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FORMULATION AND EVALUATION OF COLON SPECIFIC DRUG DELIVERY TINIDAZOLE TABLETS

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ABSTRACT

The basic aim of the present investigation is to formulate and evaluate colon specific press coated tablets of Tinidazole. Tinidazole tablets were successfully prepared using enteric coated polymers ethyl cellulose and HPMC pthallate by first preparing the core tablets and then press coated with polymers. study of the preformulation charcteristics and FTIR studies indicates that there was no interaction between Tinidazole and excipients used in the formulation .Invitro release profiles of optimized form of F6 were found to showed delayed release pattern in a very customized manner which was very much required for the colon specific drug delivery. . In vitro release profiles of optimized formulation of Tinidazole controlled release tablets (F-6) were found to be improvised and followed zero - order kinetics, hence the release of the drug from the dosage form was independent of concentration and followed Higuchi model, and hence release of drug from press coated tablet was by diffusion mechanism. The drug delivery system was designed to deliver the drug at such a time when it was needed nocturnal time.

KEY WORDS

Tinidazole, Zollinger-Ellison syndrome, FTIR, dissolution profile

INTRODUCTION

Colon is being extensively investigated as a drug delivery site. Oral colon-specific drug delivery system (CDDS) has been developed by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal (GI) tract, but rapidly releases drug in the colon following oral administration CDDS is convenient for treating localized colonic diseases, i.e. ulcerative colitis, Crohn's disease and constipation *etc.*,CDDS, also selectively deliver drug to the colon, but not to the upper GI tract. Colon is referred to as the optimal absorption site for protein and polypeptide after oral administration, because of the existence of relatively low proteolytic enzyme activities and quite long transit time in the colon [1.2]. CDDS would be advantageous when a delay in absorption is desirable from a therapeutically point of view, as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms, such as nocturnal asthma, angina and rheumatoid arthritis. A large number of polysaccharides such as pectin, amylose, guar gum, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans, dextrin and locust bean gum have been investigated for their use in colon targeted drug delivery systems.[3] Tinidazole belongs to a group of drugs called proton pump inhibitors. It decreases the amount of acid produced in the stomach. Tinidazole is used to treat and prevent stomach and intestinal ulcers, erosiveesophagitis (damage to the esophagus from stomach acid), and other conditions involving excessive stomach acid such as Zollinger-Ellison syndrome

In Peptic ulcer patients, gastric distress occurs is most likely in the late night and early morning hours.

Ulcerative pain frquently occurs after stomach emptying, following daytime meals and in the very early morning, disrupting sleep. This is attributed to high gastric secretion and slows gastric motility and emptying at night. Suppression of nocturnal gastric acid secretion is an important factor in duodenal ulcer healing. Once daily nocturnal administration of proton pumps inhibitor medications not only reduce acid secretion more effectively but also promote ulcer healing and reduce ulcer occurrence. The rational of this study is to design and evaluate an oral site-specific colon drug delivery system containing Tinidazole, which can be targeted to colon in a pH and time dependent manner.

MATERIALS

Tinidazole was obtained as a gift sample from hetero labs and ethyl cellulose, microcrystalline cellulose, cross povidone, cross caramellose sodium, sodium starch glycollate, magnesium sterate, hydroxy propyl methyl cellulose were obtained from merck specialities pvt ltd,Mumbai, india used in the formulation of tablets.

Methodology

Formulation of core tablets by direct compression:

The inner core tablets were prepared by using direct compression method. As shown in Table 1 powder mixtures of Tinidazole, microcrystalline cellulose (MCC, Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol) ,SSG, cross povidone, ingredients were dry blended for 20 min. Followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 150mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with a 8mm round punch and die to obtain the core tablet.

Formulation of mixed blend for barrier layer:

The various formulations containing Ethyl cellulose and HPMC in different compositions were weighed dry blended at about 10 min and used as press-coating material to prepare press-coated tablets respectively by direct compression method.

Preparation of press-coated tablets:

The core tablets were press-coated with 400mg of mixed blend/granules as given in Table 3. 200mg of barrier layer material was weighed and transferred into a 12mm die then the core tablet was placed manually at the center. The remaining 200mg of the barrier layer materiel was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press.

Preparation of enteric coating solution:

Polymer solution was prepared with HPMC phthalate, myvacet and colour in ethanol as solvent.

FORMULATION OF TINIDAZOLE TABLETS (COLON TARGETING DRUG DELIVERY)

Table no 1 Formulation for core tablet:

S. No.	Ingredients	F 1	F 2	F 3	F 4	F 5	F 6	F7	F8	F9
1.	Tinidazole	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
2.	Micro crystalline cellulose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
3.	Cross povidone	3.6 mg	5.4 mg	9.0 mg						
4.	Cross caramellose sodium				3.6 mg	5.4 mg	9.0 mg			
5.	Sodium starch glycolate							3.6 mg	5.4 mg	9.0 mg
6.	Magnesium stearate	2mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
	Total wt	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg	150mg

Formulation for press coat: Table no 2

Press coat	P1F6	P2F6	P3F6	P4F6	P5F6
HPMC	400	100	300	200	0
E.C	0	300	100	200	400
Total wt	400mg	400mg	400mg	400mg	400mg
Enteric coated formula					
HPMC phthalate 55	17.17mg				
Myvacet	1.72mg				
Ferric oxide (red)	2.58mg				
Ethanol	q.s				

PREFORMULATION STUDIES

Preformulation studies are performed to investigate the physical and chemical properties of a drug substance alone and also when combined with other substances such as excipients. It is the first step in the rational development of dosage forms. The use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product and at same time provides the basis for optimization of the drug product quality.

PREPARATION OF STANDARD CALIBRATION CURVE OF TINIDAZOLE IN 0.1N HCL

Preparation of standard solution:

Standard stock solution of Tinidazole was prepared in 0.1N HCL. 100 mg of Tinidazole was accurately weighed into 100ml volumetric flask and dissolved in small quantity of buffer. The volume was made up with water to get a concentration of 1000µg/ml (SS-I).

From this 10 ml solution was withdrawn and diluted to 100ml of 0.1N HCL to get a concentration of 100µg/ml (SS-II).

Preparation of working standard solutions:

Further, from (SS-II) aliquots of 0.3ml, 0.6ml, 0.9ml, 1.2ml, 1.5ml and 1.8ml were pipetted into 10ml volumetric flasks. The volume was made up with 0.1N HCL to get the final concentrations of 3,6,9,12,15 and 18µg/ml respectively. The absorbance of each concentration was measured at 285nm.The data are compiled in Table and plotted a graph.

*λ Max :*285nm.

Beer's range: 3-18 µg /ml.

PREPARATION OF STANDARD CALIBRATION CURVE OF TINIDAZOLE IN pH6.8 PHOSPHATE BUFFER

Preparation of standard solution:

Standard stock solution of Tinidazole was prepared in Phosphate buffer pH6.8. 100 mg of Tinidazole was accurately weighed into 100ml volumetric flask and dissolved in small quantity of buffer. The volume was made up with water to get a concentration of 1000µg/ml (SS-I).

From this 10 ml solution was withdrawn and diluted to 100ml of phosphate buffer pH6**.8** to get a concentration of 100µg/ml (SS-II).

Preparation of working standard solutions:

Further, from (SS-II) aliquots of 0.3ml, 0.6ml, 0.9ml, 1.2ml, 1.5ml and 1.8ml were pipetted into 10ml volumetric flasks. The volume was made up with phosphate buffer pH6**.8** to get the final concentrations of 3,6,9,12,15 and 18µg/ml respectively. The absorbance of each concentration was measured at 285nm.The data are compiled in Table and plotted a graph.

*λ Max :*285nm.

Beer's range: 3-18 µg /ml.

Table No. 3: Acceptance Criteria of Flow Properties

S. No	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair	36-40	16-20	1.19-1.25
4.	Passable	41-45	21-25	1.26-1.34
5.	Poor	46-55	26-31	1.35-1.45
6.	Very poor	56-65	32-37	1.46-1.59
7.	Very very poor	> 66	>38	>1.6

Table no 4 Relationship between Angle of Repose (θ) and flow properties

Angle of Repose (θ) (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Drug – Excipient Compatibility Study [6]:

Drug is in intimate contact with one or more excipient in all the dosage forms. Later it could affect the stability of drug. Knowledge of drug excipient interaction is useful in selecting an appropriate excipient.

Procedure:

API and excipient are taken in the ratios above mentioned and mixed together in a polybag for 5 min. Each mixture is allotted sample code for identification. 4 sets of samples were allocated where each sample mixture is divided in to 1g in to its corresponding glass vial (USP Type I) at different conditions.

All vials are properly sealed and loaded at respective conditions. The samples are to be checked for its Description, Related substance and water content by KF.

RELEASE KINETICS [11]:

Mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (R) value in various models. The model with high 'R' value is considered as the best fit on the release data.

Zero order release:

The equation for zero order release is represented as

$Q_t = Q_o + K_o t$

Where, Q_t = amount of drug released in time (t)

Q_O = initial amount of drug in solution

K_O = zero order release constant

First order release:

The equation for the first order release is represented as

$\text{Log } C = \text{Log } C_0 - Kt / 2.303$

where, C = amount of drug remaining unreleased at time (t)

C_O = initial amount of drug in solution

K = first order rate constant

Higuchi's model:

The simplified Higuchi equation is represented as

Q_t = Kt ½

where, **Q_t** = amount of drug released in time **(t)**

K = Higuchi' constant

A linear relationship between amount of drug released (Q) versus square root of time ($t^{1/2}$) is observed if the drug release from the matrix is diffusion controlled.

Hixson-Crowell model:

The simplified Hixson-Crowell equation is represented as

$Q_o^{1/3} - Q_t^{1/3} = Kt$

where, **Q_t =** amount of drug released in time **(t)**

Q_O = initial amount of drug in solution

K = cube root constant

A graphic representation of cubic root of unreleased fraction of drug versus time will be linear if geometric shape of the formulation diminishes proportionally over time.

Korsmeyer- Peppas model:

The Korsmeyer-Peppas model relates drug release exponentially to time. It is represented as

Mt / Minf = Ktn

where, **Mt / Minf** = fractional release of drug

K = constant depending on structural and geometric characteristics of the drug dosage form

n = release exponent

The value of n indicates the drug release mechanism. For a slab the value n = 0.5 indicates Fickian diffusion and values of n between 0.5 and 1.0 indicate non-Fickian mechanism. In case of a cylinder n = 0.45 instead of 0.5, and 0.89 instead of 1.0. This model is used to analyze the release of drug from polymeric dosage forms, when the release mechanism is not understood or when there is a possibility of more than one type of release mechanisms are involved.

EVALUATION OF TABLETS:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the

diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters

1. Weight variation:

20 tablets were selected randomly from the batch and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in Table No. 4

Table 4 Weight Variation Specification as per IP

Average Weight of Tablets	%Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

Hardness:

Hardness is the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester and also Pfizer, strong cobb and erwika testers. It is expressed in kg/cm^2.

Thickness:

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

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

Disintegration test:

First step in the approach of drug absorption process disintegration is the important step where the drug

Disintegration time: Uncoated tablet: 5-30 minutes.

Coated tablet: 1-2 hours

***In-vitro* release studies [7,8]**

Tablet was introduced into the basket of the LABINDIA TS 8000 USP dissolution test apparatus and the apparatus was set in motion at 50 rpm for time period of 1 hr, 5 ml of sample was withdrawn for every 5min intervals and replaced by pH6.8 phosphate buffer solutions. Samples withdrawn were analyzed by UV spectrophotometer for presence of drug using buffer solution as blank.

Dissolution parameters:

Apparatus--USP-II, Paddle Method

Dissolution Medium --pH6.8 Phosphate buffer

RPM--50

Sampling intervals (min)--5, 10, 15, 20, 30, 45, 60min.

Temperature--37 ± 0.5°C

***In-vitro* Dissolution methods for Enteric press-coated tablets[8,9,11]:**

In –vitro Dissolution studies of colon targeted drug delivery systems was done with the conventional paddle method of press coated tablets were performed at 37 ± 0.5 °C using 0.1N HCL in USP II paddle method at 50 rpm for first two hours and replaced with pH6.8 phosphate buffer. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh buffer solution maintained at the same temperature. The samples were analyzed at 285nm using a UV spectrophotometer. The lag time and percentage release were determined of each formulation.

Dissolution parameters for enteric press coated tablets:

Apparatus--USP-II, Paddle Method

Dissolution Medium -- first 2 hours 0.1 N HCl

Next 6.8pH Phosphate buffer

RPM -- 50

Sampling intervals (hrs)--1, 2, 3, 4, 5, 6, 7 and 8

Temperature--37 ± 0.5°C

Table No 6 concentration and absorbances of Tinidazole in 0.1N HCL

S.No	Concentration	Absorbance
1	0	0
2	3	0.0729
3	6	0.1559
4	9	0.2339
5	12	0.3118
6	15	0.3798
7	18	0.4682

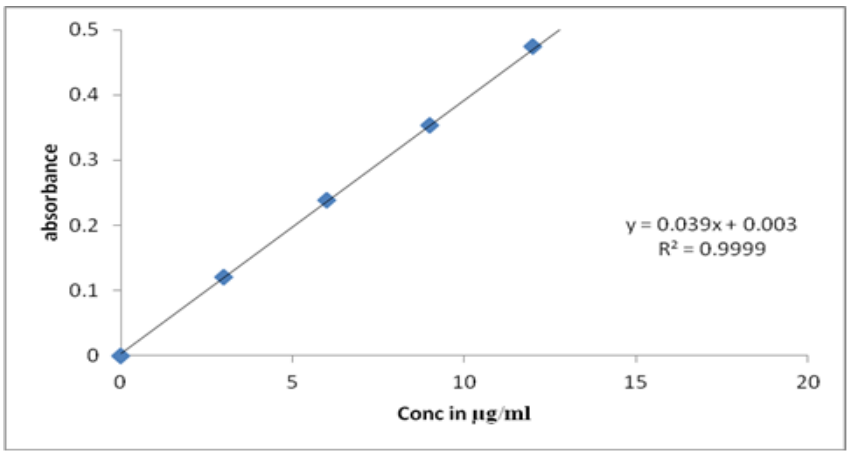

Fig No 1- calibration curve of Tinidazole

Table No 7 concentration and absorbances of Tinidazole in 6.8 pH Phosphate buffer

S.No	Concentration	Absorbance
1	0	0
2	3	0.121
3	6	0.238
4	9	0.354
5	12	0.475
6	15	0.586
7	18	0.702

DRUG EXCIPIENT COMPATIBILITY STUDIES

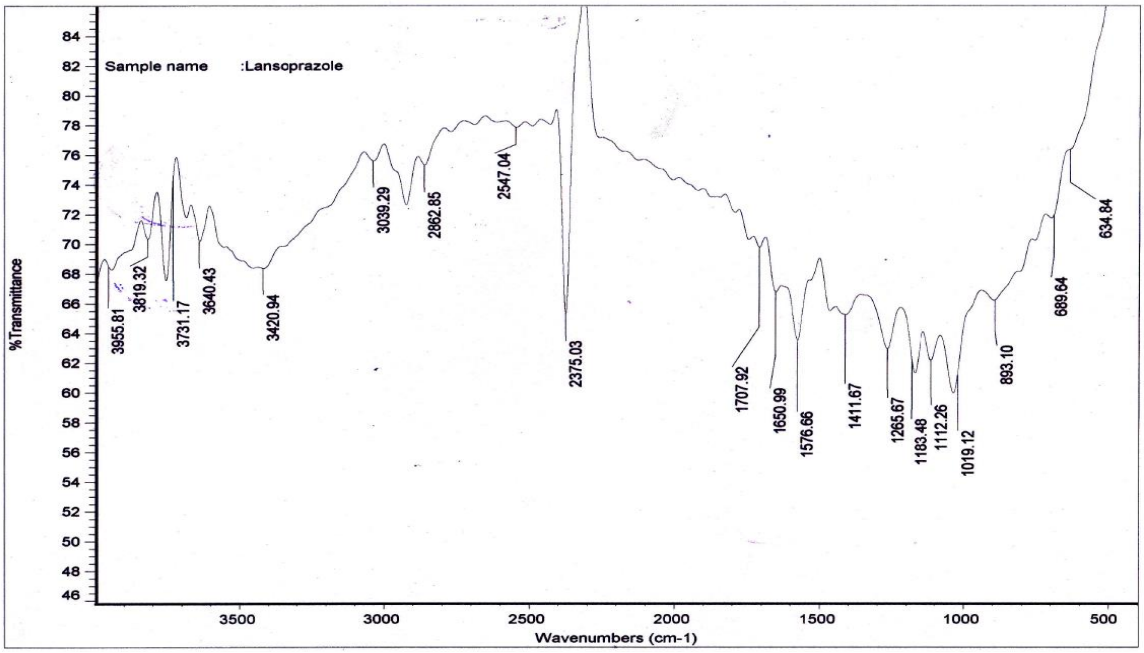

Fig No 2: FTIR Spectra of Tinidazole

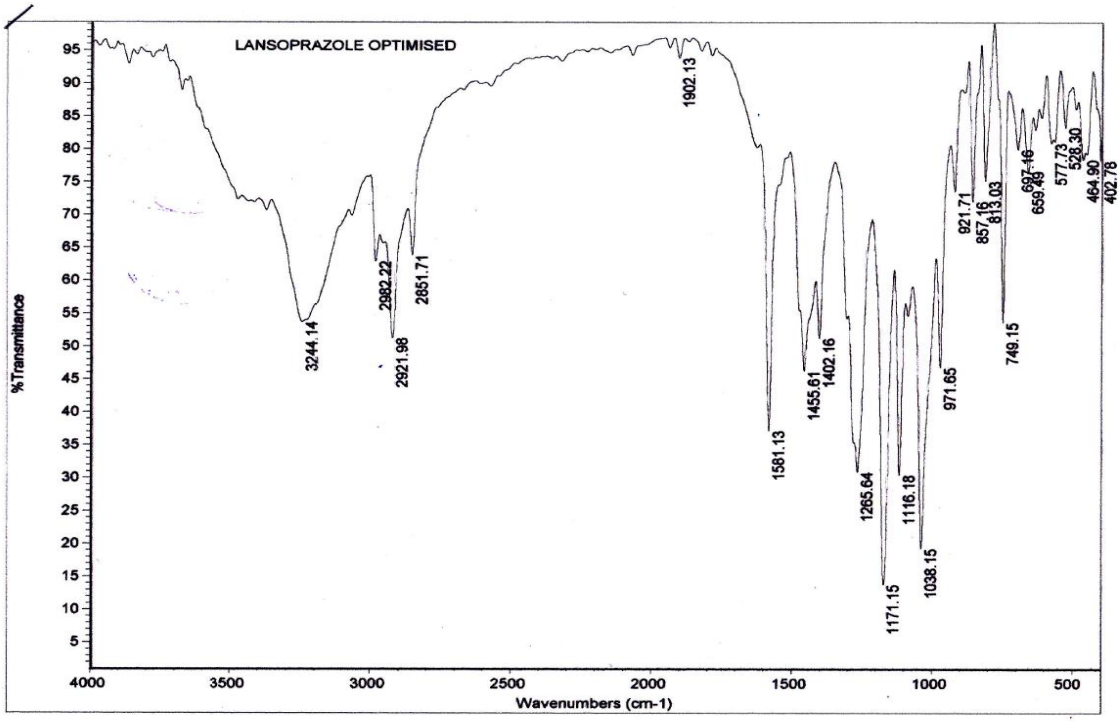

Fig No 3: FTIR Spectra of Tinidazole optimized formulation

PRE-COMPRESSION PARAMETERS

Table No 8 precompression parameters

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner's ratio
F1	21^0 55'	0.510	0.583	12.52	1.14
F2	22^0 43'	0.416	0.482	13.69	1.15
F3	25^0 02'	0.423	0.495	14.54	1.17
F4	24^0 18'	0.309	0.353	12.46	1.14
F5	26^0 89'	0.306	0.355	13.80	1.16
F6	22^0 57'	0.322	0.376	14.36	1.16
F7	25^0 98'	0.404	0.472	14.40	1.16
F8	26^0 42'	0.511	0.576	11.28	1.12
F9	24^0 62'	0.506	0.577	12.30	1.14
F10	27^0 08'	0.422	0.493	14.37	1.16

From the above pre-compression parameters, it was clear evidence that drug and excipients have good flow properties and suitable for direct compression.

POST COMPRESSION PARAMETERS

Tooling:

8mm round shape for core tablet

12mm round shape tooling for press coat.

Evaluation of rapid release core (RRCT) and press-coated tablets of Tinidazole

Tablet compression parameters:

Weight of the tablet: 200 mg (core tablet)

600mg (press coated tablet)

Hardness range:5.5Kg/cm^2 (core tablet)

7.0 Kg/cm^2 (press coat tablet)

Thickness range: 2.5 ± 0.3 mm (core tablet)

3.5± 0.3mm (press coat tablet)

Table 9 Evaluation for rapid release core

S. No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F10
1	Avg Weight (mg)	151	150	148	149	152	150	150	149	148	149
2	Hardness (Kg/cm^2)	5.1	5.3	5.6	5.1	5.2	5.3	5.4	5.7	5.8	5.4
3	Thickness (mm)	3.51	3.48	3.51	3.5	3.5	3.47	3.49	3.52	3.61	3.55
4	Friability %	0.33	0.46	0.41	0.50	0.54	0.45	0.35	0.39	0.37	0.45
5	Disintegration time	3min42sec	3min52sec	3min4sec	3min21sec	2min 16sec	2min 08sec	4min 34sec	3min 48sec	3min26sec	3min25sec

***In vitro* dissolution studies for core and press coated tablets: -**

In vitro dissolution for core tablets were done in 6.8 phosphate buffer and enteric press coated tablets were initially placed in acidic stage and next was changed with phosphate buffer.

Core tablets:

Table No 10 Dissolution for core tablet

Dissolution time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	14.4	16.2	16.1	10.4	12.1	19.1	15.0	16.4	20.4
10	22.4	30.5	10.8	18.4	22.1	35.4	24.1	28.9	27.8
20	37.3	40.1	46.8	35.4	51.7	65.4	45.6	48.6	33.5
30	52.4	73.9	73.4	60.4	66.3	76.1	66.6	61.4	41.6
45	76.0	79.4	80.3	72.6	75.4	82.0	75.4	72.4	60.4
60	80.1	82.2	85.4	81.5	88.7	97.6	80.4	79.6	77.6

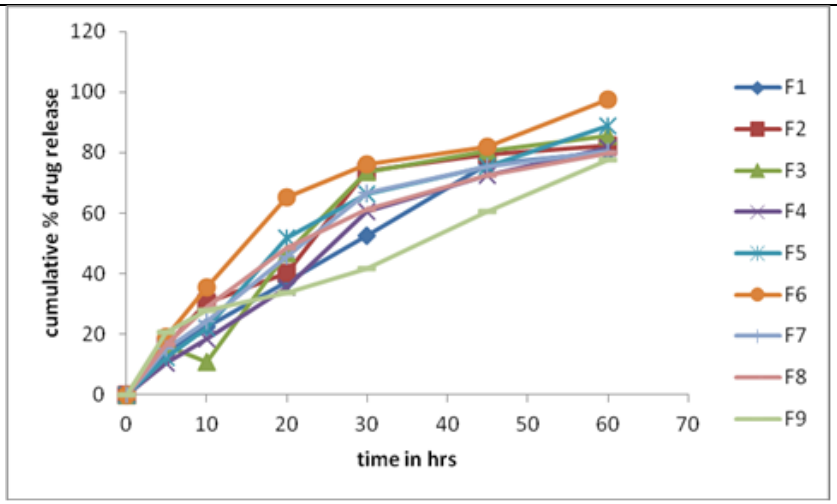

Figure No 4 Dissolution graph for formulations F1-F9

Table No 11: Evaluation for Press coated tablets

S. No	Physical parameter	P1F6	P2F6	P3F6	P4F6	P5F6
1	Avg Weight (mg)	551	550	549	549	550
2	Hardness (Kg/cm^2)	7.4	7.0	7.7	7.4	7.5
3	Thickness (mm)	2.45	2.49	2.5	2.51	2.5
4	Friability %	0.5	0.45	0.46	0.36	0.24

Table No 12 Dissolution for Enteric press coat

Time in hrs	P1F6	P2F6	P3 F6	P4 F6	P5 F6
				0.1N HCL	
1	0	0	0	0	0
2	0	0	0	0	0
	6.8 pH Phosphate buffer				
3	8	19	6	4	7
4	15	30	8.9	16	18
5	19	54	15.3	29	25
6	22	79	20.5	42	33
7	39	81	48.9	72	40
8	79	94	98.4	92	75

GRAPH FOR ENTERIC PRESS COAT FORMULATION

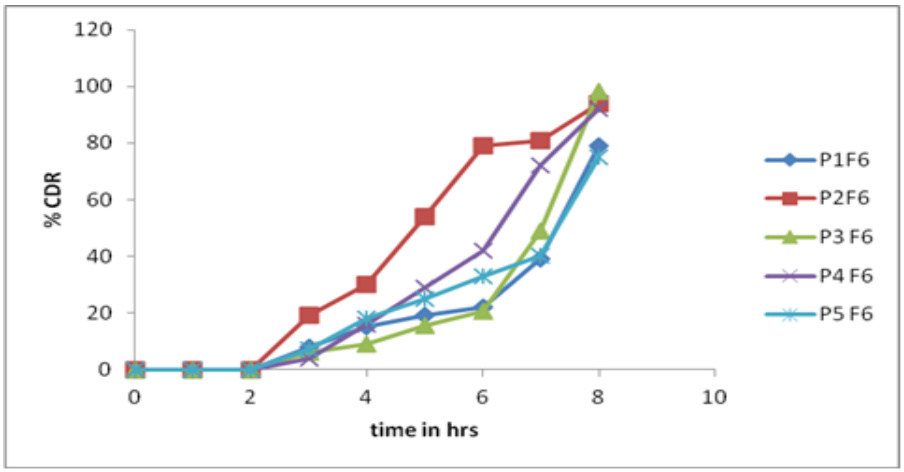

Figure No 5- Graph showing % CDR verses time in hrs for formulations P1F6 to P5F6

Kinetics of *In Vitro* Drug Release:

The dosage forms most commonly release the drug either in the zero order or in the first order pattern. Controlled release dosage forms of Tinidazole were prepared and studied for their dissolution behavior. *In vitro* release data of time points between 1 to 24 hours were considered and treated for kinetic principles.

The regression values of release kinetics of optimized formulation were shown in the table no. 13.

Table no.13: Regression values of release kinetics

	0.1 N HCl	4.5 Acetate buffer	6.8 phosphate buffer
Zero order	0.9263	0.921	0.8475
First order	0.8792	0.8957	0.7986
Higuchi	0.9922	0.9928	0.965
Korsmeyer-Peppas	0.9873	0.9809	0.9588
Hixson-Crowell	0.9461	0.9814	0.9058

The regression values of zero order are higher than the regression values of first order indicating that the release of drug is independent of the concentration. When the regression values of Higuchi, Korsmeyer-Peppas, and Hixson-Crowell were considered, the regression values were higher for Higuchi in all three mediums. It indicated that the drug was released through diffusion mechanism from the dosage form.

CONCLUSION

Suitable analytical method based on UV-Visible spectrophotometer was developed for Tinidazole λ_{max} of 285 nm was identified in 0.1N HCl solution,4.5 acetate buffer solution and 6.8 phosphate buffer solution. FT-IR spectra interference was verified and found that Tinidazole did not interfere with the excipients used.

Press coated tablets of Tinidazole (F-I- F-IX) were successfully prepared using enteric coated polymers ethyl cellulose and HPMC pthallate by first preparing the core tablets and then press coated with polymers. The tablets were evaluated for physical properties and *in-vitro* dissolution studies. Based on the results, F-6 was identified as better formulation amongst all formulations.

In vitro release profiles of optimized formulation of Tinidazole colon specific release tablets (F-6) were found to be improvised to that of reference drug release profile i.e., 100 % drug release was achieved. The manufacturing procedure was standardized and found to be reproducible.

Tinidazole release from the tablets of F-6 formulation followed zero - order kinetics, hence the release of the drug from the dosage form was independent of concentration and followed Higuchi model, and hence release of drug from matrix was by diffusion mechanism.

By this we can conclude that the colon specific drug release formulation of Tinidazole developed is the promising system for the treatment of stomach and intestinal ulcers.

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