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Design and evaluation of bilayer floating tablets of metronidazole and ranitidine

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ABSTRACT

Antibacterial and antiulcer dosage forms enable prolonged and continous input of the drug and improve the bioavailability of medications those are characterised by a narrow absorption window. The aim of the study was to design and evaluate bilayer Floating tablets of Metronidazole and Rantidine. An attempt was made to develop bi-layer tablet suitable for delivering different drugs with different release pattern like one layer of drug as immediate release to get quick relief and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose and to optimize the concentration of Polymer for Floating layer Rantidine, and to select and optimize the concentration of disintegrant for immediate release layer, Metronidazole. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. In which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a controlled release, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer.

Keywords: Antibacterial, Antiulcer, Metronidazole and Rantidine.

1. INTRODUCTION

The goal to designing bilayer tablets:

- Controlling the delivery rate of either single or two different API'S.
- To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).
- For the administration of fixed dose combinations of drugs, Prolong the drug product life cycle**,** buccal /mucoadhesive delivery systems, manufacture novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery systems.
- To adapt the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable / erodible barriers for controlled release.
- Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. In which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a controlled release, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer.

1.1 General properties of bilayer tablet dosage form

- It should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.
- It should have graceful product identity free of defects like chips, cracks, discoloration and contamination.
- Must have a chemical stability shelf life, so as not to fallow alteration of the medicinal agents.
- The bilayer tablet must release drug in a expectable and reproducible manner.
- It should have physical and chemical stability.

1.2. Various techniques for preparation of bilayer tablets

- OROS® push pull technology
- L-OROS tm technology.
- EN SO TROL technology.
- DUROS technology
- Elan.Drug.Technologies'. Dual Release Drug Delivery System

1.3. Bi-layer tablet press

The XM 12 Bi-Layer Tablet Press features a retractable second layer feeder that permits automated first layer sampling at production speeds. The first layer sampling capability also offers a hardening feature, in which the main compression station will automatically Compress the first layer tablet for in-process measurement. The two feeders are zero clearance and are configured with an integrated dust extraction manifold which cleans the die table and completely eliminates any potential for cross contamination. WipCon® solution available for potent for Small-Scale Bi-layer Applications. The KORSCH XM 12 Bi- Layer Tablet Press is a small-scale press which is ideal for product development scale-up, clinical trials and midrange production. The bi-layer execution, single-layer conversion kit and exchangeable turret offer unprecedented flexibility. The XM 12 Bi-Layer Tablet Press offers a new standard in GMP with extreme accessibility to the compression zone and a combination of quick disconnects and smooth surfaces that permit fast cleaning and changeover.7 The machine features a 5 KN tamping station, 40 KN precompression station, 80 KN main compression station, and a unique structural design that eliminates vibration to the head piece and base frame. The result is an extreme reduction in the operating noise level.

1.4. Small-scale Bi-layer

- 5 KN First Layer Tamping Force.
- 40 KN Precompression Force.
- 80 KN Main Compression Force.
- Single-Layer Conversion Capability

1.5. Bilayered tablets: quality and GMP requirements

- To produce a quality bi-layered tablet, in a validated and GMP way, it is important to select a bilayered tablet press is capable of: Preventing capping and separation of the two individual layers that constitute the bi-layer tablet.
- Providing sufficient tablet hardness.
- Preventing cross contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield.
- Precise and individual weight control of the two layers.

2. METHODOLOGY

2.1. Preformulation studies

2.1.1. Preparation of linearity plot of rantidine in 0.1N HCl

Preparation of 0.1N HCl

Take 8.5ml of HCl in distilled water and make up to 1000ml with distilled Water to get 0.1N HCl

Standard Stock solution

100 mg of Rantidine was dissolved in 100 ml 0.1N HCl to give a concentration of (1000 µg/ml)

Scanning

From the stock solution 100µg/ml was prepared in 0.1N HCl and UV scan was taken between 200 to 400 nm. The absorption maximum was found to be 313 nm and was used for the further analytical studies.

Calibration curve of Rantidine in 0.1N HCl

The standard solutions were prepared by proper dilutions of the primary stock solution with absolute 0.1N HCl to obtain working standards in the concentration range of 6-80 µg/ml of pure sample of Rantidine.

2.2. Construction of standard graph of metronidazole (0.1 N HCL)

Preparation of stock solution

Accurately weighed amount of 100 mg of Drug was transferred into a 100ml volumetric flask and dissolved with few ml of methanol then volume was made up to 100 mL with 0.1 N HCl .

The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'.

Preparation of serial dilutions for standard calibration curve

Necessary dilutions were made by using the stock solution to give the different concentrations of Metronidazole (2-12mcg/mL) solutions.

The absorbances of above solutions were recorded at λ_{max} (277nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

2.3. Drug – Excipient Compatibility Study

FTIR Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

2.4. Formulation development

The pharmaceutical development studies have to be carried out with the purpose of selecting right dosage form and a stable formulation. These studies give detailed description of all the steps involved in the process of formulation development. Such details are intended towards identifying critical parameters involved in the process, which have to be controlled in order to give reliable and reproducible quality product.

Table -1: COMPOSITION OF FLOATING LAYER

Ingredients(mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Rantidine	150	150	150	150	150	150	150
NaHCO3	52.5	52.5	52.5	52.5	52.5	52.5	52.5
HPMC K100	122.5	-	-	70	-	-	70
Xanthum Gum	-	122.5	-	-	87.5	87.5	-
Guar gum	-	-	122.5	-	-	-	-
EC	-	-	-	52.5	35	17.5	52.5
Talc	7	7	7	7	7	7	7
Magnesium stearate	7	7	7	7	7	7	7
MCC(mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	350	350	350	350	350	350	350

MCC- Micro crystalline cellulose, EC – Ethyl cellulose,HPMC – Hydroxy Propyl methyl cellulose.

Table -2: Formulation table for immediate release layer

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6
Metronidazole	200	200	200	200	200	200
Starch	10	10	-	-	-	-
CCS	20	-	20	-	14	30
SSG	-	20	-	20	-	-
PVP K30	-	-	20	20	20	20
Magnesium stearate	10	10	10	10	10	10
MCC	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	400	400	400	400	400	400

CCS: Cross caramellose sodium, SSG: Sodium starch glycolate, PVP- Poly vinyl Pyrrolidine

2.5. Formulation of bilayer matrix tablet (FLOATING LAYER)

- The Floating tablets were prepared by direct compression method.
- As shown in table powder mixtures of Rantidine microcrystalline cellulose, polymers and sodium bicarbonate were dry blended for 20 min followed by addition of Magnesium Stearate and Talc.
- The mixtures were then further blended for 10 min., 350mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with a 9mm punch and die to obtain the tablet.

2.6. Direct compression for immediate layer

All the ingredients were passed through sieve and mixed in a motor and pestle for 30min for uniform mixing. The addition of ingredients was done in a geometrical manner. Then the Metronidazole layer was compressed using 8mm round punch.

2.7. Evaluation of precompression blend

2.7.1. Flow properties

Angle of Repose

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

$$\text{Angle of repose} = \tan^{-1}(h/r)$$

where,

h = height of a pile (2 cm)

r = radius of pile base.

Procedure:

- 20gms of the sample was taken
- The sample was passed through the funnel slowly to form a heap.
- The height of the powder heap formed was measured.
- The circumference formed was drawn with a pencil on the graph paper.
- The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

2.7.2. Bulk density

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

Bulk density = M / V_0

Where M= mass of the powder;

V_0=bulk volume of the powder.

2.7.3. Tapped density

A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed.

Tap density = M / Vr

Where M = mass of the powder,

Vr = final tapping volume of the powder.

Compressibility index and Hausner ratio

The compressibility index and hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

Compressibility index = 100 × tapped density / bulk density

Hausner ratio = tapped density / bulk density

2.7.4. Size and Shape

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

2.7.5. Weight variation test

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests.. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for

Table - 3: Acceptance criteria of flow properties

Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	> 66	>38	>1.6

the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table - 4: Limits for Tablet Weight variation test

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

2.7.6. Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

2.7.7. Thickness

The thickness of the tablets was measured by vernier calipers. It is expressed in mm.

2.7.8. Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester. The tablets from each batch were used for hardness studies and results are expressed in Kg/cm^2.

2.7.9. Dissolution studies

2.7.9.1. *In vitro* dissolution studies for floating layer of rantidine

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 12 hr, at 50 rpm, 0.1 N HCl was used as a dissolution medium. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 313nm.

2.7.9.2. Kinetic analysis of dissolution data

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou et al., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t \quad (1)$$

where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log}C = \text{Log}C_0 - K_1 t / 2.303 \quad (2)$$

where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \quad (3)$$

where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \quad (4)$$

where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data

- Cumulative % drug release vs. time (Zero order kinetic model);
- Log cumulative of % drug remaining vs. time (First order kinetic model);
- Cumulative % drug release vs. square root of time (Higuchi model);
- And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

2.7.9.3. Mechanism of drug release

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \qquad (5)$$

where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table16, for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Peppas, 1985).

Table - 5: Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

2.7.9.4. *In vitro* dissolution studies for immediate release layer of metronidazole

In vitro drug release studies were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 1 hr, at 50 rpm, 0.1 N HCl was used as a dissolution medium.5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug release in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 277 nm.

2.7.9.5. Bilayered tablet punch

After the batch was optimized in both immediate release layer (F3) and sustained release layer (F5).The optimized batch in both was compressed by using same ingredients.

Table – 6: Formulation table for bilayerd tablet formulation.

Sustained Release Formula (F5)	Bilayered formulation(mg)
RANTIDINE	150
Xanthum gum	87.5
EC	35
MCC	q.s
Mg.stearate	7
Sodium bicarbonate	52.5
Talc	7
Total weight	350mg
Immediate Release Formula (F3)	
METRONIDAZOLE	200
CCS	20
PVP K 30	20
Mg.stearate	10
Total weight	400mg
Total weight of the bilayered tablet 750mg	

2.7.9.5. Dissolution study of rantidine and metronidazole from bilayer tablet

The release kinetic of optimized Ranitidine and Metronidazole from bilayer tablet was studied by conducting dissolution studies.

- Dissolution tests performed using USP Type II dissolution apparatus and 900ml of 0.1N HCL at 37± 0.5^0 C at 50rpm.
- 5ml of sample were withdrawn at the intervals of every time interval, sampling was carried out and everytime replaced with fresh 5ml of buffer.
- The absorbance of solution was recorded at 313nm and 277nm using buffer as blank.
- The result was calculated as Percentage drug release of Ranitidine and Metronidazole.

3. RESULTS AND DISCUSSION

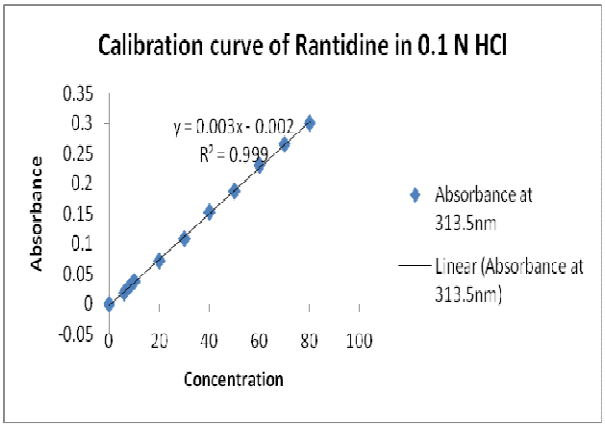

Figure - 1: Calibration curve of Rantidine in 0.1N HCl.

The standard graph of Metronidazole has shown good linearity with R^2 values 0.9993 in 0.1 N Hcl and which suggests that it obeys the "Beer-Lambert's law".

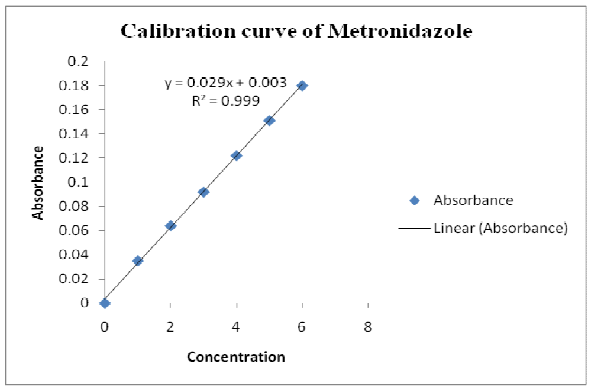

Figure - 2: Calibration curve for Metronidazole in 0.1N HCl at 277nm

3.2. Compatibility studies

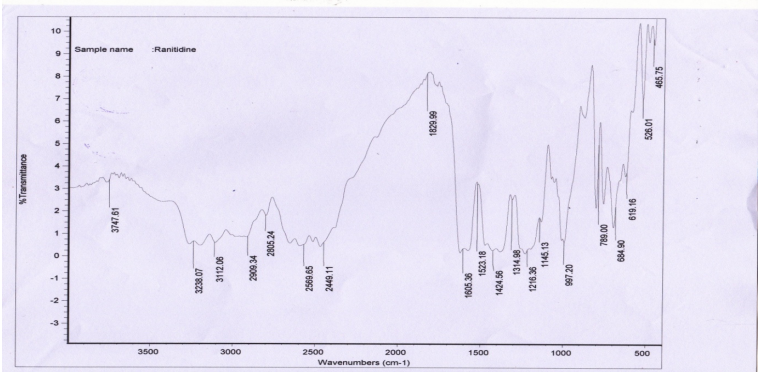

Figure - 3: FTIR spectra of Rantidine , Metronidazole pure drug of bilayered tablet

Table – 7: Evaluation of pre compression parameters for floating layer of rantidine

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	29.36	0.35	0.41	14.63	1.17
F2	32.35	0.33	0.4	17.50	1.21
F3	25.21	0.31	0.36	13.89	1.16
F4	27.08	0.34	0.39	12.82	1.15
F5	26.32	0.36	0.42	14.29	1.17
F6	29.51	0.3	0.37	18.92	1.23
F7	27.43	0.35	0.42	16.67	1.20

From the above pre-compression parameters it was clear evidence that powdered blend has excellent flow properties.

3.4. *In-vitro* Buoyancy studies

Table - 8: *In-vitro* Buoyancy studies.

F.CODE	Buoyancy Lag time (min)	Total floating time(hrs)
F1	18	4
F2	10	6
F3	5	>8
F4	25	3
F5	10	>12
F6	7	10
F7	6	6

3.5. Post Compression Parameters for Sustained Release Tablet

Table - 9: Post Compression Parameters for Sustained Release Tablet

Formulations	Weight variation	*Hardness*	Thickness (mm)	Friability (%)
F1	350	7.5	2.3	0.45
F2	352	7.3	2.5	0.48
F3	349	6.5	2.7	0.50
F4	351	7.6	2.3	0.52
F5	350	7.5	2.1	0.40
F6	348	7.5	2.4	0.49
F7	352	7.3	2.3	0.41

3.6. In-Vitro Drug Release Studies for Floating tablets

Table -10: Cumulative percentage drug release of Floating layer

Time(hrs)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
0.5	59	36	25	91.42	11.05	25.8	39.5
1	66.8	51.63	37.6	100.2	22.57	37.2	55.9
2	85.1	63.63	49.8	101.6	30.31	43.6	77.3
3	98.7	72.94	66.3		34.73	55.8	86.4
4		86.3	79.8		38.68	63.7	91.5
6		97.5	83.9		50.05	74.9	100.28
8			94		67.1	89.5	
10					84.15	100.34	
12					95.52		

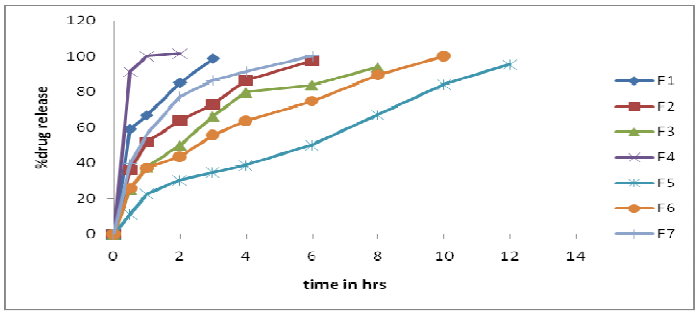

Figure – 4: Dissolution graph for Floating Tablets.

3.7. Kinetic release models

Table - 11: Release kinetics for F5 formulation for Floating layer

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	7.300243632	-0.09328534	27.02261421	0.927791717
Intercept	9.46986711	2.068834844	-7.27212068	0.994780181
Correlation	0.988676295	-0.93585635	0.979283304	0.758374413
R 2	0.977480817	0.875827116	0.95899579	0.57513175

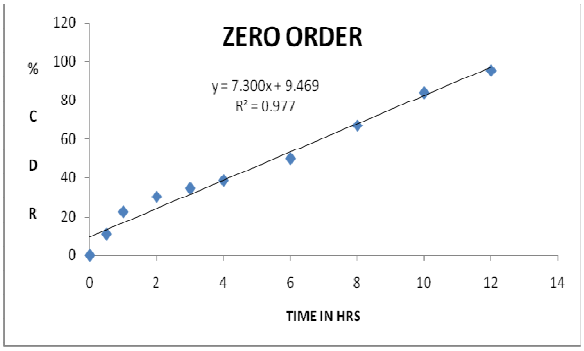

Figure - 5: zero order release graph for F5 sustained release formulation.

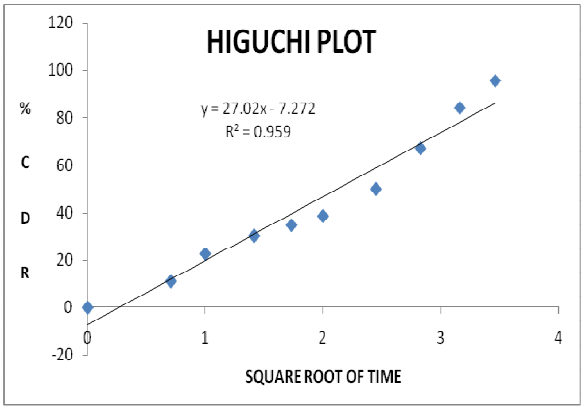

Figure - 6: Higuchi model graph for F5 sustained release formulation.

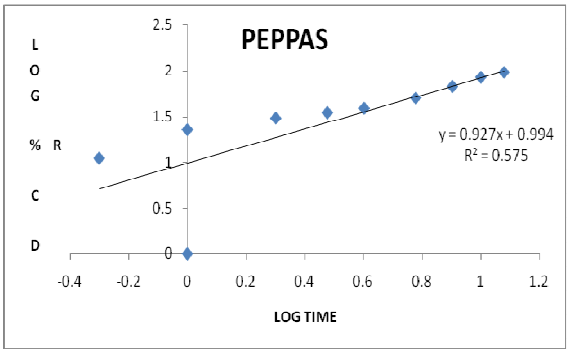

Figure - 7: Peppas model for F5 sustained release formulation.

Figure - 8: First order release graph for F5 sustained release formulation.

From the table, it was confirmed that the F1, F2, F3, F4, F6, F7 of floating layer does not fulfill the sustained release theory up to 12 hrs. And also from the table, it was also confirmed that the formulation made with combination of Xanthum and EC (F5) showed maximum drug release up to 12hrs.

3.8. Evaluation of immediate release layer of metronidazole

3.8.1. Precompression parameters

Table - 12: Precompression Parameters of Metronidazole

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	25.64	0.33	0.38	13.16	1.15
F2	27.13	0.35	0.41	14.63	1.17
F3	26.34	0.29	0.33	12.12	1.14
F4	27.5	0.32	0.37	13.51	1.16
F5	28.4	0.31	0.37	16.22	1.19
F6	27.9	0.37	0.43	13.95	1.16

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

3.8.2. Post compression evaluation parameters for immediate release formulation

The results of the uniformity of weight, hardness, thickness and friability of the tablets are given in Table. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 398 to 402mg. The hardness of the tablets ranged from 3.1 to 3.6kg/cm^2 and the friability values were less than 0.5% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from to 2.1 to 2.5mm. Thus all the physical attributes of the prepared tablets were found be practically within control.

Table - 13: Post compression parameters for immediate release tablets.

Formulations	Average weight (mg)	*Hardness Kg/cm²*	Thickness (mm)	Friability (%)
F1	400	3.4	2.1	0.29
F2	399	3.5	2.3	0.25
F3	400	3.1	2.5	0.30
F4	402	3.3	2.2	0.41
F5	401	3.6	2.4	0.52
F6	398	3.2	2.2	0.49

3.8.3. Dissolution for immediate release tablet of Metronidazole

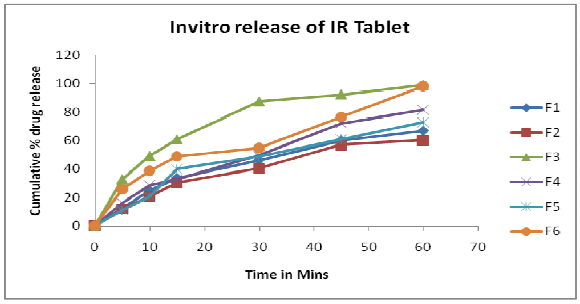

Figure - 9: Dissolution graph for formulations F1-F6.

3.8.4. Bilayered tablet compression

After the batch was optimized in both immediate release layer (F3) and Floating layer (F5). The optimized batch in both was compressed by using same ingredients.

3.8.5. Dissolution study (Bilayered tablets)

Table 14 : Dissolution data for bilayered tablet.

Time	Bilayered tablet (IR + SR)
0.1N Hcl as dissolution medium for immediate release tablets (dose 200mg)	
60min	99.05
0.1N Hcl as dissolution medium for floating tablets (dose 150mg)	
1hr	22.10
2hr	30.60
3hr	33.39
4hr	39.50
6hr	50.31
8hr	66.89
10hr	85.04
12 hr	95.24

4. CONCLUSION

- The Bilayered tablets containing Rantidine and metronidazole were successfully prepared by direct compression method respectively.
- The physiochemical evaluation results for the powdered blend of all trials pass the official limits in angle of repose, compressibility index.
- The prepared blend for IR release were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F3 contains the average thickness of 2.5 average hardness of 3.1, average weight of 400, friability of 0.30.
- The prepared dry mixer for floating tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F5 contains the average thickness of 2.1 average hardness of 7.5, friability of 0.40.
- The F5 formulation which releases the Rantidine in sustained manner in up to 12 hours and Metronidazole immediate release F3 formulation showed 99% drug release with in 60min.

Hence it may be summarized that the tablets prepared by direct compression method for sustained release layer and immediate release layer might be a perfect and effective formulation to treat the disorder.

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