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Formulation and Evaluation of Metronidazole Enteric Coated Tablets for Colon Targeting



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ABSTRACT

Colon specific drug delivery has gained importance for the delivery at colonic region by use of various drugs to treat both local and systemic diseases. Local diseases include Chron's disease, ulcerative colitis, colorectal cancer, amoebiasis etc. The active ingredient Metronidazole has to be delivered to the colon for effective action against trophozoites of *E. histolytica* and *Giradia lamblia*, wherein the respective trophozoites reside in the lumen of caecum and large intestine and adhere to colonic mucus and epithelial layers. Formulating Metronidazole as conventional tablets give side effects which occur due to absorption of drug from upper part of GIT and the pharmacokinetic profile of Metronidazole indicates that the drug is completely absorbed in approximately 1 hr after a single dose. So, various synthetic hydrophilic polymers are used to control the drug delivery and target the drug to the intestine using enteric coated polymers. The aim of the present study was to formulate core tablets using different polymers such as HPMC K 15M and HPMC K100M in different ratios and the core tablets were coated with an enteric polymer. The prepared tablets were evaluated for weight variation, hardness, friability, content uniformity and *in vitro* drug release study first in 0.1N HCl followed by in pH 7.4 phosphate buffer.

INTRODUCTION

Oral controlled release formulations for the small intestine and colon have received considerable attention in the past 25 years for a variety of reasons including pharmaceutical superiority and clinical benefits derived from the drug release pattern that are not achieved with traditional immediate (or) sustained release products.

By definition, colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). The site specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer¹. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the delivery system arrives into the colon.

The present study is aimed to formulate and evaluate enteric coated tablets of Metronidazole² for colon targeted drug delivery, which may decrease side effects that occur due to absorption of drug in upper part of GIT and to achieve high local concentration of drug in colon, for the effective treatment of diseases of colon³. Metronidazole is the preferred drug used in treatment of the Amoebiasis, Giardiasis, Trichomoniasis and anaerobic infections⁴⁻⁵. These drugs are to be delivered to the colon for their effective action against trophozoites of *E. histolytica* and *Giardia lamblia* wherein the respective trophozoites reside in lumen of the caecum and large intestine and adhere to colonic mucus and epithelial layers. But pharmacokinetic profile of Metronidazole indicates that drug is completely absorbed in approximately 1 h after a single dose of 500mg. So, various synthetic hydrophilic polymers are used to control the drug delivery and target the drug to the colon. The main objective of the study is to formulate enteric coated tablets of Metronidazole to target the drug to the colon as well as to prolong drug delivery in the colon, to reduce the side effects that occur due to absorption of drug in the upper part of GIT, to investigate the effects of various polymers on the formulation, when used in different concentrations.

MATERIALS AND METHODS

Metronidazole was procured as gift sample from Provizer Pharma, Hyderabad. HPMC K15M and HPMC K100M were obtained from SD Fine Chemicals, Hyderabad. Microcrystalline cellulose, talc and magnesium stearate were purchased from Hi Pure Chemicals, Hyderabad. Sodium carboxy methyl cellulose was procured from Vijaya Lakshmi Chemicals, Hyderabad, cellulose acetate phthalate from Triveni Chemicals, Gujarat.

PRECOMPRESSION PARAMETERS

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

1. Bulk density (D_b)⁶: It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

$$D_b = \frac{M}{V_0}$$

Where, M is the mass of powder,
 V_0 is the bulk volume of the powder.

2. Tapped density (D_t)⁶: It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$$D_t = \frac{M}{V_1}$$

Where, M is the mass of powder,
 V_t is the tapped volume of the powder.

3. Carr's index (%) ⁷: The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$\text{Carr's index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

4. Hausner's ratio: Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

5. Angle of repose (θ): It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose,

h is the height in cms,

r is the radius in cms.

COMPATIBILITY STUDIES

Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious product. Accurately weighed quantity of drug and other excipients were mixed properly and one milligram of the sample was taken and mixed with 10 mg of dried powered potassium bromide. These quantities are usually sufficient to give a disc of 10-15 mm diameter and pellet of suitable intensity by a hydraulic press. The powdered mixture was taken in a diffuse reflectance sampler and the spectrum was recorded by scanning in the wavelength region of IR 4000-400 cm^{-1} in an FT-IR Spectrophotometer. The IR spectrum of the drug was compared with that of the mixture to check for any possible drug- excipients interaction.

FORMULATION OF METRONIDAZOLE CORE TABLETS

Weigh Metronidazole, HPMC K 15M, HPMC K 100M, Sodium Carboxy Methyl Cellulose, Micro Crystalline Cellulose and PVP K 30. Pass the above ingredients through sieve no 4.

Weigh Talc and Magnesium Stearate. Pass Talc and Magnesium Stearate through sieve no 60. The above powder mass was blended uniformly. The above blended mass was compressed using a tablet compression machine in 12 mm punch. The details are captured in Table 1.

ENTERIC COATING OF TABLETS

The prepared tablets were coated with Cellulose acetate phthalate solution using spray coating technique. Coating solution was prepared by mixing cellulose acetate phthalate with triethyl citrate with continuous stirring and volume was made by isopropyl alcohol and dichloromethane. The core tablets are loaded in coating pan and kept for pre warming for 30 min and the tablets were coated with enteric coating solution under fixed process parameters. The details are given in Table 2 & 3.

EVALUATION OF METRONIDAZOLE TABLETS

1. Weight Variation ⁸: Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight. The percentage deviation can be determined by using the following formula:

$$\% \text{ Deviation} = 100 * \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}}$$

The tablet passes the test, if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

2. Friability ⁹: Friability of the tablets was checked by using Roche Friabilator. Percent friability was calculated using the formula given below:

$$\text{Percent friability} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} * 100$$

Conventional compressed tablets that loose less than 0.5% to 1% of weight are considered acceptable.

3. Hardness ⁹: Hardness or tablet crushing strength is defined as force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet. It was measured using Monsanto tablet hardness tester.

4. Content Uniformity Test ⁹: Ten tablets were finely powdered. 100 mg of the powder was accurately weighed and transferred to a 100 ml volumetric flask containing 50 ml of methanol and allowed to stand for 6 h with intermittent sonication to ensure complete solubility of drug. The solution was made up to volume and filtered. After filtration, diluted suitably and estimated for Metronidazole content at 254 nm by using UV -VIS spectrophotometer and methanol as a blank. The drug content was calculated using the standard calibration curve.

5. *In vitro* drug release study ¹⁰: The *in vitro* dissolution study of Metronidazole enteric coated tablets were determined using USP XXIII type II (paddle) dissolution apparatus. The paddle rotation speed of 100 rpm and temperature of $37 \pm 0.5^\circ\text{C}$ was maintained. Aliquots (5 ml) of the solution were collected at predetermined time intervals from the dissolution apparatus and samples were replaced with fresh dissolution medium. Firstly the dissolution medium was 0.1N HCl for 2 hrs then it was replaced with pH 7.4 phosphate buffer. Absorbance of these solutions was measured at 277 nm in 0.1 N HCl and at 319 nm in pH 7.4 phosphate buffer and cumulative percentage drug release was calculated.

6. Drug Release kinetics ¹¹: Dissolution data was fitted to zero order, first order, Hixon-crowell Higuchi equations and Korresmeyer-Peppas to determine the kinetics of drug release.

RESULTS AND DISCUSSION

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose and the results were shown in Table 4. The angle of repose values obtained for the formulations ranged from 25.48 to 30.40. The compressibility index values for the formulations ranged from 11.36 to 21.8. The Hausner's ratio values for the formulations ranged from 1.12 to 1.25. This indicates the powder blend has good flow property.

IR spectra of individual Metronidazole and the combination of drug with polymers were shown in Table 5. The study indicates that the chemical structure of the drug is likely to be unaffected

due to the addition of excipients of the drug. The presence of the peaks confirms undisturbed structure of drug and excipients in the above formulation. Hence, there is no drug – excipient interaction. The details are given in Graph 1 to 4.

The weight variation of the tablets was within the limits of 5%. The measured hardness of tablets in all batches was ranged from 6.0 – 6.2 kg/cm². Friability values were found to be less than 1% in all prepared formulations and considered to be satisfactory. Drug content was in the range of 99.17 to 100.2 % indicating good content uniformity in the all formulations. The details are given in Table 6.

The calibration curves of Metronidazole were shown in Graphs 5 & 6.

It was found that the release of drug in F12 gave the better release than other formulations. When the amount of polymer is increased the drug release decreased. The sustainability of the drug in F12 was found to show good targeted site controlled drug delivery, as it showed 96% drug release for 24 hrs. *In vitro* drug release profiles were given in Graphs 7 & 8.

From the release kinetics data, F12 follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism leading to conclusion that a release mechanism of drug followed combination of diffusion and erosion. The results were shown in Table 7.

CONCLUSION

The present study has been satisfactorily attempted to formulate enteric coated tablets of Metronidazole for oral administration, with a view of targeting the drug to colon and to prolong the drug release in colon. Preformulation studies indicate that the powder blend has good flow properties. Post compression parameters revealed that all were found to be acceptable. Formulation F12 showed good targeted site controlled drug delivery, as it showed 96% drug release for 24 hrs and it follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism. Thus, the formulated enteric coated tablets seem to be a potential candidate for targeted and sustained drug delivery of Metronidazole for the treatment of diseases of colon.

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TABLES & GRAPHS

Table 1: Composition of Metronidazole Core Tablets

INGREDIENTS	FORMULATION CODE											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metronidazole	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K 15M	50	100	150	200	250	300	-	-	-	-	-	-
HPMC K 100M	-	-	-	-	-	-	50	100	150	200	250	300
Sodium CMC	50	50	50	50	50	50	50	50	50	50	50	50
Microcrystalline cellulose	290.6	240.6	190.6	140.6	90.6	40.6	290.6	240.6	190.6	140.6	90.6	40.6
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Talc	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
PVP K 30	7	7	7	7	7	7	7	7	7	7	7	7
Total (mg)	900	900	900	900	900	900	900	900	900	900	900	900

Table 2: Enteric coating composition

S. No.	Ingredient	Quantity (%)
1.	Cellulose acetate phthalate	40
2.	Triethyl citrate	6
3.	Isopropyl alcohol	q.s.
4.	Dichloromethane	q.s.

Table 3: Parameters of Coating Process

PARAMETERS OF COATING PROCESS	RANGE
Pan Charge	3.5 Kg
Pan speed	14 rpm
Inlet Temperature	52-58°C
Exhaust air temperature	40
Bed Temperature	35
Spray rate	50 g/min
Distance Between spray gun and tablet bed	15 cm

Table 4: Pre-compression parameters

Formulation code	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose(θ)	Compressibility index (%)	Hausner's ratio
F1	0.462	0.591	26.06	21.8	1.25
F2	0.469	0.561	25.42	21.39	1.19
F3	0.46	0.55	25.62	16.36	1.19
F4	0.59	0.68	29.19	13.04	1.15
F5	0.49	0.57	30.40	14.04	1.16
F6	0.48	0.55	26.06	12.72	1.14
F7	0.46	0.53	25.38	13.20	1.15
F8	0.43	0.49	26.72	12.24	1.14
F9	0.41	0.47	27.94	12.76	1.14
F10	0.39	0.44	25.48	11.36	1.12
F11	0.55	0.64	26.21	14.06	1.16
F12	0.53	0.61	25.74	13.11	1.15

Table 5: FTIR Interpretation

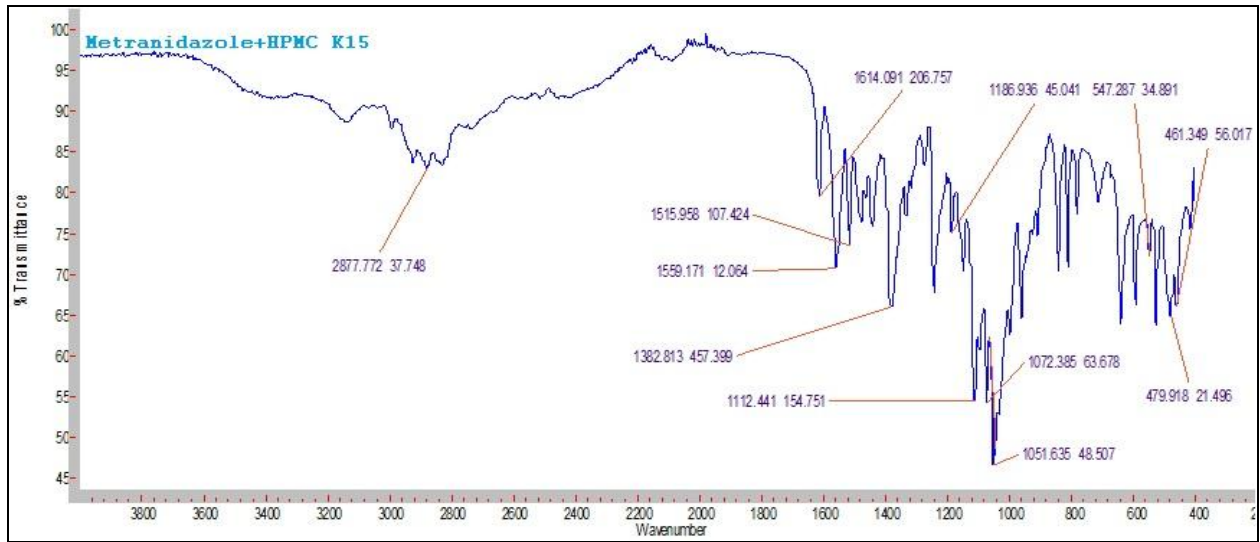
S.NO	INTERPRETATION	FT-IR ABSORPTION BANDS			
		PURE DRUG	DRUG+HPMCK 100M	DRUG+HPMC K15M	DRUG +Sodium CMC
1	NO ₂ stretching mode	1540.325	1540.850	1559.171	1541.019
2	C-N stretching mode	1150.843	1110.673	1112.441	1151.539
3	C=C stretching mode	1670.948	1671.501	1614.091	1671.624
4	C-H Stretching mode	2929.704	2929.42	2877.37	2928.456

Table 6: Post-compression parameters

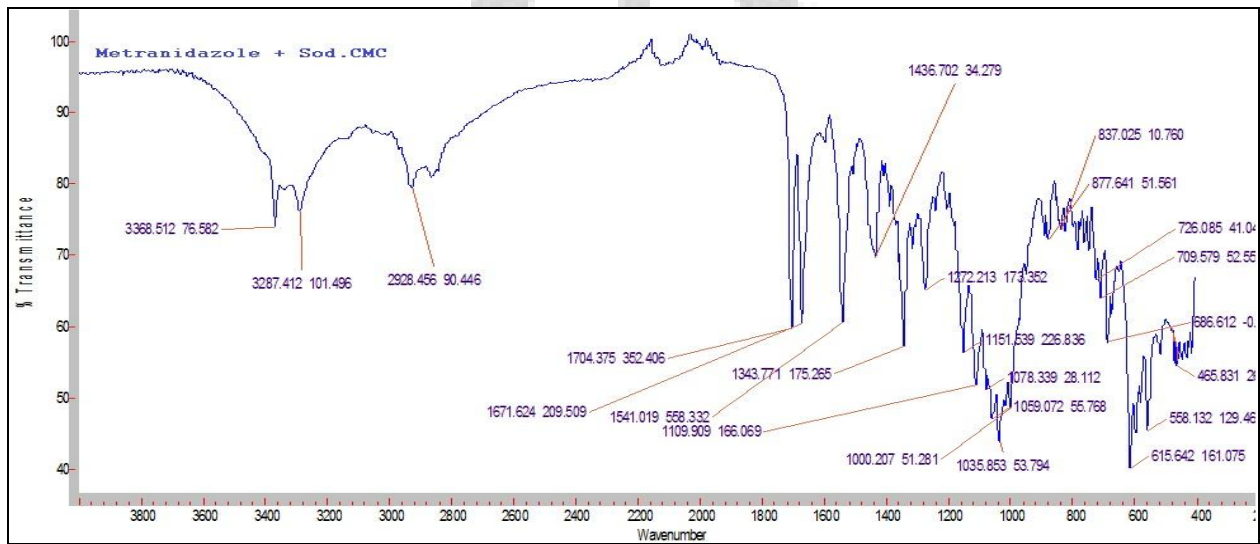
Formulation code/Parameter	Hardness (kg/cm ²)	Weight variation (%)	Friability (%)	Content uniformity (%)
F1	6.2	Pass	0.18	99.17
F2	6.0	Pass	0.22	99.44
F3	6.0	Pass	0.43	98.64
F4	6.0	Pass	0.20	99.42
F5	6.1	Pass	0.19	99.17
F6	6.1	Pass	0.22	99.44
F7	6.1	Pass	0.45	99.64
F8	5.9	Pass	0.24	100.2
F9	5.9	Pass	0.38	99.89
F10	6.0	Pass	0.12	99.97
F11	6.0	Pass	0.24	99.24
F12	6.0	Pass	0.16	99.62

Table 7: Release kinetics for F-12

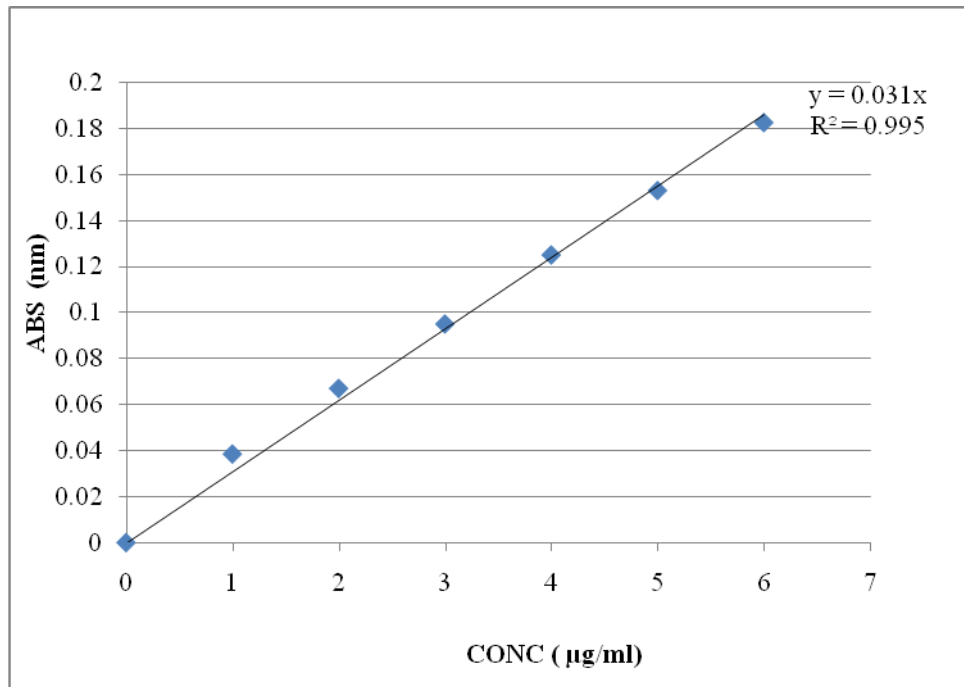
Formulation code	Zero order	First order	Higuchi Matrix	Korsmeyer-Peppas		Best Fit model
	R ²	R ²	R ²	R ²	n	
F-12	0.951	0.917	0.955	0.992	0.6	Peppas



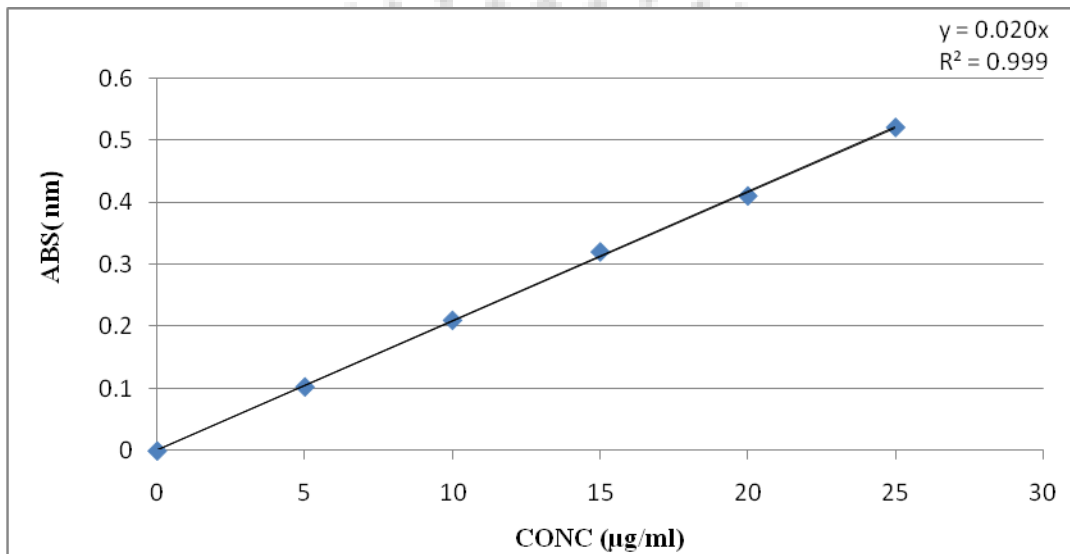
Graph 3: FT-IR spectra for Metronidazole and HPMC K 15M



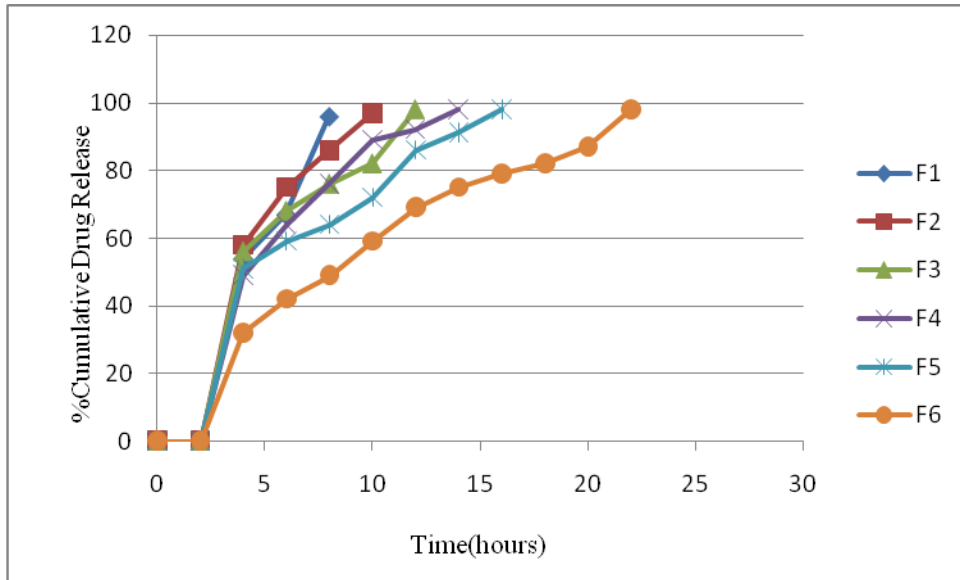
Graph 4: FT-IR spectra for Metronidazole and sodium CMC



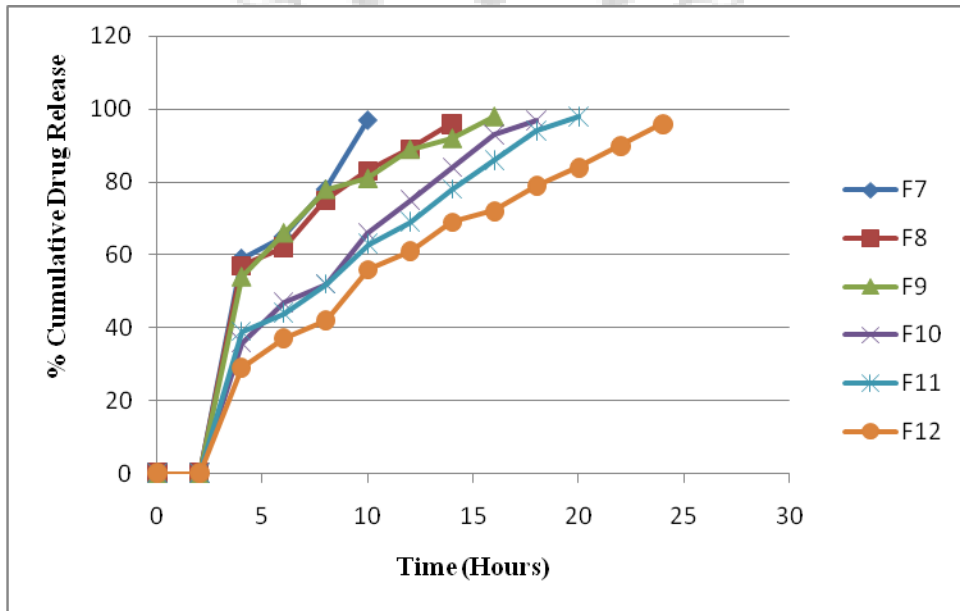
Graph 5: Standard Curve of Metronidazole in 0.1N HCl



Graph 6: Standard curve of Metronidazole in pH 7.4 phosphate buffer



Graph 7: Dissolution profile for the formulations (F1-F6)



Graph 8: Dissolution profile for the formulations (F7-F12)