

INTRODUCTION

The development of a new dosage form based on the uses of polysaccharides in targeted delivery of colon plays a significant role in research due to the overwhelming advantages such as treatment of colorectal infections, ulcerative colitis, Crohn's disease, irritable bowel syndrome, amoebiasis, and colorectal cancer.[1] The release of drug toward the specific part of the body such as tissue and other organs, or at particular absorption site, for increasing therapeutic efficiency, targeted delivery system is used widely.[2] Drugs that have instability in gastric pH, solubility issues, short half-life, specific absorption window, and also the drug delivered specifically to the colon without absorption at the upper part of GIT that allows a higher concentration of the drug to reach the colon with minimal absorption.[3,4]

The characteristic of the colon such as longer transit time, near-neutral pH, reduced digestive enzymatic activity, targeted delivery of the colon is greatly achieved.[5] Coating of drugs with pH-sensitive polymers such as eudragit S100, and eudragit L100 aimed to protect the drug core from gastric and small intestinal fluids.[6]

Amoebiasis is an infection of the large intestine caused by *Entamoeba histolytica*, a single-cell protozoan parasite, which invades the colonic epithelium.[7] Metronidazole (1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole) is one of the prototype nitroimidazole antimicrobials, antiprotozoal, antibacterial medication used for the treatment of anaerobic and protozoal infections.[8] As a prodrug, unionized metronidazole is taken by an obligate anaerobic organism and is subsequently reduced to an active intermediate product.[9] Reduced Metronidazole causes DNA strand breaks, thereby inhibiting synthesis of DNA and bacterial cell growth. Conventional dosage form of Metronidazole is absorbed almost completely, with bioavailability >90% but to treat

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amoebiasis in the colon, produces minimum therapeutic action with unwanted side effects like convulsive seizures, encephalopathy, and aseptic meningitis.[10,11] Moreover, maximum therapeutic activity in the colon is achieved by Metronidazole with polysaccharides, which is degraded by colonic enzymes and is coated with pH-sensitive polymer to overcome degradation in the upper part of gastrointestinal tract.[12] The mannitol and avicel pH 101 are used as the protective agents and inert insoluble polymer respectively in which drug release rate depends on them.[13]

MATERIALS AND METHODS

Excipients for Core Tablets

Metronidazole hydrochloride was obtained as a gift sample. Xanthan gum and Lactose monohydrate were procured from Himedia, Chitosan from Aldrich chemistry, Avicel pH 101 was from Fluka Analytical, Mannitol from Rankem, and Magnesium stearate from LobaChemie Private Ltd.

Excipient for Coating Solution

Eudragit S 100 and Eudragit L 100 were obtained from Yarrow Pharma (Mumbai), Acetone was obtained from SDFCL, Talc from Reachem. Dibutylphthalate, Isopropanol, Titanium dioxide were purchased from LobaChemie Pvt. Ltd.

Preformulation Studies

Determination of melting point

Digital melting point apparatus is used to determine melting point by the capillary method. The temperature at which the drug gets melted completely is recorded.

Determination of solubility

Solubility of Metronidazole Hydrochloride is performed by saturation solubility method. The drug solution is prepared with various solvents such as pH 1.2, 7.4, 6.8, and water.

Determination of λ max

Metronidazole hydrochloride drug solution is prepared using buffer was scanned by double-beam ultraviolet (UV) spectroscopy (UV- 1650 PC, Shimadzu Corporation) between the range of 200 nm and 400 nm.

Method of Preparation

Preparation of drug-loaded tablets

The core tablets containing 200 mg of Metronidazole Hydrochloride tablets were obtained by direct compression technique. The formula of different core formulations is listed in [Table 1]. The drug is mixed with xanthan gum/chitosan for 10 min and then passed through #30 mesh sieve. Avicel pH 101, mannitol, lactose monohydrate were added in geometric dilution. To this mix, add magnesium stearate for 15 min. The blend was directly compressed into tablets having 400 mg as average weight using a Minipress tablet punching machine (RIMEK, Ahmedabad, India).[11,13]

Coating of drug-loaded tablets

Preparation of coating solution

The formulation for coating with pH-sensitive polymer (eudragit S 100, eudragit L 100), opacifier (talc), plasticizer (dibutylphthalate) was mixed with solvents mixture of acetone, isopropanol, and water in the varying proportion are given in the Table 2. For inner coating and outer coating solution, weigh the accurate amount of eudragit S 100 and eudragit L100 respectively, is mixed with half of the solvent mixture to make a paste by using a high-speed homogenizer (Homogenizer Omni GLH 850). And then add talc gradually to make suspension with the remaining portion of solvent mixture. Finally, add dibutyl phthalate and then stir for 20 min.

Coating methodology

The double-layered system of Metronidazole tablets was prepared by dip-coating technique. The tablet core was preheated to about 40°C by using the dryer and it is dipped into the solution containing coating material. The coated tablets are primarily dried using a heat blower and secondarily with a tray drier at 50°C.[14] The core tablet gained 5 ± 2% weight after coating with eudragit S100 as an inner layer. After complete drying, the outer layer by eudragit L100 with weight gain of 5 ± 2% is done.

Evaluation of CODES™ Formulation

Precompression evaluation of metronidazole hydrochloride powder system

Micromeritic properties of the blends were evaluated by determining the properties such as bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose. The angle of repose of powder blend is obtained by the fixed funnel technique. The bulk density was determined by placing a specific mass of powder blend in a graduated cylinder and measuring the volume. The tapped density is obtained by powder blend containing the graduated cylinder is supposed to tap many times until the constant volume is obtained. Hausner's ratio is a number that relates to a powder or granules material's flowability. From the measured value of bulk density and tapped density, the value of the hausner ratio and carr's index was determined.[15]

Fourier transform infrared spectroscopy (FT-IR) analysis

The FT-IR spectra of Metronidazole Hydrochloride and excipient used in the CODES™ technology were analyzed to

Table 1: Formulation of metronidazole hydrochloride core tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Metronidazole HCl	200	200	200	200	200	200	200	200
Xanthan gum	100	100	100	100	–	–	–	–
Chitosan	–	–	–	–	100	100	100	100
Avicel PH 101	40	60	40	60	40	60	40	60
Mannitol	60	40	–	–	60	40	–	–
Lactose	–	–	60	40	–	–	60	40
Magnesium stearate	10	10	10	10	10	10	10	10

Table 2: Formulation of the coating solution

S.No	Ingredients	For 50 ml
1	Eudragit S 100/L100 (6%w/v)	3 g
2	Dibutyl phthalate (15% of polymer)	0.3 g
3	Talc (50% of polymer)	1.5 g
4	Titanium dioxide	100 mg
5	Acetone	20 ml
6	Isopropanol	20 ml
7	Water	7.5 ml

find any sign of interaction between drug and excipients were determined by potassium bromide pellet method using (FT-IR 8400 Shimadzu 240V, Shimadzu corporation).[16,17]

Quality control for coated tablets

The coated tablets are under visual inspection to find out sticking and picking, roughness, orange peel effect, bridging and filling, blistering, and hazing/dull film.

Evaluation of compressed coated tablets

Hardness

The hardness of the tablets was determined by using a hardness tester (ERWEKA TBH 125, Erweka India Pvt. Ltd, Mumbai). The randomly select core tablets from each formulation were placed between the anvil of the hardness tester. And read the breaking point of the tablets in Newton (9.807 Newton = 1 kg) on the digital screen of the tester.

Friability

The friability of the tablet was evaluated using a friability tester (INWEKA, India Pvt. Ltd, Mumbai). Weigh twenty tablets before placing them into the rotating drum of the friabilator and record the initial weight of the tablet. The drum was rotated at 25 rpm for up to 5 min. After complete rotation, the tablet from the drum is again subjected to determine the final weight to evaluate % friability.

Weight variation test

According to the Indian Pharmacopoeia, weigh 20 tablets of Metronidazole Hydrochloride individually using an electronic balance (AY 220, Shimadzu Corporation, Japan). By determining average weight, % deviation is calculated by comparing individual weight to the average weight.

Thickness

The thickness of coated tablets is measured by a screw gauge.[11]

Disintegration time

The disintegration of the double-layered coated system was performed according to the Indian Pharmacopoeia 1996. The USP disintegration apparatus (LAB INDIA DT 1000, Lab India analytical Pvt. Ltd, Mumbai) was used to perform the disintegration test. The disintegration medium used in the evaluation is 0.1 M HCl (pH 1.2) for 2 h and phosphate buffer (pH 6.8) for 1 h maintaining a temperature of 37 ± 2°C. The time taken for the tablet to disintegrate completely was recorded.

In vitro dissolution studies

The drug release of Metronidazole Hydrochloride was examined by using USP Type I (basket) dissolution apparatus (LAB INDIA DS 8000, Lab India Analytical Pvt. Ltd, Mumbai) at a standard condition of 50 rpm at 37 ± 0.5°C. To evaluate the dissolution profile of CODES™ tablets in gastrointestinal fluids, a dissolution test was performed using three consecutive media. The coated tablet from each formulation is subjected to 0.1 M HCl (pH 1.2) for 2 h as the average gastric emptying time is about 2 h. Then, the dissolution medium is replaced with phosphate buffer (pH 7.4) and tested for drug release for 3 h as the average small intestine transit time is about 3 h. And finally, the dissolution medium is changed into phosphate buffer (pH 6.8). A sample of 5 ml was withdrawn from a particular time interval and replaced with an equal amount of fresh medium. The sample was suitably diluted if necessary and estimated spectrophotometrically using UV/Visible double beam spectrophotometer and cumulative percentage drug release was calculated.[16]

Drug release kinetics

The release behavior of the double-layered system was determined in GF, IF, and CF pH. Zero-order (1), First-order (2), Higuchi (3), and Korsmeyer-Peppas (4) models were used to fit the drug release behavior of the system to examine the drug release mechanism.[18]

$$F = kt \quad (1)$$

$$Ln\ (1-F) = -kt \quad (2)$$

$$F = kt^{1/2} \quad (3)$$

$$F = kt^{n} \quad (4)$$

where F is the cumulative release rate of the drug at time t, k is the kinetic constant of the various mathematical models, and n is the release index of the Korsmeyer-Peppas model. A value of $0.5 < n < 1$ indicates that drug release occurs through a combination of diffusion and erosion mechanisms, whereas $n < 0.5$ indicates that release is dominated by the Fick diffusion mechanism.[19]

RESULTS AND DISCUSSION

Preformulation Studies of Metronidazole Hydrochloride

The melting point by the capillary method was found to be 165°C. The solubility study of Metronidazole Hydrochloride was determined in solvents of different pH is shown in Table 3. The λ max of Metronidazole Hydrochloride is found to be 318 nm in phosphate buffer (pH - 6.8).

Evaluation of CODES™ Formulation

Precompression evaluation of metronidazole hydrochloride powder system

The precompressed parameters such as bulk density, tapped density, angle of repose, Carr's index, and hausner's ratio are determined and shown in Table 4. From the obtained data, angle of repose reveals that the formulation (F5, F6, F7, F8) exhibits excellent flow properties and within the Indian Pharmacopoeia limits. Moreover, the above formulations achieve good flow behavior within the range of 19.73 ± 0.7–22.63 ± 2.2 for carr's index and 1.24 ± 0.01–1.29 ± 0.03 for Hausner ratio.

Table 3: Saturation solubility

Solvent	Solubility (mg/ml)	Inference
Distilled water	14.98	Sparingly soluble
Phosphate buffer 7.4	24.372	Sparingly soluble
Phosphate buffer 6.8	19.46	Sparingly soluble
0.1 M HCl	208.285	Slightly soluble

FT-IR analysis

The FT-IR spectrum of pure Metronidazole Hydrochloride and excipient used in the core tablets are examined and results that, there is no interaction between them.

Evaluation of compressed coated tablets

The post-compressed parameters such as hardness, friability, weight variation, thickness, and disintegration time of all formulations are evaluated and shown in [Table 5]. The hardness of all formulations within the Indian Pharmacopoeia ranges from 45 ± 1 to 50.33 ± 1.5 Newton. The percentage friability did not exceed 1% of the tablet weight of all formulations indicates that tablets are mechanically stable and withstand handling and transportation. The weight variation results that the individual tablet weight is within the range of around ±5%. The thickness of all formulations was found within range of 3.48 ± 0.06 mm–3.66 ± 0.04 mm showing uniform tableting.The disintegration time of all formulation ranges from 154.3 ± 4 min to 186 ± 5 min and indicates tablets passes the disintegration test of enteric-coated tablets.

In vitro dissolution studies

In-vitro drug release study was performed for all CODES™ formulations and it is compared with the marketed formulation. The percentage drug release profile comparison was given in [Figure 1]. According to the data, formulation F6 shows maximum drug release of 75.75% in the phosphate buffer (pH 6.8) than other formulations. The gastro resistance polymer retards drug release to the stomach and small intestine. The dissolution rate was influenced by the thickness of the coated layer and the release pattern of a biodegradable polymer.

In vitro drug release kinetics

The drug release kinetics of CODES™ formulation was subjected to various drug release kinetics models given in

Table 4: Micromeritic properties of pre-compressed powder system

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Hausner's ratio	Carr's index
F1	0.71±0.01	0.99±0.01	31.46±1.52	1.38±0.03	27.60±1.9
F2	0.75±0.03	0.98±0.02	34.72±0.46	1.31±0.07	23.67±4.2
F3	0.74±0.03	0.99±0.03	30.81±0.93	1.34±0.05	25.72±3.1
F4	0.71±0.02	0.97±0.01	31.88±0.42	1.36±0.03	26.80±1.8
F5	0.77±0.01	0.97±0.005	35.75±1.71	1.26±0.01	20.82±1.2
F6	0.76±0.02	0.98±0.005	35.14±1.91	1.29±0.03	22.63±2.2
F7	0.76±0.02	0.97±0.01	36.85±2.09	1.27±0.02	21.50±1.8
F8	0.78±0.01	0.98±0.01	37.66±2.80	1.24±0.01	19.73±0.7

(Mean±standard deviation, *n*=3)

Table 5: Evaluation of coated tablets

Formulation	Hardness (Newton)	Thickness (mm)	Friability (%)	Weight variation (mg)	Disintegration time (min)
F1	45.0±1.0	3.50±0.32	1.23±0.03	436.6±4.5	154.3±4
F2	50.0±1.0	3.50±0.03	0.31±0.02	434.6±6.6	158.3±3
F3	42.6±1.5	3.34±0.03	0.22±0.02	436.3±3.0	168.2±6
F4	45.6±2.0	3.53±0.03	0.19±0.02	440.0±2.0	166.3±6
F5	46.6±2.0	3.62±0.09	0.32±0.01	436.0±2.0	171.1±3
F6	50.3±1.5	3.48±0.06	0.19±0.01	441.0±2.0	186.0±5
F7	47.0±1.0	3.66±0.04	0.23±0.04	437.6±3.5	182.3±6
F8	49.0±0.1.0	3.50±0.06	0.27±0.02	435.6±4.1	173.6±4

Table 6: *In vitro* release kinetics (F6)

Kinetic models	R^2 value	AIC value
Zero-order	0.4731	103.59
First-order	0.4172	104.80
Higuchi	0.2906	107.16
Korsmeyer-Peppas	0.9593	74.8608

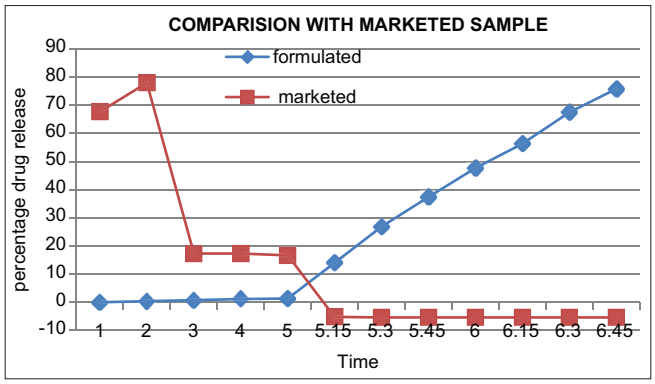

Figure 1: *In-vitro* drug release of F6 compared with marketed formulation

[Table 6]. The mechanism of drug release was non-fickian diffusion (super case II) with erosion mechanism. Since they fitted with korsmeyer-peppas models as their r^2 in the range 0.9593 with n value above 1.

Effects of biodegradable polysaccharide

From the *in-vitro* dissolution data, formulation with the use of chitosan has more potential than other polysaccharides to deliver the drug in the colon. Because of mucoadhesive properties, it adheres to the mucosa and chitosan gets degraded by the enzymes, lysosomes, which are highly concentrated on the colonic mucosa.[20] Thus, the controlled release of drug is achieved by the biodegradable polymer, chitosan in the ratio of 1:4.

Effects of the plasticizer

The plasticizer plays an important role in the preparation of coated tablets. The process of coating with pH-dependent polymer is influenced by the ratio of plasticizer used. The polymer with 20% of plasticizer shows sticky nature to the substrate[21] and 10% shows the bridging defects in the coated film. Both of them failed to drug release in the colon. And 15% of plasticizers produced the uniform distribution of film with high potential drug release.

CONCLUSION

To sum up everything that has been stated that design and development of CODES™ technique, Metronidazole Hydrochloride is successively targeted to the colon. Among all the formulations F6 shows maximum drug release of 75.75% at 7 h. Chitosan shows more potential in controlled release because of mucoadhesive properties and ratio of plasticier also influence quality control of film. The FT-IR spectrum reveals that there is no drug interaction with drug and polymers. Briefly to conclude that CODES™ technology is a promising method for approach to deliver drug to the colon due to the controlled release of biodegradable polysaccharides and gastric resistance polymer.

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