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Research Article

FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS OF TINIDAZOLE

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ABSTRACT

The purpose of present investigation was to develop and evaluate gastro retentive drug delivery system of Tinidazole. These floating tablets were prepared with the objective to obtain site-specific drug delivery and to extend its duration of action. More over the floating system of Tinidazole will provide increased local and systemic action in stomach. Floating tablets were formulated by various materials like hydroxyl propyl methylcellulose HPMC (K 4M, K15M), xanthum gum, microcrystalline cellulose as swelling agent and gas generating agent like sodium bicarbonate. All the formulations were evaluated for floating properties, swelling characteristics and drug release studies. *In-vitro* drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow zero order release and best fitted into peppas model. The floating lag time were found to be significantly increased with the increasing concentration of the polymers. After the dissolution study of prepared Tinidazole floating tablet it was concluded that the formulation F16 with HPMC K15M and xanthum gum shows better controlled release effect (98.48%). The release kinetic data implies that the release mechanism of all the formulations was zero order kinetics and best fitted into peppas model.

Keywords: Tinidazole, HPMC, Xanthum gum, Microcrystalline cellulose.

INTRODUCTION[1-9]

Tinidazole is an anti-parasitic drug used against protozoan infections. It is widely known throughout Europe and the developing world as a treatment for a variety of amoebic and parasitic infections. It was developed in 1972. A derivative of 2-methylimidazole, it is a prominent member of the nitro imidazole antibiotics.

There has been considerable research over the last decade on the possibility of controlled and site specific delivery to the GIT by controlling the gastrointestinal transit of orally administered dosage forms using gastro retentive drug delivery system (GRDDS). Such GRDDS possess the ability of retaining the dosage forms in gastrointestinal tract (GIT) particularly, in the stomach for long period the transit time in GIT i.e., from the mouth to the anus, varies from one person to another. It also depends upon the physical properties of the object ingested and the physiological conditions of the alimentary canal. Several drugs are absorbed to the most extent in the upper part of the small intestine. Many drugs show poor bioavailability (BA) in the presence of intestinal metabolic enzymes like cytochrome P450 (CYP3A), abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon. Drugs having site-specific absorption are difficult to design as oral CRDDS because only the drug released in the region preceding and in close vicinity to the

absorption window is available for absorption. After crossing the absorption window, the released drug goes waste with negligible or no absorption. This phenomenon considerably decreases the time available for drug absorption after its release and expose the success of the delivery system.

The GRDDS can improve the controlled delivery of the drugs which exhibit an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring its optimal bioavailability. After oral administration, Tinidazole is well-absorbed and distributed. The drug is not primarily metabolized by hepatic enzymes. The terminal half-life of Tinidazole is about 12-14 hours. The objective of this study was to developed gastric floating drug delivery system containing Tinidazole and having a bulk density lower than that of gastric fluid and remaining buoyant on the stomach contents. To achieve the objective low density polymers such as hydroxypropyl methylcellulose HPMC (K15M, K4M), xanthan gum, sodium alginate was used.

EXPERIMENTAL

Materials and methods

Tinidazole was obtained as a gift sample from Hetero drugs, Hyderabad, Telangana, India. Hydroxypropyl methylcellulose K15M, xanthan gum, hydroxypropyl methyl cellulose K4M, microcrystalline cellulose, polyvinylpyrolidine K-25, magnesium stearate, ethylcellulose and sodium bicarbonate were obtained from SD Fine Chemicals, Mumbai, Maharashtra, India. Talc was obtained from Merck Life Sciences, Mumbai, India.

Preparation of gastro retentive floating tablets[10-12]

Floating tablets containing Tinidazole were prepared by wet granulation technique using variable concentrations of HPMC K15M, HPMC K4M, ethylcellulose, xanthan gum, MCC and PVP K25 with sodium bicarbonate.

Different tablet formulations were prepared by wet granulation method. All the powders were passed through 60 mesh sieve the required quantity of drug and lower density polymer were mixed geometrically and then tablets are compressed in compression machine at specified pressure with 11 mm round punch. The results are furnished in Table 1.

Pre-formulation studies[13]

Determination of melting point

Melting point of Tinidazole was determined by capillary method. Fine powder of Tinidazole was filled in glass capillary tube (previously sealed on one end). The capillary tube is tied to thermometer and the thermometer was placed in fire. The powder at what temperature it will melt was noticed.

Solubility

- Slightly soluble in water
- Soluble in 0.1N HCl
- Slightly soluble in pH 6.8 and pH 7.4 buffer.
-

Solubility studies were performed by taking excess amount of Tinidazole in different beakers containing the solvents. The mixtures were shaken for 24 hours at regular intervals. The solutions were filtered by using Whatman filter paper grade no. 41. The filtered solutions are analyzed spectrophotometrically.

Compatibility studies[14-20]

Compatibility with excipients was confirmed by carried out IR studies. The pure drug and its formulations along with excipients were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Identification of Tinidazole

A solution of Tinidazole containing the concentration 10 µg/ ml was prepared in 0.1N HCl and UV spectrum was taken using Systronics UV/Vis double beam spectrophotometer. The solution was scanned in the range of 200-400nm.

Preparation of standard calibration curve of Tinidazole

10 mg of Tinidazole was accurately weighed and transferred into 10 ml volumetric flask. It was dissolved and diluted to volume with 0.1N HCl to give stock solution containing 1000µg/ml. From the above stock solution, 1ml taken in 10ml volumetric flask and makeup the volume upto 10ml with 0.1N HCl to give a stock solution containing 100 µg/ml.

The standard stock solution was then serially diluted with 0.1N HCl to get 5 to 30 µg/ml of Tinidazole. The absorbances of the solution were measured against 0.1N HCl as blank at 275 nm using UV spectrophotometer respectively. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve and were shown in Figure 1.

Evaluation of powder blend

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was

adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\mathbf{Tan\ \theta = h/r}$$

Where, h and r are the height and radius of the powder cone.

Bulk density and tapped density

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced into 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following equations.

LBD = Weight of the powder blend/Untapped volume of the packing

TBD = Weight of the powder blend/Tapped volume of the packing

Compressibility index

Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$Carrs\ index(\%) = \frac{[(TBD-LBD)]}{TBD} \times 100$$

Evaluation of tablets

Weight variation test

To study weight variation twenty tablets of the formulation were weighed using an Essae electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1N HCl, the drug content was determined measuring the absorbance at 275 nm after suitable dilution using a Shimadzu UV-Vis double beam spectrophotometer 1700.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Thickness

The thickness of the tablets was determined by using vernier calipers. Five tablets were used, and average values were calculated.

Friability test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The % friability was then calculated by,

$$\%\ Friability = \frac{Winitial - Wfinal}{Winitial} \times 100$$

% Friability of tablets less than 1% are considered acceptable.

The hardness, thickness and friability results are tabulated in Table 2 and Table 3.

***In-vitro* buoyancy studies**[21,22]

The *in-vitro* buoyancy was determined by floating lag time method. The tablets were placed in 250 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

***In-vitro* dissolution studies**[23-27]

The release rate of Tinidazole from floating tablets was determined using *United States Pharmacopoeia* (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37±0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 8 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl.

Absorbance of these solutions was measured at 275 nm using a Shimadzu UV-Vis double beam spectrophotometer 1700. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

RESULTS AND DISCUSSION

The saturation solubility of Tinidazole was carried out at 25^0C using 0.1N HCl, 6.8 phosphate buffer, pH 7.4 phosphate buffer and purified water. The maximum absorbance of the Tinidazole in 0.1N HCl, was found to be 275 nm. Hence the wavelength of 275 nm was selected for analysis of drug in dissolution media.

The formulations F-1 to F-18 have, bulk density was vary between 0.421 gm/ml to 0.471 gm/ml, Tapped density was 0.478 gm/ml to 0.551 gm/ml, the compressibility index was 11.9 to 14.5 and Hausner's ratio was 1.133 to 1.169. It indicates the developed formulation possesses good flow properties.

The formulations F-1 to F-18 have, average weight vary between 498.06 mg to 500.03 mg, hardness was vary between 4.6 kp to 5.9 kp, Thickness was vary between 3.10 mm to 3.16 mm, percentage of friability was vary between 0.46 % to 0.89 %, percentage of drug content was vary between 96.21 % to 100.02 %. It indicates all the above results were in limits.

The floating lag time (FLT) of all prepared Tinidazole floating tablets were found in the range of 38 sec to 81 sec and also Total Floating Time (TFT) or Total Buoyancy Time (TBT) shows more than 5 hours for formulations F1-F3, 7 hours for formulations F4-F6, 8 hours for formulations F7-F9, 10 hours for formulations F10- F12, 12 hours for formulations F13-F18.

The optimized formulation F16 have regression coefficient (R^2) values of zero order, first order, higuchi and korsmeyer peppas were 0.991, 0.778, 0.886 and 0.953 respectively. The optimized batch follows zero order drug release kinetics and best fitted into peppas model. The results are given in Table 4. The zero order and peppas plots were shown in Figure 2 and Figure 3.

From the above results, there was no significant change in the optimized formulation physicochemical parameters at storage condition 40°C±2°C/75±5%RH for 6 months, there was no significant change in the optimized formulation *in-vitro* dissolution profile at storage condition 40°C±2°C/75±5 %RH for 6 months.

FTIR Spectroscopy

When Tinidazole was studied in combination with polymers, no change in melting point of Tinidazole was observed, no additional peaks were observed indicating compatibility of materials. Sharp melting peaks were observed for Tinidazole. IR spectra of Tinidazole and optimized formulation were shown in Figure 4 and Figure 5.

CONCLUSION

From the compatibility studies, it is concluded that, HPMC K15M, HPMC K4M, xanthan gum, PVPK-25, ethylcellulose, MCC, sodiumbicarbonate, talc were compatible with drug Tinidazole and thus suitable for the formulation of Tinidazole floating tablets. Tinidazole tablets were fabricated by wet granulation method. *In-vitro* drug release study is performed for 12 hrs. Optimized formulation (F16) containing HPMC K15M, xanthan gum, showed better release compare to other formulations and it followed zero order kinetics and best fitted with peppas model. From this study, it was concluded that HPMC K15M and xanthan gum can be used in formulation of Tinidazole gastro retentive floating drug delivery system by using wet granulation method.

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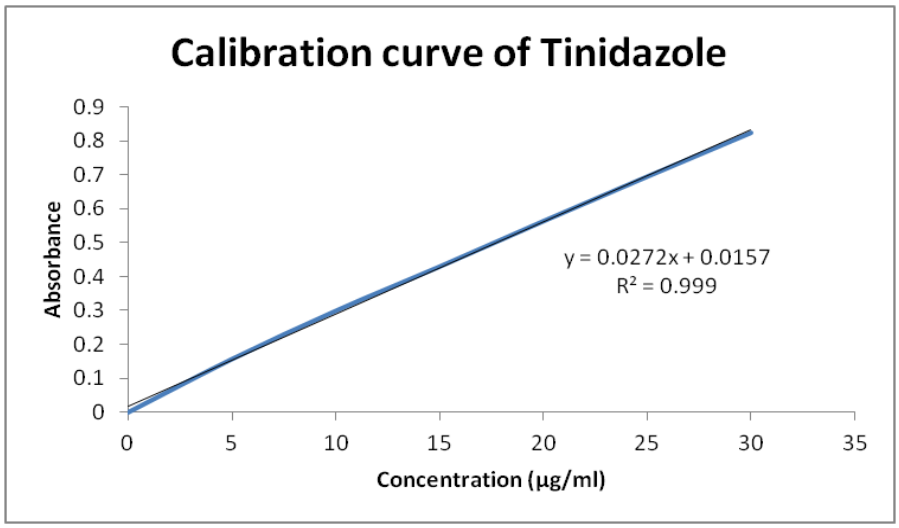

Fig. 1: Standard calibration curve of Tinidazole

Fig. 2: Zero order plot of Tinidazole (F16)

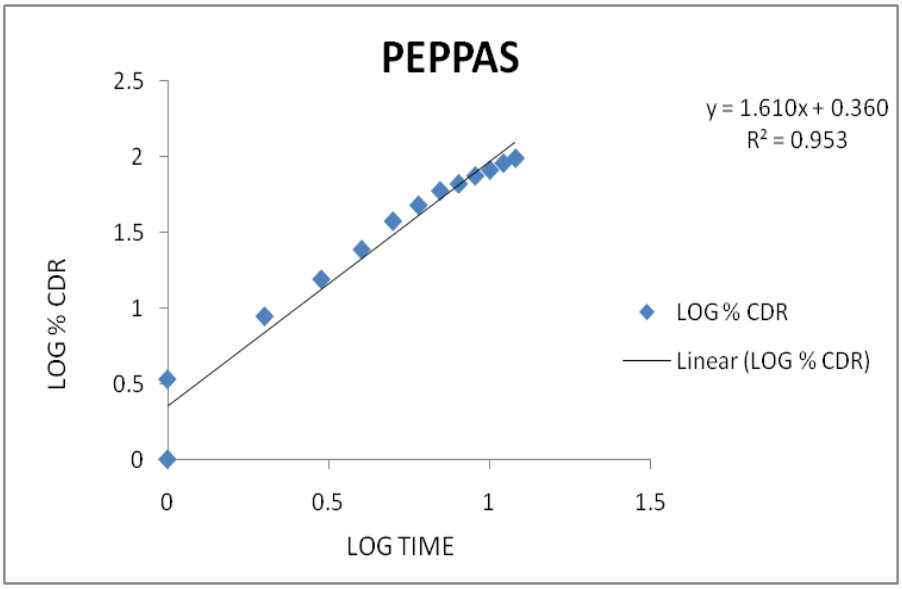

Fig. 3: Peppas plot of Tinidazole (F16)

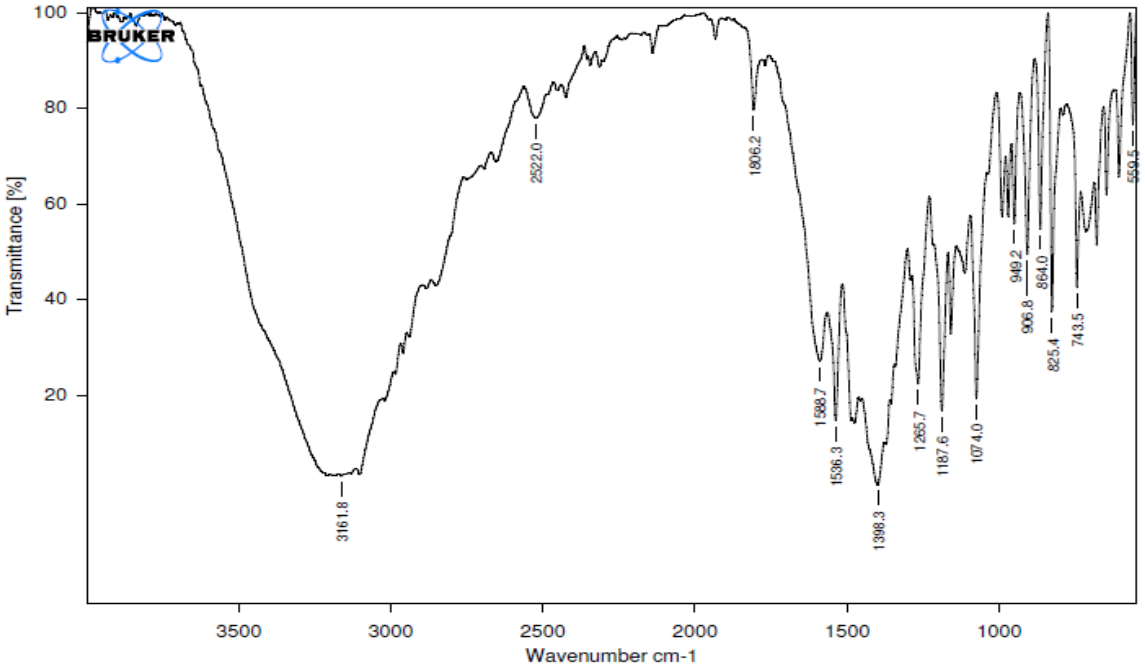

Fig. 4: IR Spectra of Tinidazole

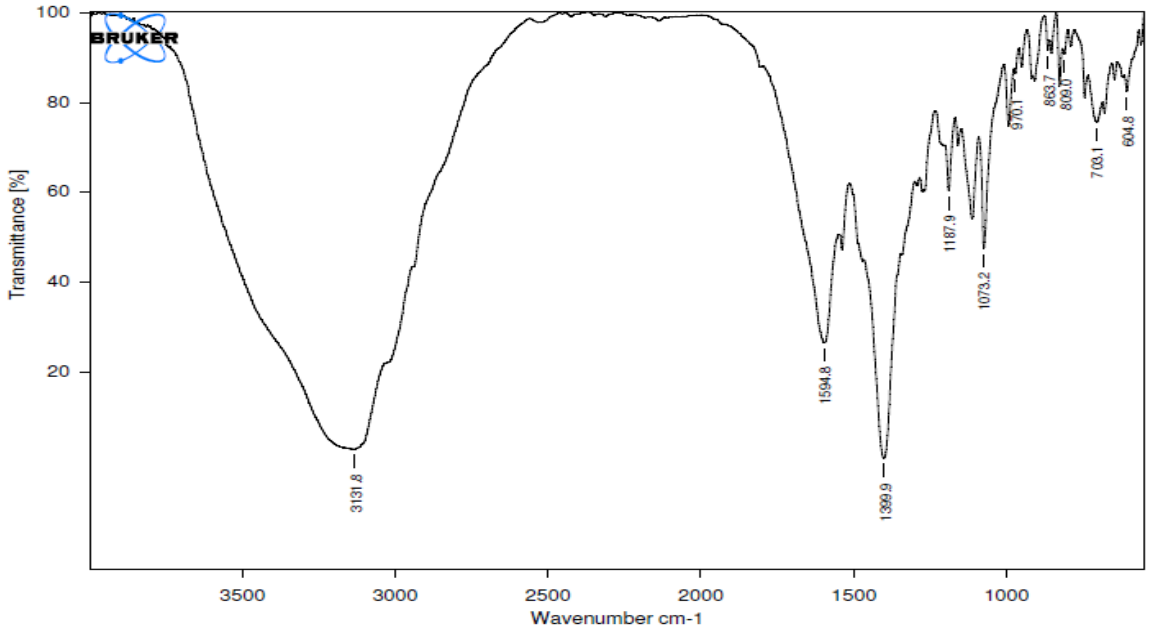

Fig. 5: IR Spectra of Tinidazole optimized formulation

Table 1: Composition of different formulations of Tinidazole

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Tinidazole	200	200	200	200	200	200	200	200	200	200
HPMC K15M	100	--	--	100	--	--	100			150
Xanthan gum	--	100	--	--	100	--		100		--
HPMC K4M	--	--	100	--	--	100			100	--
PVPK-25	50	50	50	75	75	75				--
Ethyl cellulose	--	--	--	--	--	--	25	25	25	25
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
$NaHCO_3$	50	50	50	65	65	65	65	65	65	50
Mg. stearate	10	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5	5
Total (mg)	500	500	500	500	500	500	500	500	500	500

Ingredients(mg)	F11	F12	F13	F14	F15	F16	F17	F18
Tinidazole	200	200	200	200	200	200	200	200
HPMC K15M	--	--	75	--	75	75	--	75
Xanthan gum	150	--	75	75	--	75	75	--
HPMC K4M	--	150	--	75	75	--	75	75
PVPK-25	--	--	--	--	--	--	--	--
Ethyl cellulose	25	25	25	25	25	50	50	50
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
$NaHCO_3$	50	50	50	50	50	50	50	50
Mg. stearate	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5
Total (mg)	500	500	500	500	500	500	500	500

Table 2: Evaluation of physical parameters of floating tablets (F1 to F9) of Tinidazole

Parameters	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)	3.10 ±0.02	3.12 ±0.01	3.10 ±0.05	3.14 ±0.04	3.12 ±0.01	3.16 ±0.02	3.11 ±0.04	3.10 ±0.02	3.12 ±0.03
Hardness (Kg/cm^2)	4.6 ±0.21	4.8 ±0.35	5.2 ±0.54	4.7 ±0.10	5.1 ±0.24	4.9 ±0.63	4.8 ±0.51	5.3 ±0.21	5.1 ±0.35
Friability (%)	0.46 ±0.01	0.47 ±0.02	0.49 ±0.01	0.51 ±0.03	0.56± 0.02	0.47 ±0.01	0.58 ±0.02	0.69 ±0.02	0.72 ±0.05

The values represent mean ± S.D; n=5.

Table 3: Evaluation of physical parameters of floating tablets (F10 to F18) of Tinidazole

Parameters	Formulation Code								
	F10	F11	F12	F13	F14	F15	F16	F17	F18
Thickness (mm)	3.14 ± 0.01	3.12 ± 0.02	3.15 ± 0.01	3.11 ±0.03	3.10 ±0.02	3.13 ±0.02	3.12 ±0.06	3.13 ± 0.01	3.10 ± 0.02
Hardness (Kg/cm^2)	5.3 ± 0.25	5.7 ± 0.52	5.2 ± 0.42	5.9 ± 0.48	5.2 ± 0.31	5.1 ± 0.26	5.6 ± 0.84	5.4 ± 0.17	5.7 ± 0.16
Friability (%)	0.74 ±0.01	0.71 ± 0.02	0.65 ±0.01	0.63 ±0.03	0.76 ±0.01	0.81 ±0.02	0.86 ±0.01	0.76 ± 0.03	0.89 ± 0.01

The values represent mean ± S.D; n=5.

Table 4: Drug release kinetics of optimized formulation (F16) of Tinidazole

Formulation code	Zero order	First order	Higuchi	Peppas	
	r^2	r^2	r^2	r^2	n
F16	0.991	0.778	0.886	0.953	1.610

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