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"Formulation and Evaluation of Tinidazole Raft Forming Tablet for Gastro-Retentive Drug Delivery System"

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ABSTRACT:
The present research work aim was to formulate and evaluate Tinidazole raft forming tablet Prepared by direct compression method. Tinidazole is a BCS II drug with poor solubility and high permeability causing poor systemic absorption and narrow absorption window. Tinidazole raft forming tablet prepared by using Sodium alginate which is gel forming agent and HPMC K4M are used in different concentrations.
The prepared raft forming tablets were evaluated for various parameters like thickness, weight variation, hardness, friability and drug content uniformity. FTIR and DCS studies reveal that there are no interactions means drugs and excipients are compatible with each other. Compared to all formulations F6 showed the best Raft weight determination as well as buoyancy lag time.
The formulation containing Sodium alginate and HPMC K4M with higher amount shows the higher Raft formation as compared to other batches. The raft weight was measured and found to increase with increase in sodium alginate concentration. Formulation F6 gave better controlled drug release and floating properties in comparison to the other formulations.

KEYWORDS: Tinidazole, GRDDS, Raft forming mechanism, Controlled release, Floating lag time

I. INTRODUCTION:

Gastro-retentive drug delivery system [GRDDS]:

Oral administration is the most convenient route for any drug delivery to the systemic circulation with high patient compliance and flexibility in formulation [1,2]. Gastro retentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs[3].

Controlling the gastric residence time (GRT) with gastro retentive drug delivery (GRDDS), which provide a new and better choice for drug therapy, is one of the most effective methods for developing a sustained and stable drug delivery profile in the GIT[4]. By continuously releasing the drug for a long time before it reaches the absorption site, GRDDS can enhance the controlled delivery of drugs with an absorption window and ensure their efficient bioavailability[5].

Raft forming system: [6]

The highest point of digestive juices forms a layer as a result of raft formation process. Here, upon contact with stomach fluid, a gel-forming solution (such as sodium alginate or bicarbonates) swells and forms a sticky gel containing entangled CO_2. The process involved in raft development includes the growth of a thick, solid gel when it comes into touch with stomach juices. Each area of the gel swells to form a persistent layer known as a raft. Due to the low mass thickness created by CO_2 development, this raft floats on gastric liquids. Alginate gels are used in raft forming systems

A raft-forming concept use for treatment of Helicobacter pylori (H. pylori) disorders in the GI system. For formation of raft, the dosage form must contain gelling agents, swelling agents, bicarbonates and must have low density i.e, <1 gm/cm^3. These agents when in contact with gastric fluid, swells forming a viscous cohesive gel. Swelling and gel forming agents mostly include sodium alginate, alginates, pectins, etc. Bicarbonates most commonly used are sodium bicarbonate, potassium bicarbonates, calcium carbonates, etc.[7] The drug will release from the raft in controlled and continuous manner just prior to absorption window where the absorption of drug will occur at site of absorption. Thus this system is suitable for obtaining a controlled drug delivery system.

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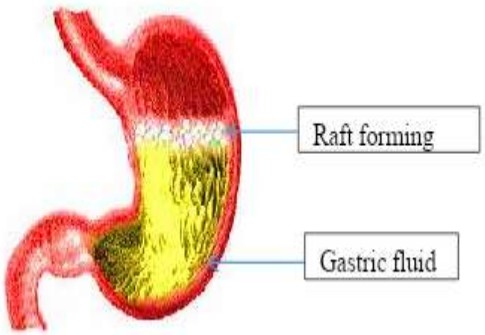

Fig No.1: Schematic illustration of barrier formed by raft forming system

Tinidazole, a derivative of 2-methylimidazole, is chemically identified as 1-[2-(ethyl sulphonyl) ethyl]-2-methyl-5-nitroimidazole and serves as a systemic anti-protozoal agent.[8] It is extensively utilized for treating trichomoniasis and giardiasis, and is also prescribed for pediatric patients over three years old to treat intestinal amebiasis and amebic liver abscess caused by Entamoeba histolytica. Classified as a class II drug, tinidazole has low aqueous solubility, which poses a significant barrier to systemic drug absorption.[9]

II. MATERIALS AND METHODS

Materials: Tinidazole was obtained as gift sample from Orbiton pharma, Surat. HPMC K4M, Sodium alginate and Microcrystalline cellulose was procured from powder pack chem laboratory. Tartaric acid procured from Acme chemicals, Mumbai. Sodium bicarbonate was procured from Suvchem Laboratory Chemicals. Talc and magnesium stearate was procured from Loba Chemie Pvt. Ltd., Mumbai. All chemicals were of analytical grade.

Tabel No.1: The composition of all formulations

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tinidazole	300	300	300	300	300	300	300	300	300
HPMC K4M	25	75	25	25	25	125	75	75	125
Sodium alginate	50	12.5	50	12.5	31.2	50	12.5	31.2	31.2
Tartaric acid	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Sodium bicarbonate	75	75	75	75	75	75	75	75	75
Microcrystalline cellulose	130	117	30	167	149	80	67	99	49
Total	600	600	600	600	600	600	600	600	600

Methods: Formulation of Tinidazole Raft Forming Tablet by Direct Compression Method. In direct compression method the raw materials size reduced and the required excipients are added and directly compressed.

1. All material were accurately weighed and passed through 60 mesh sieve accordingly and (Talc and magnesium stearate were added last).

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2. Mixing and transferred to glass mortar and triturated until mixed uniformly.
3. The mixture was then compressed by direct compression using Karnavati Machinery punching machine.

PREFORMULATION PARAMETER

1. Organoleptic Properties: [10]

Description of the drug is the first line indication for purity for its identification. 1.0 gm. of Tinidazole was weighed and transferred into a clean, dry petri dish and physical appearance, color ,odor, taste were observed carefully .

2. Melting point determination:

Melting point of Tinidazole was carried out by capillary method using digital melting point apparatus.

3. Solubility

Tinidazole is soluble in ethanol, DMSO, and dimethyl formamide (DMF), among other organic solvents. The solubility of Tinidazole in these solvents is approximately 0.2, 10, and 20 mg/ml, respectively.

4. Analysis of API by UV Visible spectrophotometer [11]

100 mg of Tinidazole was accurately weighed and transferred into 100 ml ethanol in volumetric flask (to get 1000 µg/ml). In volumetric flask from above stock solution 10 ml was pipette out and diluted up to 100 ml with ethanol (to get 100 µg/ml solution). Then from above stock solution 1 ml was pipette out and diluted upto 10 ml with ethanol (to get 10 µg/ml solution). From IInd stock solution 0.2, 0.4, 0.6, 0.8 and 1.0 ml were transferred into 10 ml volumetric flask and diluted with ethanol up to the mark to obtain Tinidazole concentration of 2, 4, 6, 8 and 10 µg/ml respectively.The prepared solution i.e. 10 µg/ml concentration was scanned for λmax from 200-400 nm in UV visible spectrophotometer.

5. FTIR Analysis [12]

The infrared spectra of pure drugs and all formulations were recorded by using a Fourier transform infrared spectrophotometer (Schimadzu FTIR). A base line correction was made using dried potassium bromide and then the spectrum of the pure drug. Weighed amount of drug (3 mg) was mixed with 100 mg of potassium bromide (dried at 40 - 50 ^{o} C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The mixture was compressed into transparent disks in a moisture free atmosphere and IR spectra were obtained. The scanning range was selected between 4000 and 400 cm^{1}.

6. DSC Analysis

DSC measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. The sample was hermetically sealed in an aluminium and heated with continuous purge of argon and compared with the reference sample. Thermal behavior of the samples was investigated and scanned from 10 to 200 ^{o}C at rate of 10 ^{o}C/min.

PRECOMPRESSION PARAMETER [13, 14]

Precompression involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance and is characterized with the goal of designing optimum drug delivery system. Precompression parameters of powder were bulk density, tapped density, carr's index, hausner's ratio, angle of repose determined for each formulation.

CHARACTERIZATION OF RAFT FORMING TABLET

1. Thickness and diameter: [15]

For the determination of diameter and thickness, vernier caliper was used. The dimensions were calculated in millimeters.

2. Hardness: [16]

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^{2}. 5 tablets were chosen randomly and tested for hardness.

3. Weight variation: [17]

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. According to Indian Pharmacopoeia, 20 tablets were selected at random, weighed together and then individually, to calculate the average weight. The mean and standard deviation were determined.

4. Friability test: [18]

Twenty tablets were initially weighed (W1) and transferred into the Friabilator. The Friabilator was operated at 25 rpm for 4 minutes in which tablets are subjected to combined effect of

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shock and abrasion in a plastic chamber dropping the tablets at a height of 6 inch in each revolution. The tablets were de dusted and weighed again (W2).

% friability = (W1 - W2 / W1) × 100

Where, W1= weight of tablets before test

W2 = weight of tablets after test

5. Drug content uniformity: [19]

Tablets from formulation was taken and dropped in 100ml 0.1N HCl in a beaker. After 24 hrs. or when the drug is released completely the same sample was withdrawn (about 1ml) and diluted to 10ml with 0.1N HCL and absorbance was taken at 278 nm using UV spectrometer. From the standard graph % drug release was calculated.

6. Floating lag time: [20]

The floating lag time the tablet constantly floats on the dissolution medium (i.e. duration of floating) in the dissolution medium. The tablets were placed in a 100 ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time.

7. Raft weight determination:

Raft forming tablet was placed inside a pre-weighed (W_1) glass beaker containing 150 ml HCL buffer. The beaker was kept undisturbed for 30 min. for completion of raft formation. When the raft formation was completed, after raft development, the total weight of the beaker was measured again (W_2).

Raft volume = (W_2-W_1)

Where, W1= weight of glass beaker before test

W2 = weight of glass beaker after test

8. In-Vitro Dissolution test: [21]

Using a USP type II paddle type dissolution apparatus, the drug release for different batches of the produced Tinidazole raft forming tablets was studied. The method of dissolving 900 ml of 0.1 N HCl buffer were used. The temperature was maintained at 37°C ± 0.5°C with continuous stirring at a rate of 50 rpm. To maintain the sink condition, a sample of 5 mL volume was withdrawn at pre-determined time intervals of 10, 20, 30, 45, 60 and 75 min and replaced with the same volume of fresh medium maintained at 37±0.5ºC so as to maintain constant volume. Samples were filtered through 0.45 µm Millipore membrane filter and analyzed by UV-Visible spectrophotometer.

9. Stability studies: [22]

The selected formulations were subjected for three month stability study as per ICH guidelines. The selected formulations were placed in a wide mouth glass bottles, mouth of the bottle was tightly closed and packed in aluminum foils. In the present study, stability studies were carried out at 25ºC/60% and 40ºC/75% RH for a specific period of 3 months for the selected formulations.

III. RESULTS AND DISCUSSION:

PREFORMULATION STUDTY:

1. Organoleptic Properties:

Table No. 2: Organoleptic characteristics of API

Sr. No.	Organoleptic Analysis	Result
1	Color /Appearance	Light yellow
2	Odor	Characteristic
3	Taste	Bitter

2. Melting point determination:

The melting point was carried out by using capillary tube method. Melting point of Tinidazole was found to be in the range of 125^{o} C.

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Table No. 3: Determination of melting point of Tinidazole

Sr. No.	Tinidazole Melting Point	
	Observed value	Standard value
1.	125 ^{o}C	126-128 ^{o}C

3. Solubility:

Studies of different commonly used solvents i.e. water, 0.1 N HCL (pH1.2) , pH 7.4 Phosphate buffer, methanol ,ethanol, dimethyl formamide were used to carry out solubility studies of Tinidazole. Saturated solutions of Tinidazole were prepared by adding excess drug to vehicles and shaking on shaker for specific period of time under constant vibration.

Table No. 4: Solubility of Tinidazole

Sr. No.	Solvents	Interpretation
1.	Water	Insoluble
2.	0.1 N HCL	Soluble
3.	pH 7.4 Phosphate buffer	Sparingly Soluble
4.	Ethanol	Freely Soluble
5.	Methanol	Freely soluble
6.	Dimethyl formamide (DMF)	Soluble

4. UV Visible Spectrophotometer analysis:

- **Determination of λ max (maximum wavelength):**

The weight amount of Tinidazole drug was dissolved in ethanol in a 100 ml volumetric flask to frame a stock arrangement of 100 µg/ml. The stock arrangement was then pipetted into a 10 ml volumetric flask, and the volume was raised of 10 µg/ml.

The subsequent solution was then examined in the range of 200 and 400 nm with an UV- spectrophotometer (Shimadzu UV 1900 i). The UV range was recorded and the most elevated worth acquired with the authority monograph's UV range. Determination of wavelength (λ max) of Tinidazole was obtained by scanning the ethanolic stock solution. The maximum absorbance has occurred at 278 nm which is near to standard.

Table No. 5: Maximum wavelength (λ max) of Tinidazole

Drug	λ max	
	Actual λ max	Observed λ max

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Tinidazole	280 nm	278 nm

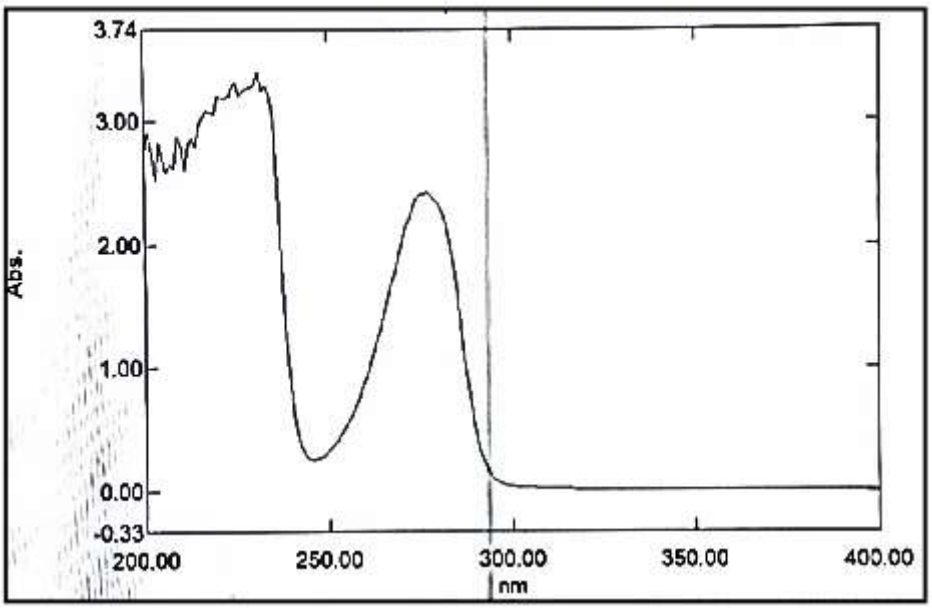

Fig No. 2: UV Spectrum of Tinidazole

- **Plot of calibration curve:**

Calibration curve of Tinidazole in ethanol by UV spectrophotometer was found at 278 nm. The absorbance obtained was tabulated in below and graph was obtained by plotting absorbance Vs concentration.

Table No. 6: Absorbance of Tinidazole in Ethanolic stock solution

Concentration (ug/ml)	Absorbance
0	0
2	0.121
4	0.221
6	0.345
8	0.450
10	0.556

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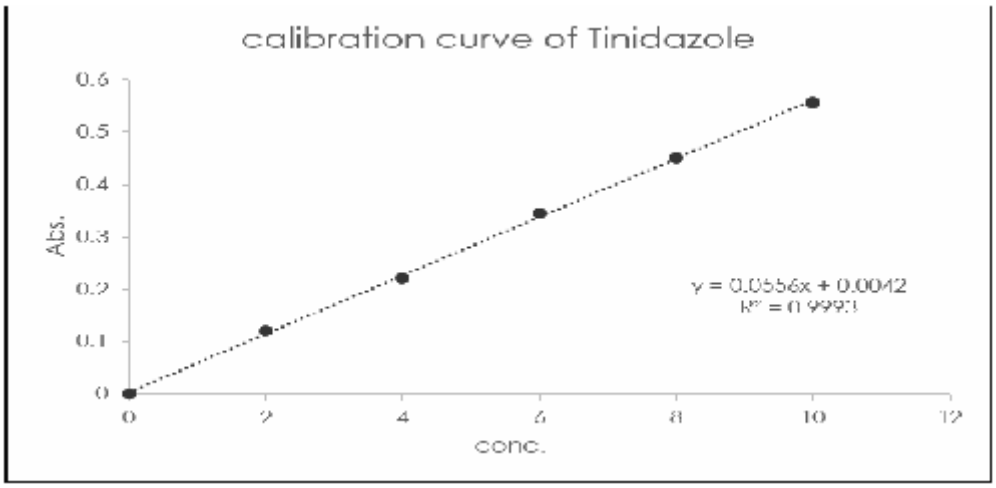

Fig No. 3: Calibration curve of Tinidazole in Ethanolic stock solution

5. Drug study by FTIR Spectroscopy:

The drug was identified by the FTIR spectrum of the sample which shows characteristic absorption of the various functional group of Tinidazole. Potassium bromide IR disc was prepared using 1mg of Tinidazole on Hydraulic Pellet press which was scanned of 4000- 400 cm^{-1} re in FTIR and obtained IR Spectrum was compare with reference spectrum of Tinidazole. Ths spectrum of tinidazole were found to be drug is pure.

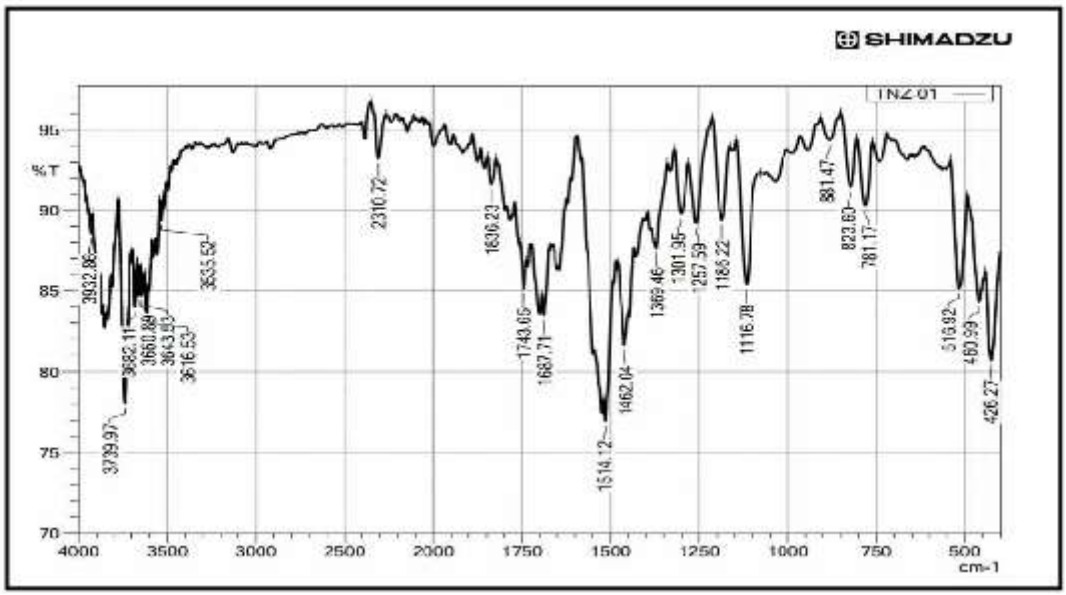

Fig No. 4: FTIR of Tinidazole drug

- **Drug Excipients Compatibility Studies by FTIR spectroscopy:**

The IR spectrum indicates that there was no interaction between drugs and studied excipients. Results of the drug interaction studies suggest that all the studied excipients are compatible with tinidazole. All the characteristic peaks of tinidazole were present in the spectrum of drug and polymer mixture, indicating compatibility between drug and polymer. The spectrum confirmed that there is no significant change in the chemical integrity of the drug.

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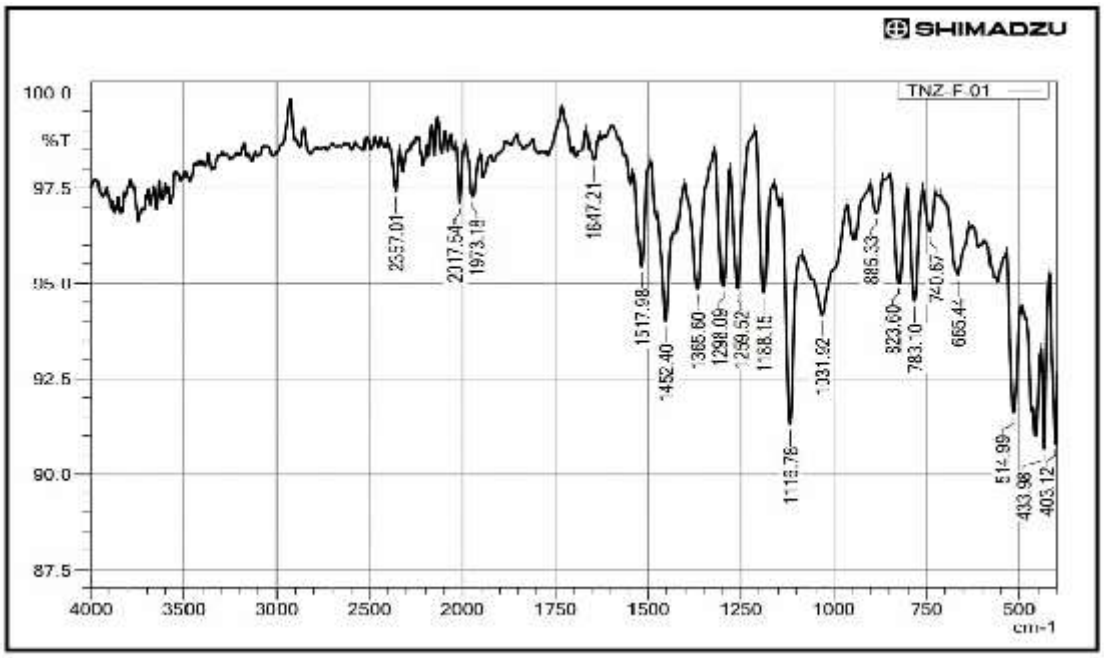

Fig No. 5: FTIR of Tinidazole with Physical mixture

6. DSC Analysis:

DSC studies of each drug were carried out using DSC. The DSC thermo gram of the drug showed a sharp endothermic peak at 124.42 ^{o}C, corresponding to the melting point of the drug.

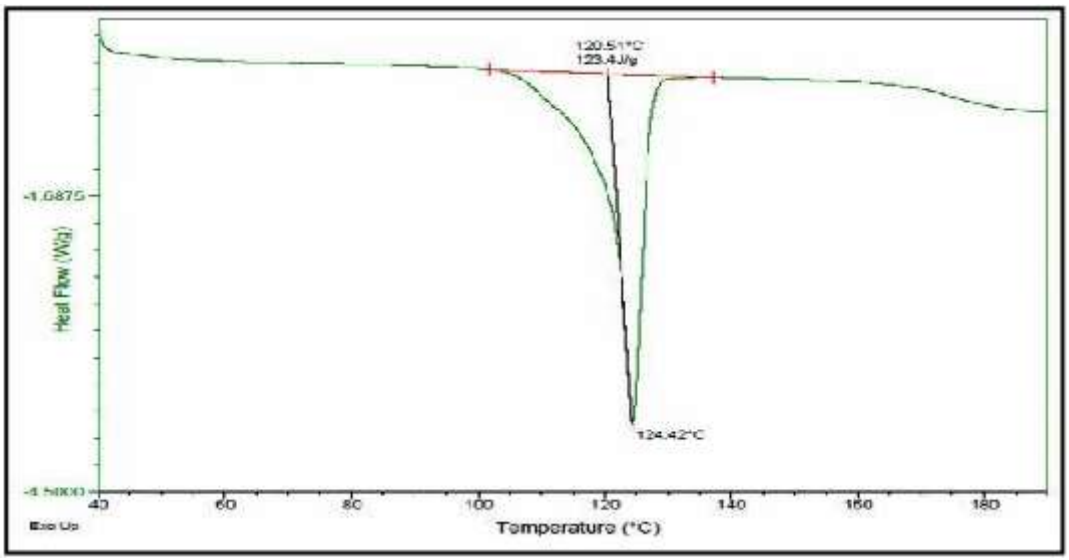

Fig No. 6: Thermal Spectra of Tinidazole

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PRECOMPRESSION EVALUATION:

Table No. 7: Pre-compression parameters for Tinidazole raft forming tablets

Batch code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose
F1	0.29±0.01	0.33±0.04	12.65±0.03	1.13±0.02	36.38±0.02
F2	0.29±0.03	0.32±0.03	13.89±0.02	1.10±0.03	33.98±0.03
F3	0.35±0.02	0.39±0.02	12.34±0.04	1.20±0.03	37.99±0.02
F4	0.42±0.01	0.40±0.01	14.56±0.01	1.23±0.01	31.76±0.04
F5	0.35±0.04	0.35±0.03	13.54±0.01	1.15±0.02	38.54±0.03
F6	0.28±0.02	0.38±0.03	15.67±0.03	1.16±0.01	39.55±0.01
F7	0.34±0.02	0.41±0.02	12.44±0.02	1.24±0.03	32.79±0.01
F8	0.30±0.01	0.34±0.01	15.12±0.04	1.07±0.03	33.87±0.0
F9	0.37±0.03	0.36±0.04	12.34±0.02	1.14±0.01	34.56±0.03

CHARACTERIZATION OF RAFT FORMING TABLET:

1. Pysicochemical Evaluation

The physicochemical evaluation of tablet include the tablet thickness, tablet hardness, weight variation and percentage friability. It was carried out tablet thickness found to be 2.8±0.03 to 3.3±0.03 mm. Hardness of tablet formulations (F1-F9) was found to be in the range of 4.5 ± 0.2 kg / cm^2 to 5.2 ± 0.04 kg/cm^2. Weight variation of tablet formulation was found to be in 595.65 mg ± 605.50 mg which is in acceptable limit. The friability result for formulations (F1-F9) was found to be in the range of 0.25 ± 0.01 to 0.51 ± 0.02.

Table No. 8: Evaluation parameters for Tinidazole raft forming tablets

Batch	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)
F1	3.0±0.01	595.65±0.22	4.5±0.2	0.25±0.01
F2	2.9±0.05	599.75±1.22	5.0±0.1	0.30±0.06
F3	3.1±0.02	600.67±4.89	4.5±0.12	0.45±0.44
F4	3.2±0.02	601.23±2.06	5.0±0.16	0.55±0.82
F5	3.0±0.04	599.98±0.78	5.5±0.09	0.21±0.03

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F6	3.2±0.01	598.09±5.99	5.2±0.65	0.34±0.09
F7	2.8±0.03	601.23±1.22	5.1±0.74	0.42±0.44
F8	3.3±0.03	600.65±3.03	5.0±0.23	0.36±0.65
F9	3.2±0.02	605.50±0.66	5.2±0.04	0.51±0.02

2. Drug content:

The average drug content for each formulation was calculated from the absorbance values. The drug content for the prepared raft forming tablets were found within the range of 96.24 ± 0.51 to 99.63 ± 0.65. The results are shown in the table.

Table No. 9: Drug content

Batch	Drug content (%)
F1	98.78±0.57
F2	97.08±0.39
F3	95.46±0.11
F4	98.81±0.68
F5	96.24±0.51
F6	99.63±0.65
F7	98.5±0.12
F8	97.5±0.59
F9	98.3±0.13

3. **Floating lag time**

Floating lag time for all the formulations was determined in 0.1N HCl buffer, and the values were within the range from 40 ± 4 to 60 ± 5 s. The results are clearly indicating that floating time increases by increasing polymer concentration.

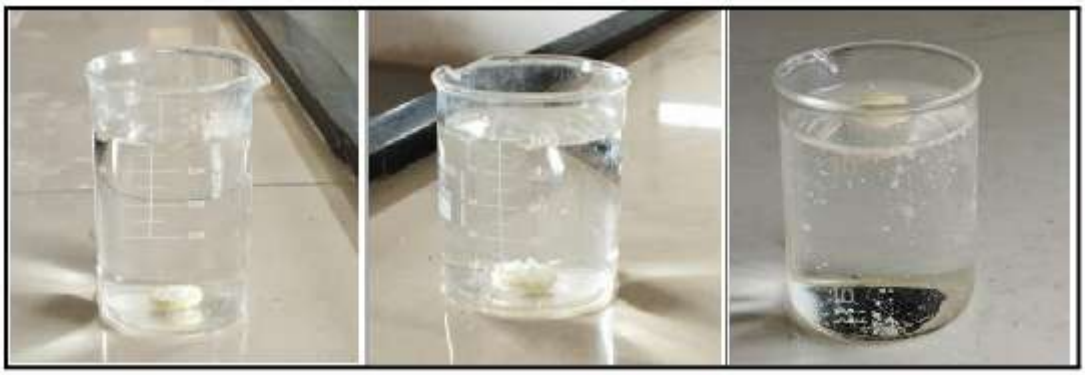

Fig No. 7: Floating behavior of Tinidazole tablet

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Table No. 10: Floating lag time

Batch	Floating lag time (sec)
F1	52±02
F2	45±01
F3	49±09
F4	40±06
F5	45±05
F6	60±02
F7	43±07
F8	48±08
F9	51±04

4. Raft weight determination:

Raft weight was measured after completion of raft formation for each formulation and was found in the range of 5.57 ± 1.87 to 7.88 ± 1.95 gm. Batch F4 was found to have lowest raft weight among all the formulation and whereas F6 batch resulted in maximum raft weight.

Fig No. 8: Raft formation of Tinidazole floating table

Table No. 11: Raft weight determination

Batch	Raft weight (gm)
F1	7.21±1.07
F2	5.73±1.04
F3	6.62±1.08

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F4	5.57±1.07
F5	5.88±1.05
F6	7.88±1.05
F7	6.57±1.07
F8	5.62±1.08
F9	5.73±1.04

5. In-vitro dissolution study:

In vitro dissolution of Tinidazole, raft forming tablets were carried out in 0.1 N HCl buffer solution under sink condition up to 8h. The result which are got in vitro drug release for F1 to F9. The formulation formulated by direct compression technique was obtained in the range of 77.66 ± 2.30 to 94.32 ± 1.79 %. Here in all batch of F1 to F9 the dissolution rate was found to be increase linearly with increasing sodium alginate concentration. The batch F6 showed 94.32 ± 1.79 % drug release respectively. This was highest drug release compared to all formulations. By the dissolution data of formulation F1 to F9 it was concluded that the formulation of F6 prepared with Sodium alginate (10%) and HPMC K4M (15%) was showed the highest drug release. The values are shown in the table.

Table No. 12: In-vitro drug release for all formulations of Tinidazole raft forming tablets

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	28.51	35.14	23.31	33.25	29.04	31.83	24.78	32.47	34.61
2	34.56	49.23	34.87	42.98	33.87	48.09	35.56	43.23	40.55
3	40.44	63.07	46.14	55.75	41.14	62.01	45.73	56.06	50.36
4	48.23	72.98	56.98	65.56	49.22	71.54	54.87	64.23	69.97
5	65.51	85.25	62.38	79.18	68.16	86.38	63.16	77.81	68.95
6	78.23	89.08	73.99	84.99	75.31	87.43	72.93	85.52	72.98
7	81.19	92.86	81.95	85.95	83.84	91.96	84.02	87.75	80.77
8	89.35	93.87	95.44	92.56	96.31	98.45	92.01	94.06	94.78

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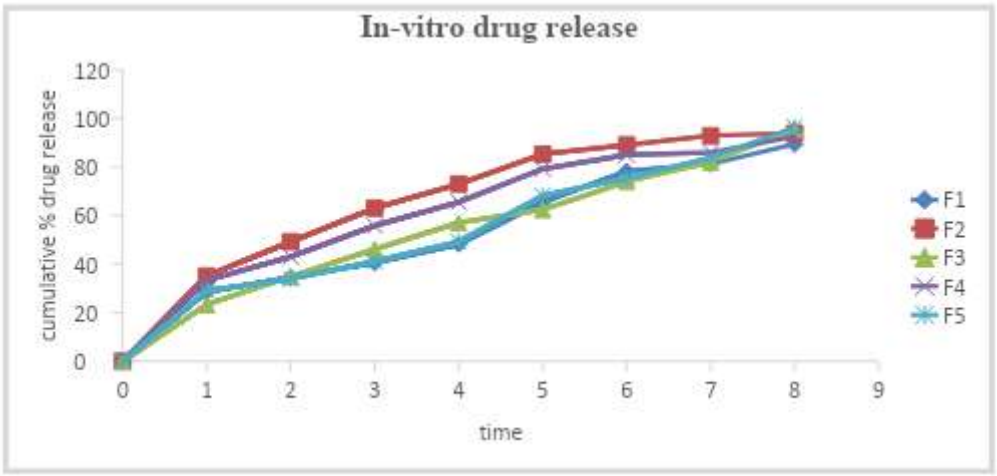

Fig No. 9: In-vitro drug release of F1-F5

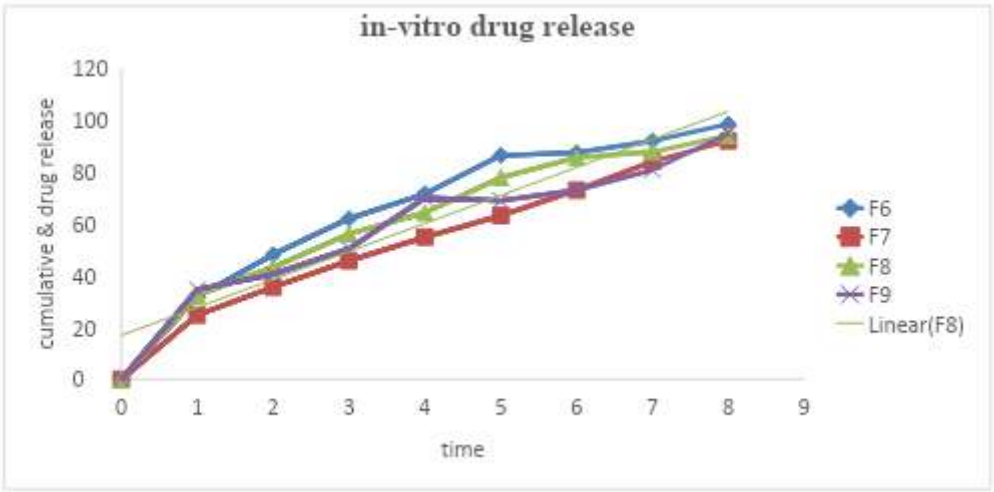

Fig No. 10: In-vitro drug release of F6-F9

6. Stability studies:

The batch F6 has shown best results among the all formulations hence, it has selected forS stability study. The optimized sustained release formulation was subjected to stability studies at 40 ^{o}C ±2 ^{o}C / 75% RH ± 5% for 3 months.

The product was evaluated for following parameters:

- Weight variation
- Hardness
- Friability
- Drug content
- Dissolution analysis

Storage condition - at 40°C±2°C/75%RH±5%

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Table No. 13: Stability data

Test	30 days	60 days	90 days
Weight variation(mg)	599 ± 0.55	598 ± 0.65	599 ±0 .41
Hardness (kg/cm^2)	5.5	5.5	5.4
Friability (%)	0.46	0.46	0.45
Drug content (%)	99.68±0.05	99.-08±0.45	98.32±0.09

The stability studies for optimized formulation F6 was carried out based accelerated stability conditions and study of various parameters carried out at 0, 30, 60, 90 days of intervals and the results found satisfactorily and that reveals that the optimized formulation was stable under accelerated condition.

Table No. 14: Dissolution data of % cumulative drug release for formulation F6

Time (hrs)	0 days	30 days	60 days	90 days
0	0	0	0	0
1	31.25	31.20	31.15	30.58
2	47.67	47.56	47.34	47.26
3	61.89	61.67	61.55	61.32
4	72.40	72.35	72.30	72.25
5	85.75	85.70	85.65	85.60
6	87.32	87.26	87.20	87.14
7	91.83	91.76	91.60	91.47
8	98.29	98.26	98.21	98.19

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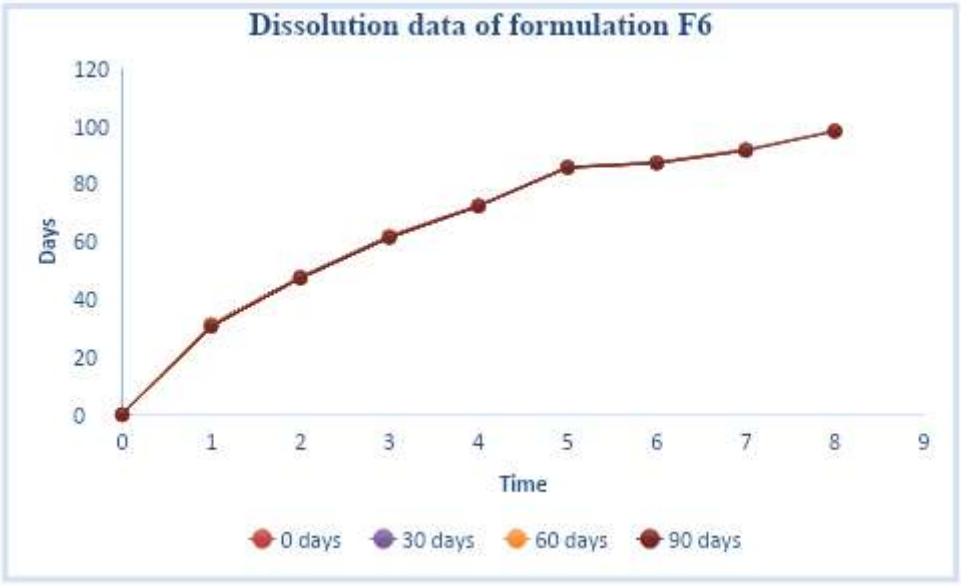

Fig No. 11: Dissolution stability data for sample F6

The stability studies for optimized formulation F6 was carried out based accelerated stability conditions and study of various parameters carried out at 0, 30, 60, 90 days of intervals and the results found satisfactorily and that reveals that the optimized formulation was stable under accelerated condition.

IV. CONCLUSION:

Tinidazole is a systemic anti-protozoal agent. Tinidazole is widely used for the treatment of trichomoniasis, giardiasis and paediatric patients older than three years of age and for the treatment of intestinal amebiasis and amoebic liver abscess caused by E. histolytica

F6 batch is an optimum formulation and passes all physiochemical tests Based on evaluation parameters, such as high drug content and floating lag time, it was indicated that the F6 formulation batch was an optimum batch.The % drug release and raft weight determination were found to be within acceptable limits.

The results of the dissolution studies indicated that the polymer concentration is having a substantial effect on the drug release from the tablets. Formulation F6 shows better controlled drug release and floating properties in comparison to the other formulations. The optimized formulation (F6) was shown good floating lag time up to 60±02 sec and raft weight up to 7.88 ± 1.05 g respectively.

The formulation containing Sodium alginate and HPMC K4M with higher amount shows the higher Raft formation as compared to other batches. It was found that increase in sodium alginate concentration significantly increase in raft formation and hence achieved controlled release of drug.

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