

Research Article

Formulation and In-vitro Evaluation of compression coated tablet of Tinidazole for Colon Specific Drug Delivery System

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Abstract

Compression coating is one of the strategies for delivering drug to the colon based on gastrointestinal pH & transit time concept. The aim of the present study is to formulate colon targeted drug delivery of Tinidazole compression coated tablets by using different ratios of Chitosan and Pectin. Compression coated tablets have been coated with carbapol 934P which enables drug release at the pH of colonic fluid. Core tablets of Tinidazole (300 mg) were prepared by using swellable and pH Dependent polymers like chitosan and pectin in which PVP-K30 was used as Binder. Drug release profile was evaluated in simulated gastric fluid, intestinal fluid and simulated colonic fluid. The drug release studies were performed according to the USP paddle method by using 0.1N HCl for 2 hours, pH 7.4 phosphate buffers for 3 hours and pH 6.8 phosphate buffers up to 24 hours without using rat caecal content. Compression coated tablets containing chitosan as polymer released 95-99% of Tinidazole in simulated colonic fluid, whereas tablets containing pectin as polymer released 94-99% of Tinidazole. The stability study for pre-

pared tablets at 40°C and 75% relative humidity for 6 weeks showed no significant change in physical appearance, drug content uniformity and *in vitro* drug release pattern. From the result it can be concluded that formulation F3 (Chitosan compression coated tablets) and formulation F5 (Pectin compression coated tablets) were suitable for colonic drug delivery as drug release was found to be maximum when compared to other formulations.

Key Words: Tinidazole, Colon Drug Delivery System, Amoebiasis, Chitosan, Pectin, Compression Coated Tablets.

Introduction:

Tinidazole is classified in the WHO Essential Medicines List as Anti-amoebic, Anti-Giardiasis, and Anti-bacterial. It is used in combination with other antibiotics and either bismuth compounds or proton pump inhibitors for treatment of peptic ulcer disease caused by *Helicobacter pylori*. Because of its activity against anaerobic bacteria, Tinidazole has also been employed in the treatment of periodontal disease.¹

Chemically, Tinidazole is, 1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole, which inhibits nucleic acid synthesis. It had especially high activity *in vitro* and *in vivo* against the anaerobic protozoa against *T. vaginalis* and *E. histolytica*.¹

Oral administration of conventional dosage forms normally dissolves in the gastrointestinal fluid and then the absorption of drugs primarily depends upon physicochemical characteristics of the drug. Conditions become critical when a drug needs to be delivered only to the colon or when a drug needs to be protected from the pH and enzymatic environment of upper gastrointestinal tract. Colon targeted drug delivery can be defined as drug delivery into the lower gastrointestinal part known as the colon.^{2,3}

Colon specific drug delivery has gained increased importance not just for the delivery of drugs in the treatment associated with the colon, but also as a potential site for the systemic delivery of therapeutic peptide and proteins. To achieve successful colon targeted drug delivery, a drug needs to be protected from degradation, release and/or absorption in the upper portion of the GI tract and then to be

ensured abrupt or controlled release in the proximal colon.^{4,5}

The colon targeted drug delivery has a number of important implications in the field of pharmacotherapy. Oral colon targeted drug delivery systems have recently gained importance for delivering a variety of therapeutic agents for both local and systemic administration. Targeting of drugs to the colon via oral administration protect the drug from degradation or release in the stomach and small intestine. It also ensures abrupt or controlled release of the drug in the proximal colon. Various drug delivery systems have been designed that deliver the drug quantitatively to the colon and then trigger the release of drug. Different types of polymers which can be used in formulation of colon targeted drug delivery systems such as Chitosan, Pectin, Chondroitin sulphate, Cyclodextrins, Dextran, Guar gum, Inulin, Amylose and Locust bean gum.^{6,7}

The aim of the present study is to formulate colon targeted drug delivery of Tinidazole compression coated tablets by using different ratios of chitosan and pectin. Carbopol 934P coating is given for compression coated tablets which makes them able to release the drug at the pH of colonic fluid. A combined mechanism of release is seen, which combines specific biodegradability of polymer and pH. Dependent drug release from the compression coated tablet.

MATERIALS

Tinidazole was gifted from Abbott Healthcare Pvt. Ltd, Goa. Chitosan and Carbopol 934P from Ozone international, Mumbai. Pectin was obtained from Sisco Research Laboratories Pvt. Ltd., Mumbai. PVP K-30 obtained from Qualikems fine chemicals Pvt.ltd, Gujarat. Whereas Microcrystalline cellulose from Loba chemical pvt. Ltd., Talc from Nice chemicals Pvt., Ltd., Cochin and Magnesium stearate from NR Chemicals, Mumbai. Methanol, Hydrochloric acid, Potassium dihydrogen phosphate, Sodium hydroxide from SD Fine Chem., Ltd.

METHODS

PREPARATION OF TINIDAZOLE CORE TABLETS:

Six compression coated tablet formulations each

containing 300 mg of Tinidazole and weighing 500 mg tablets were prepared by direct compression techniques using Chitosan and Pectin matrices. Tinidazole, Polymers (Chitosan and Pectin), PVP-K30 (as binder), and Microcrystalline Cellulose were triturated well and sieved through sieve no. 60 and mixed thoroughly by using mortar and pestle. To the above powder mass lubricants (Talc and Magnesium stearate) were added and mixed thoroughly. The powder is evaluated for pre compression parameters. The powder was then compressed using 10 mm flat-faced punch using a chamunda tablet punching machine. The total weight of the tablet was maintained 500 mg.

The different ratios of chitosan and pectin core tablets of tinidazole were compression coated by using one coat formulation. The compression coat formulations were prepared using Carbopol 934 Pand Chitosan (Table. 2). Initially, 40% of coat weight was placed in a 12.4 mm die cavity of a Chamunda tablet punching machine followed by carefully centering the core tablet and addition of remainder of coat weight. The coating material was compressed around the core tablet with high compression force.

Compatibility Studies:

The compatibility of drug and polymers under experimental condition is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental condition and affect the shelf life of product.

This is confirmed by Infrared light absorption scanning spectroscopy. It is most powerful technique for chemical identification of drug.

Method: The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

EVALUATION OF TABLETS:

PRE-COMPRESSION PARAMETERS:¹⁰

Prior to the compression, the powder blends of various batches were evaluated for their bulk and tapped density and from these values compressibility index and Hausner's ratio were calculated. While the flow properties of the powder blend

were accessed from the angle of repose. The evaluation parameters were studied before and after addition of lubricants to check and compare the inherent flow properties of powders.

POST-COMPRESSION PARAMETERS:

Shape and Color of Tablets: ¹⁰

Uncoated tablets were examined under a lens for the shape of the tablet, and color was observed by keeping the tablets in light.

Uniformity of Thickness: ¹⁰

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using Vernier caliper.

Hardness test: ¹⁰

Hardness indicates the ability of a tablet to withstand mechanical shocks while packaging, handling and transportation. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and analyzed for hardness. The mean values were calculated.

Friability test: ¹⁰

It is the phenomenon where by tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) 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 (W_{fin-}

al). The % friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

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

Weight Variation Test: ¹⁰

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed in the weight of a tablet by U.S. Pharmacopoeia.

Drug Content uniformity: ¹⁰

Twenty tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 50 mg of tinidazole was transferred in to a 100 ml volumetric flask and extracted with 0.1N Hydrochloric acid solution, filtered and kept a side for 2 hours. Dilute 10 ml of the resulting solution to 250 ml with 0.1N HCl and the absorbance of the resulting solution at the maximum at 321 nm using a Shimadzu UV-Visible spectrophotometer.

Water uptake studies (swelling study):^{10, 11}

The swelling behavior of polymer can be characterized by measuring its water uptake ability.at appropriate time intervals, each tablet was removed from its water with forceps, briefly patted with clean tissue paper to remove the solution wetting its surface and weighed. The swelling study was done in distilled water medium at 37°C. The results were expressed as %of water uptake (% of swelling) in function of time (hours). The method was used to record water uptake in triplicate. The results were plotted using % of swelling vs. time (hours).

Ingredients (mg/tablet)	Formulation Code					
	F1	F2	F3	F4	F5	F6
Tinidazole	300	300	300	300	300	300
Chitosan	50	75	100	--	--	--
Pectin	--	--	--	100	125	150
Pvp-K30 (As Binder)	10	10	10	10	10	10
Microcrystalline Cellulose	131	106	81	81	56	31
Magnesium Stearate	4	4	4	4	4	4
Talc	5	5	5	5	5	5
TOTAL	500	500	500	500	500	500

Table. 1: Composition of Colon Targeted Core Tablets of Tinidazole

Ingredients (mg/tablet)	Weight in mg
Chitosan	20
Carbopol 934P	160
Pvp-K30(As Binder)	10
Magnesium Stearate	6
Talc	4
Total	200
* Quantity in mg for one tablet	

Table. 2: Composition of Carbopol 934P Coat Formulation Tinidazole

The % of swelling was calculated by using following formula.

$$\text{Percent of swelling} = \frac{(\text{Wet weight} - \text{Original weight})}{\text{Original weight}} \times 100$$

In vitro Disintegration Time: ¹¹

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications.

Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated intestinal fluid) maintained at $37 \pm 2^\circ\text{C}$ as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at $37 \pm 2^\circ\text{C}$. The time in seconds or minutes taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. Enteric coated tablets pass the test if each of the six tablets disintegrates in not more than 60 minutes in the Simulated Intestinal Fluid.

In vitro Dissolution Studies¹²:

The compression coated tablets of tinidazole to remain intact in the physiological environment of stomach and small intestine was assessed by conducting in vitro drug release studies. Drug release studies were carried out using a USP Type II test apparatus (Paddle Type). (Apparatus Type II, 100 rpm, $37 \pm 1^\circ\text{C}$) for 2 hrs in 0.1 N HCl (900 ml) as the average gastric emptying time is about 2 hr. Then the dissolution medium was replaced with pH-7.4 phosphate buffer (900 ml) and tested for drug release for 3 hrs as the average small intestinal transit time is about 3 hr. After 5 hrs, the dissolution medium was replaced with pH 6.8 Phosphate buffer (900 ml) and tested for drug release up to 24 hr. At

the end of the each time period 10 ml of the samples were taken. From which 1ml is diluted to 10ml with respective dissolution medium and analyzed for tinidazole content at 317 nm. A 10 ml volume of fresh and filtered respective dissolution medium was added to make the volume after each sample withdrawal.

Curve Fitting Analysis ¹³

The mechanism of drug release was studied by fitting the dissolution data in different models.

- Zero order equation.
- First order equation.
- Higuchi model equation
- Korsmeyer Peppas equation

Drug Release Kinetics

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug released vs. time, first order (Equation 2) as log cumulative percentage of drug remaining vs. time, and Higuchi's model (Equation 3) as cumulative percentage of drug released vs. square root of time.

$$C + K_0t \quad (1)$$

Where K_0 is the zero-order rate constant expressed in units of concentration/ time and t is the time in hours. A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$\log C + \log C_0 - kt/2.303 \quad (2)$$

Where C_0 is the initial concentration of drug, k is the first order constant, and t is the time. (Bourne 1963)

$$Q + K t^{1/2} \text{ _____ (3)}$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Mechanism of Drug Release

To evaluate the mechanism of drug release from Matrix tablet, data for the first 60% of drug release were plotted in Korsmeyer et al's equation (Equation 4) as log cumulative percentage of drug released vs. log time, and the exponent n was calculated through the slope of the straight line.

$$M_t/M_\infty = K t^n \text{ _____ (4)}$$

Where M_t/M_∞ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers.

Stability Studies ^{14, 15}

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

In the present study, Stability studies were carried out at 40°C /75% RH for a specific time period up to 6 weeks for best formulations.

Results and discussion

Preparation of Standard Calibration Curve of Tinidazole

The standard calibration curve of tinidazole was obtained by plotting Absorbance v/s. Concentration. The standard calibration curve shows the slope of 0.025, 0.037, 0.047 and correlation coefficient of 0.999. The curve was found to be linear in the concentration range of 5-45 µg/ml (Beer's range) at 321 nm. Compressed coated tablets of tinidazole were prepared by using direct compression method. Before Compression, the powder blends were subjected to Pre-compression evaluation parameters to determine the flow properties and the compressibility. The results of the Pre-compression evaluation are as given below. The values of angle of repose were found to be in the range of 25^o.8' to 29^o.6'. All formulations showed the angle of repose within 30^o, which indicates a

good flow property of the powder. The loose bulk density and tapped bulk density for all the formulations varied from 0.47 gm/cm³ to 0.53gm/cm³ and 0.52gm/cm³ to 0.60gm/cm³ respectively. The values of Hausner's ratio were found to be in the range of 1.11 to 1.19. This percent compressibility of powder mix was determined by Carr's compressibility index which lied within the range of 10.16 to 16.94.

Tablets are subjected to punching and evaluated for post compression parameters. Tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variation as per pharmacopoeial specification. Its weight varied between 514.0 to 539.0 mg. The drug content uniformity was found in the range of 97.42% and 98.77%. (Acceptable limit) and the Hardness of the tablet was found between 5.2 to 5.8 kg/cm². The tablet thickness was found to be around 3.7 to 4.1 mm, Friability of tablet was found below 1% indicating good mechanical resistance. All formulations showed disintegration time less than 45 minutes. Among the two polymers used, pectin (Formulation F3) showed less disintegrating time.

In vitro Dissolution Studies

All the formulations were subjected for the *in vitro* dissolution studies using Tablet Dissolution Apparatus USP Type II (Paddle type). The samples were withdrawn at different time intervals and analyzed at 317 nm. Cumulative drug release was calculated on the basis of mean amount of tinidazole present in the respective tablet. The results obtained in the *in vitro* drug release for the formulations F1 to F6 are tabulated. The plots of cumulative % drug release V/s. time are shown in Figure. The Dissolution rate was found to decrease linearly with increasing concentration of polymer. Formulations F1, F2 and F3 containing drug plus chitosan polymer with carbopol 934P coating have recorded drug release 96.31%, 95.26% and 98.77% respectively, at the end of 24 hours. Formulations F4, F5, F6 containing drug plus pectin polymer with Carbopol 934P coating have recorded drug release 94.97%, 99.72% and 96.51% respectively, at the end of 24 hours. In all the formulations the drug release was near to 100% within 24 hours. The relative efficiency of different ratios of polymers to improve the dissolution rate of tablets was in order, Chitosan: F3>F1>F2 and Pectin: F5>F6>F4.

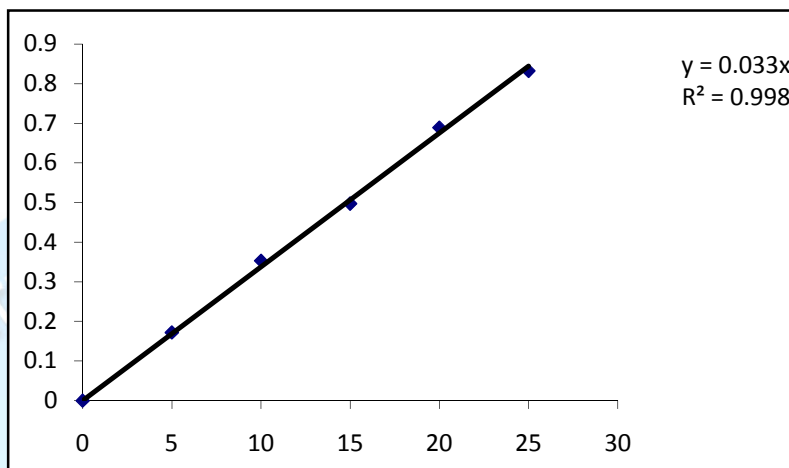


Fig. 1: Standard Calibration Curve of Tinidazole in 0.1 N HCl

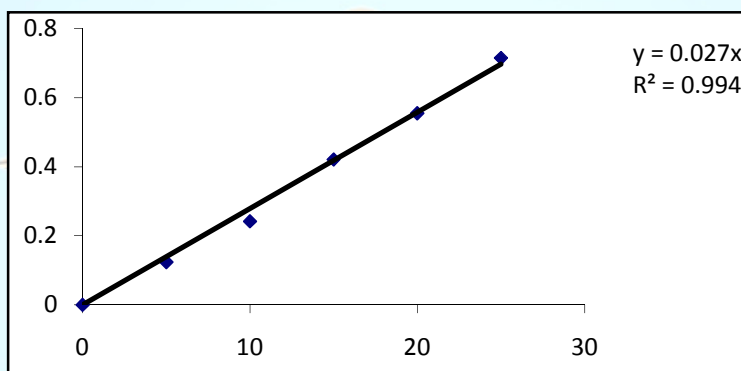


Fig. 2: Standard Calibration Curve of Tinidazole in Phosphate buffer 7.4

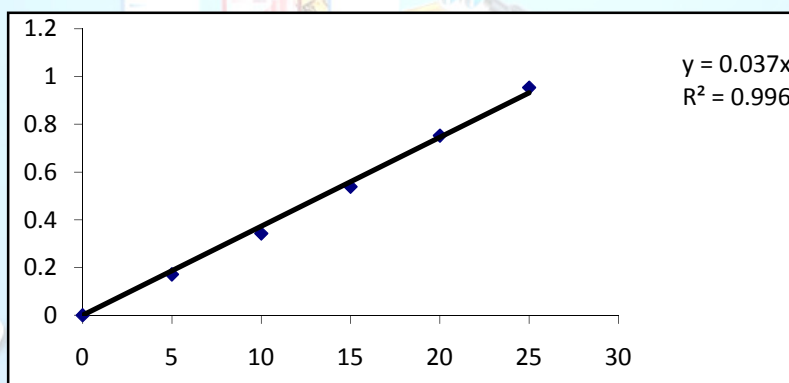


Fig. 3: Standard Calibration Curve of Tinidazole in Phosphate buffer 6.8

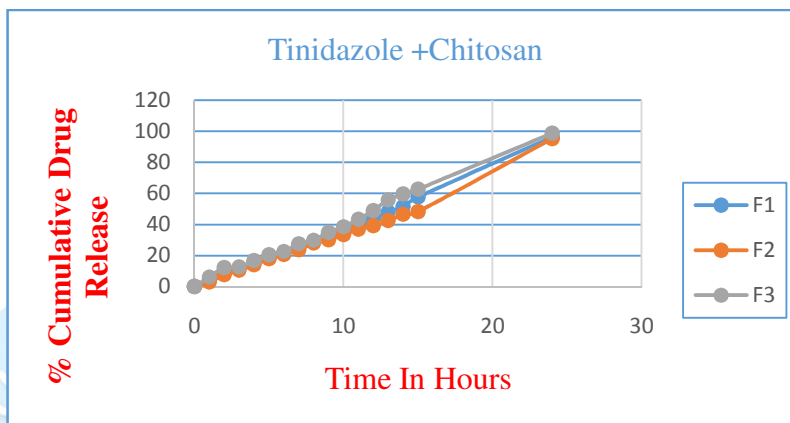


Fig. 4: In Vitro Dissolution profile of the formulations F1, F2, F3 in 0.1N HCl, pH. 7.4 phosphate buffer, pH. 6.8 phosphate buffer

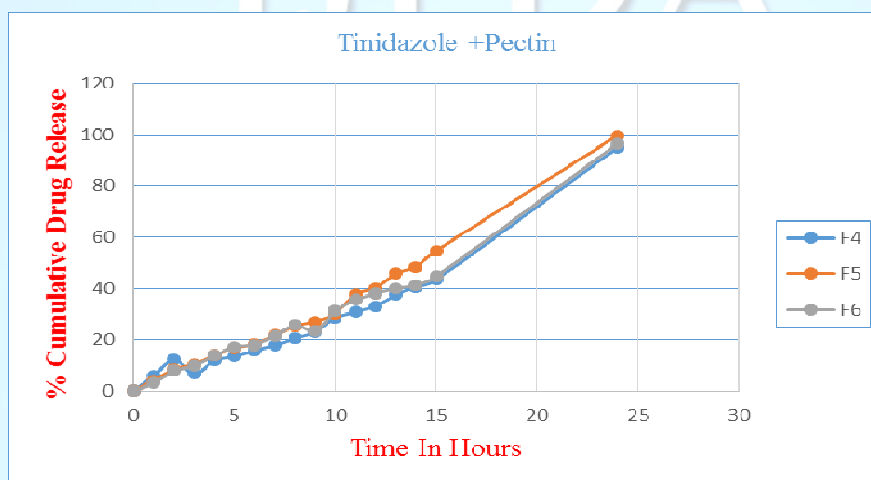


Fig. 5: In Vitro Dissolution profile of the formulations F4, F5, F6 in 0.1N HCl, pH. 7.4 phosphate buffer, pH. 6.8 phosphate buffer

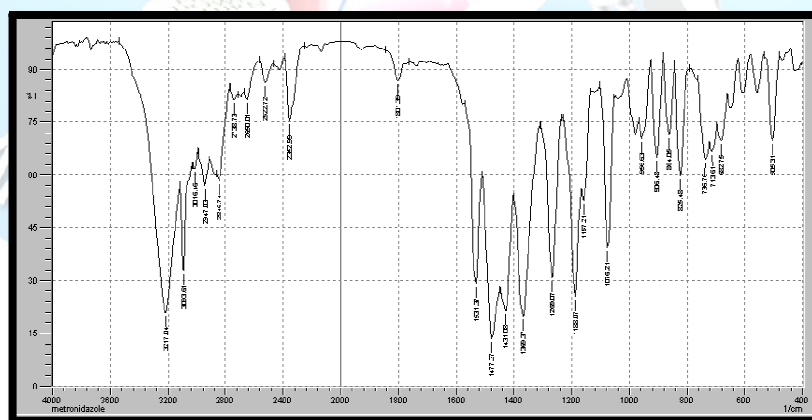


Fig. 6: IR Spectrum of Tinidazole pure drug

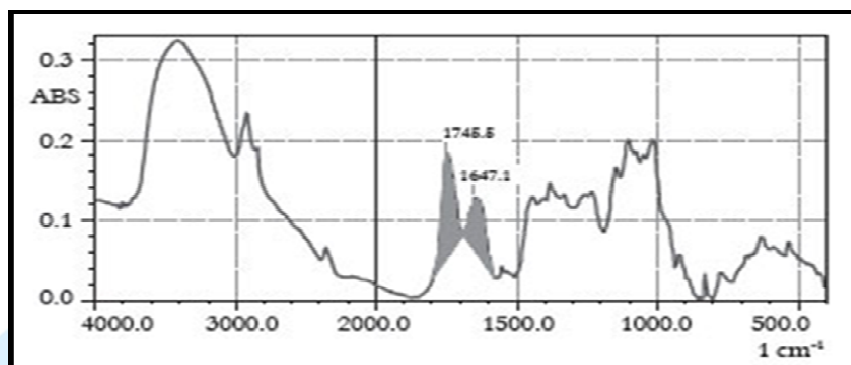


Fig. 7: IR Spectrum of pectin showing two wavelengths

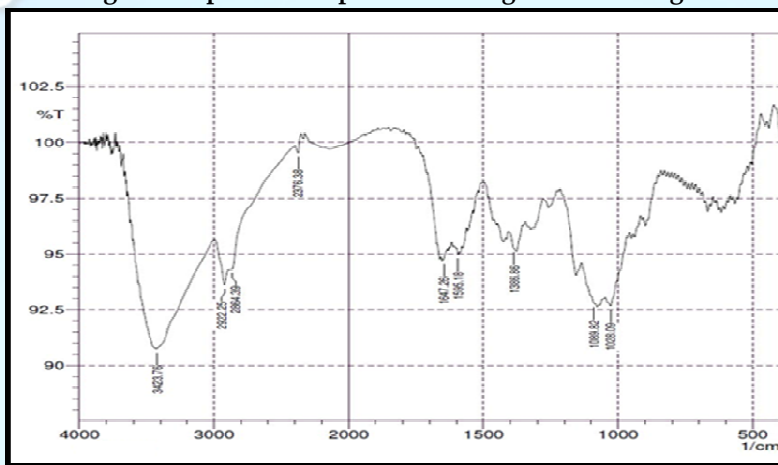


Fig. 8: IR Spectrum of Tinidazole Formulation

Formulation	Angle of	Bulk Density	Tapped Density	Compressibility	Hausner's
F1	28°.3'	0.47	0.56	16.07	1.19
F2	29°.6'	0.53	0.59	10.16	1.11
F3	28°.7'	0.46	0.52	11.53	1.11
F4	29°.6'	0.49	0.59	16.94	1.20
F5	26°.7'	0.51	0.58	12.06	1.13
F6	25°.8'	0.52	0.60	13.33	1.15

Table. 3: Evaluation of Pre-compression Parameters

Formulation code	Thickness (millimeter)	Hardness (kg/cm²)	Weight variation (mg)	Friability (%)
F1	3.7	5.4	520	0.39
F2	4.5	5.8	532	0.36
F3	4.1	5.6	528	0.49
F4	3.9	5.2	517	0.56
F5	4.1	5.3	514	0.53
F6	4.1	5.4	539	0.49

Table. 4: Post Compression Parameters of Tinidazole Tablet

Formulation code	Disintegration time (minutes)	Drug content uniformity (%)	% swelling in time
F1	39	98.36	2.4 in 1hr
F2	35	97.42	4 in 2hr
F3	31	98.51	6 in 3hr
F4	32	98.23	8.4 in 4hr
F5	34	98.39	11.2 in 5hr
F6	45	98.77	16.4 in 6 hr

Table. 5: Post Compression Parameters of Tinidazole

pH 1.2HCl, 900ml, USP-II (Paddle) Apparatus 1000 rpm, 37± 0.5°C						
TIME (hours)	% Cumulative Drug Release					
	F1	F2	F3	F4	F5	F6
1	3.96	2.88	6.12	6.12	4.32	3.24
2	9.72	7.56	12.24	12.24	8.64	7.92
pH 7.4 Phosphate buffer, 900ml, USP-II (Paddle) Apparatus 100 rpm, 37± 0.5°C						
3	11.88	10.44	12.64	6.79	10.44	9.94
4	15.30	13.95	16.74	11.88	14.08	13.86
5	18.36	18.00	20.43	13.59	16.74	17.23
pH 6.8 Phosphate buffer, 900ml, USP-II (Paddle) Apparatus 100 rpm, 37± 0.5°C						
6	21.60	20.65	22.59	15.88	18.36	18.09
7	26.50	23.71	27.54	17.77	21.82	21.60
8	28.89	27.94	29.83	20.65	25.33	25.65
9	33.39	30.10	34.83	23.13	27.18	23.53
10	37.03	33.30	38.47	28.53	30.33	31.18
11	39.33	36.94	43.33	30.82	37.71	35.59
12	43.42	39.15	48.91	33.12	40.18	38.07
13	48.15	42.48	55.80	37.53	45.85	40.00
14	51.48	46.53	59.53	40.59	48.42	41.35
15	57.60	48.24	62.68	43.42	54.76	44.77
24	96.31	95.26	98.77	94.97	99.72	96.51

Table. 6: In Vitro Dissolution profile of the formulations

Time in Week	Formulation F3 stored at 40°C / 75% RH		
	Physical appearance	% Drug content	In vitro dissolution studies
2	+++	98.36	98.72
4	+++	97.79	98.82
6	++	97.98	98.77

+++ = Same as on zero day, ++ = Slight change in color

Table. 7: Stability data of F3 formulation [Stability studies: Best formulation was chosen and stability studies were performed]

Time in Week	Formulation F5 stored at 40°C / 75% RH		
	Physical appearance	% Drug content	In vitro dissolution studies
2	+++	98.10	99.72
4	+++	98.24	98.38
6	++	99.02	98.48

+++ = Same as on zero day, ++ = Slight change in color

Table. 8: Stability data of F5 formulation

Drug Release Kinetics: The zero-order rate describes the systems where the drug release rate is independent of its concentration. The first order describes the release from systems where the release rate is concentration dependent. Higuchi's model describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined. The values of different models for all formulations are calculated. The dissolution data was fitted to Zero Order, First Order, Higuchi Model and Korsmeyer-Peppas model to analyze the drug mechanism. The correlation coefficient for (r^2) Zero Order ranges was found to be 0.9513 to 0.9946; First Order ranges from 0.7102 to 0.8015, Higuchi model ranges from 0.7787 to 0.888 and that of Korsmeyer-Peppas model ranges from 0.8849 to 0.9715. (Figure 5 and 6)

Stability Studies: The Formulations F3 and F5 were selected for stability studies on the basis of their high cumulative % drug release. The stability studies were carried out at 40°C/75% RH for all the selected formulations up to 6 weeks. For two week time interval the tablets were analyzed for Drug Content Uniformity, Hardness, *In Vitro* Disintegration Time, Friability and *In Vitro* Drug Release up to 6 weeks. These formulations showed not much variation in any parameter. From these results it was concluded that, Formulations F3 and F5 are stable and retained their original properties.

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