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FORMULATION AND EVALUATION OF FLOATING TABLETS OF TINIDAZOLE

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ABSTRACT

Floating matrix tablets of tinidazole were developed to prolong gastric residence time and increase drug absorption further increasing the bioavailability. It is an anti-parasitic. Floating tablets of tinidazole formulated to increase gastric residence and there by improve its therapeutic efficacy. By using different polymers such as carbopol, guargum, sodium alginate, and eudragit prepare formulations f1, f2, f3, f4, f5, f6, f7, f8, f9. Formulated tablets showed satisfactory results for various post compression evaluation parameters like thickness, hardness, weight variation, floating lagtime, total floating time, content uniformity and invitro drug release. Formulation f2 gave better-controlled drug release and floating properties in comparison to the other formulations.

Keywords: Anti-parasitic, increase gastric resistance, carbopol, guargum.

INTRODUCTION

Oral route is the most convenient and extensively used route for drug administration. This route has high patient acceptability, primarily due to ease of administration. Over the years, oral dosage forms have become increasingly sophisticated with major role being played by controlled release drug delivery systems (crdds) release drug at predetermined rate.

Drug delivery technologies are advanced enough to design any dosage form that can deliver drugs at a constant rate for extended periods of time ranging from days to years. And yet most oral controlled release dosage forms deliver drugs for only 12hrs.Oral delivery for 24hrs is possible for some drugs; such are absorbed well throughout gastro intestinal tract (git). Thus, the real issue in the development of oral controlled release dosage forms is how to extend the time for drug absorption from final intestine. For example, oral dosage forms may have to stay in the stomach or somewhere in the upper small intestine until the entire drug is released for desired period of time. Designing platforms that target upper small intestine is rather difficulty, since they would have to be adhesive type systems that selectively adhere to jejunum, ileum surface. However, it is difficult to place oral dosage form sat selected sites in the small intestine. For this reason, research efforts have been focused on platform to extend gastric retention time (grt).

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process.

GASTRORETENTIVE DRUG DELIVERY SYSTEMS

The development of oral crdds has been hindered by the inability to localize the system in the selected regions of the git. There has been considerable research over the last decade on the possibility of controlled and site specific delivery to the git by controlling the gastro intestinal transit of orally

administered dosage forms using gastro retentive drug delivery systems (grdds).Such grdds possess the ability of retaining the druging it particularly in the stomach for long periods (s.S.davis 2005).
The idea of gastro retention stems from the need to localize drugs at specific region ofgit such as stomach in the body. Often the extent of drug absorption is limited by the residence time of the drug at absorption site. The transittime in giti. e., from the mouth to anus, varies from one person to another. It also depends upon the physical properties of the object ingested and the physiological conditions of the alimentary canal. In addition, the relatively brief g.i. transittime (8-12 hr) for most of the drugs impedes the formulation of once daily dosage form. Many drugs show poor bioavailability (ba) in the presence of intestinal metabolic enzymes like cytochromep450 (cyp3a), abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon. This non uniform distribution of cyp3a causes regional variability in the absorption of drugs that are the substrates of enzymes.

FLOATING DDS (FDDS)

Floating systems, first described by davies in1968, have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy. In 1985, mojaverian et al. Reported that the amount, nature and caloric content of the food .The main drawback is the passivity of the operation. It depends on the air sealed in the dry mass centre following hydration of the gelatinous surface layer and hence the characteristics and amount of polymer (hwang.S. J1998)

Classification of FDDS

Based on the mechanism of buoyancy, floating systems can be classified into two distinct categories

A. Non-effervescentsystems.[11-14].
B. Effervescentsystems.[15,16].

A. Non-effervescent systems

1. Hydrodynamically balanced systems (HBS)

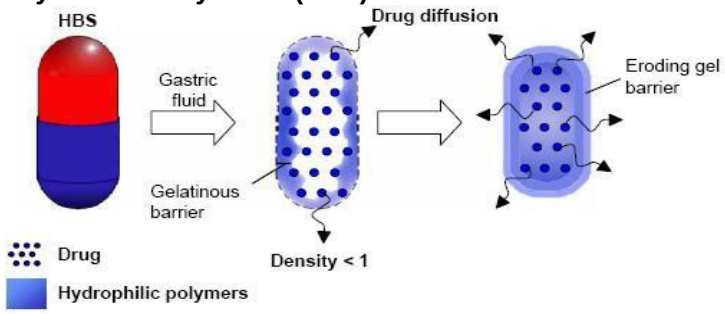

Fig. 1: Hydrodynamically balanced systems

The gelatinous polymer barrier formation results from hydrophilic polymer swelling. Drug is released by diffusion and erosion of the gel barrier.
The HBS must comply with three manor criteria L.J. Caldwellet al 1988

1. It must have sufficient structure to form a cohesive gel barrier
2. Itmustmaintainanoverallspecificgravitylowerthanthatofgastriccontentsi.e.,1.004-1.01g/ml
3. It should dissolve slowly enough to serve as are servoir for the delivery system

A bilayer tablet canalso be prepared to contain one immediate-release and other sustained-release layer. Immediate-release layer delivers the initial dose whereas SR layer absorbs gastric fluid and forms a colloidal gel barrier on its surface Shethetal 1978.

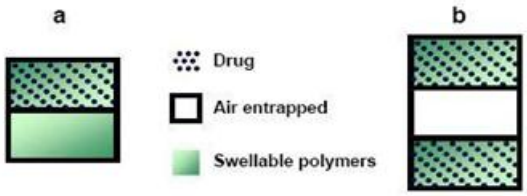

Fig. 2: Improvement in HSB

The main drawback is the passivity of the operation. It depends on the air sealed in the dry mass centre following hydration of the gelatinous surface layer and hence the characteristics and amount of polymer (Hwang.S. J 1998).

2. Intra gastric floating drug delivery device

The device comprised of a drug reservoir encapsulated in a microporous compartment having pores along its top and bottom surfaces. The peripheral walls of the drug reservoir compartment were completely sealed to prevent any physical contact of the undissolved drug with the stomach walls. The floatation chamber caused the system to float in the gastric fluid [Yuasa.Hetal1996], developed intra gastric floating SR granules of diclofenac sodium using polymer solution of hydroxypropylcellulose L grade(HPC-L) and ethylcellulose, and calcium silicate as a floating carrier, which has a characteristically porous structure with numerous pores and alarge individual pore volume. The coated granules acquired floating ability from the air trapped in the pores of calcium silicate when they were coated with a polymer(Singh. Brahma N.,Kwon H.Kim2000).

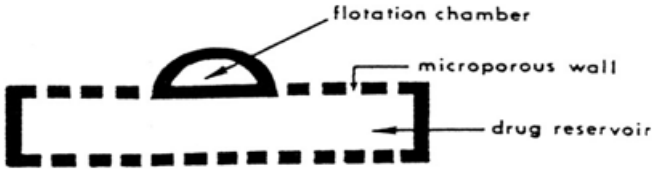

Fig. 3: Intra gastric floating drug delivery device

3.Floating tablets

Single-unit floating tablets prepared based on polypropylene foam powder and matrix-forming polymer. Incorporation of highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. A 17% wt/wt foam powder (based on mass of tablet) was achieved *in vitro* for at least 8 hours. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively(Shweta Arora etal 2005 & Streubel Aet al2003)

4.Floating Microspheres

Conventionally, the drug-loaded microspheres have been developed by emulsification and solvent-evaporation method. Example was preparation of hollow microspheres (microballoons), loaded with ibuprofen in their outer polymer shell. The ethanol-dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^{o}C. The gas phase generated in dispersed polymer droplet by evaporation ofdichloromethaneformedaninternalcavityinmicrospheresofpolymerwithdrug.The micro balloons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hr *in vitro*.

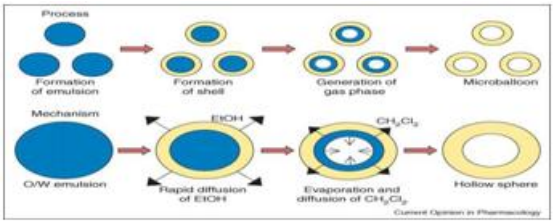

Fig. 4: Floating Microspheres

B. Effervescent systems or Gas generating systems

ADDS can be made to float in the stomach by incorporating a floating chamber with may be filled with vacuum, air or inert gas. The gas in the floating chamber can be introduced either by the effervescent reaction between organic acids and bicarbonate salts or by the volatilization of an organic solvent.

1. Effervescent reaction Tablets

Floatability can also be achieved by generation of gas bubbles. CO2 can be generated in situ by incorporation of carbonates or bicarbonates, which react with acid—either the natural gastric acid or co-formulated as citric or tartaric acid. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation.

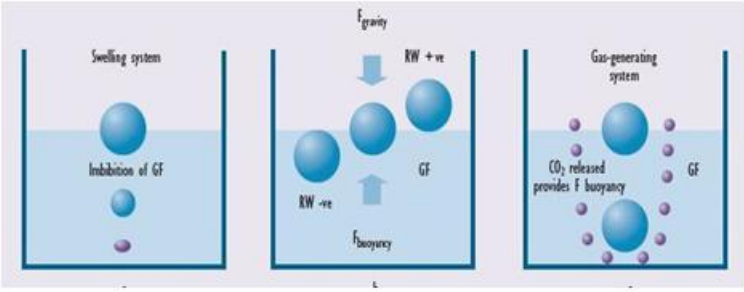

Fig. 5: Formation of CO2 in gas generating systems

Beads

Floating alginate beads using gas forming agents (calcium carbonate and sodium bicarbonate) and studied the effect of CO2 generation on the physical properties, morphology, and release rates. The study revealed that the kind and amount of gas-forming agent had a profound effect on the size, floating ability, pore structure, morphology, release rate, and mechanical strength of the floating beads. It was concluded that calcium carbonate formed smaller but stronger beads than sodium bicarbonate. Calcium carbonate was shown to be a less-effective gas-forming agent than sodium bicarbonate but it produced superior floating beads with enhanced control of drug release rates. *In vitro* floating studies revealed that the beads free of gas-forming agents sank uniformly in the media while the beads containing gas-forming agents in proportions ranging from 5:1 to 1:1 demonstrated excellent floating (100%)[20].

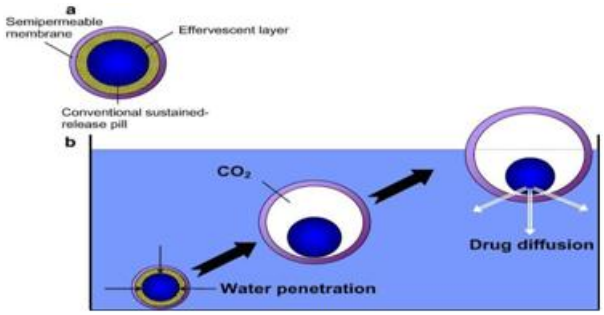

Fig. 6: Effervescent Beads

2.Volatile liquid containing systems

The GRT of a DDS can be sustained by incorporating an inflatable chamber, which contains a liquid i.e., ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach, shown in (Fig. 7).

Two patents on FDDS issued to the Alza Corporation disclosed drug delivery devices for the controlled and continuous administration of medicinal agents.

These ***Gastro-inflatable drug delivery devices*** are osmotically controlled floating systems containing a hollow deformable unit that can convert from a collapsed to an expanded position, and returns to the collapsed position after an extended period. The deformable system consists of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the drug and the second chamber contains the volatile liquid.

The device inflates, and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of a bioerodible plug made up of PVA, polyethylene etc. that gradually dissolves causing the in flatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach.

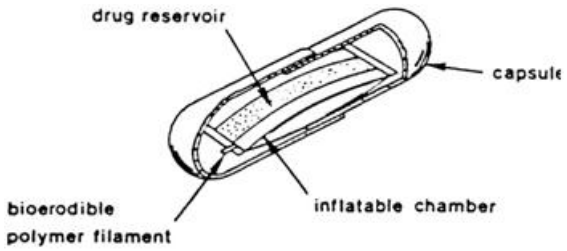

Fig. 7: Gastro-inflatable drug delivery device

Intragastric osmotically controlled *DDS* consists of an osmotic pressure-controlled drug delivery device and aninflatable floating support ina bioerodible capsule, when the device reaches the stomach, bioerodible capsule quickly disintegrates to release the DDS. The floating support is made up of a deformable hollow polymeric bag containing a liquid that gasifies at a body temperature to inflate the bag. The osmotic-pressure controlled drug delivery device consists of two compartments

- A drug reservoir compartment
- An osmotically active compartment

The drug reservoir compartment is enclosed by a pressure-responsive collapsible bag, which is impermeable to vapors and liquids and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing.

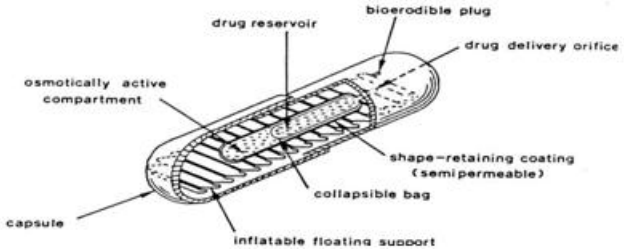

Fig. 8: Intragastric osmotic controlled drug delivery system

C. Raft-forming systems

Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates orbi carbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles (Fig. 9) on contact with gastric fluid. Formulations also typically contain antacids such as Aluminum hydroxide or Calcium carbonate to reduce gastric acidity. Because raft-forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment.

Fig. 9: Schematic illustration of the barrier formed by a raft-forming system

D. Low-density systems

Gas-generating systems inevitably have a lag time before floating on the stomach contents, during which the dosage form may undergo premature evacuation through the pyloric sphincter. Low-density systems (<1 g/cm3) with immediate buoyancy have therefore been developed. They are made of low-density materials, entrapping oil or air. Most are multiple unit systems, and are also called ‘‘microballoons’’ because of the low-density core.

Table 1: METHODOLOGY
LIST OF MATERIALS AND SUPPLIERS

S.no.	Ingredients	Supplier
1.	Tinidazole	Supplied by pharma train
2.	Carbopol974p	Sdfine chemicals,mumbai
3.	Polyethyleneoxide	Sdfine chemicals,mumbai
4.	Guargum	Sdfine chemicals,mumbai
5.	Sodiumbicarbonate	Sdfine chemicals,Mumbai
6.	Citric acid	Sdfine chemicals,mumbai
7.	Avicelph102(mcc)	Fmc biopolymer,mumbai
8.	Talc	Sdfine chemicals,mumbai
9.	Magnesium stearate	Sdfine chemicals,mumbai

Table 2: Formulation of Tinidazole floating tablets by wet granulation method

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tinidazole	200	200	200	200	200	200	200	200	200
Carbopol	50	75	100	-	-	-	-	-	-
Polyethylene oxide	-	-	-	50	75	100	-	-	-
Guar gum	-	-	-	-	-	-	50	75	100
Sodium bi carbonate	50	50	50	50	50	50	50	50	50
Citric acid	30	30	30	30	30	30	30	30	30
Pvpk30	30	30	30	30	30	30	30	30	30
Mcc	130	105	80	130	105	80	130	105	80
Talc	5	5	5	5	5	5	5	5	5
Mg.stearate	5	5	5	5	5	5	5	5	5
Total weight	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

Table 3: LIST OF EQUIPMENT’S

S.no	Name of the equipment	Model
1	Electronic weighing balance	Scale-tec
2	Friabilator	Roche friabilator electrolab, Mumbai
3	Laboratory oven	Dtc-00r
4	Compression machine	Cmd(cadmach)
5	Tablet hardness tester	Pfizerhardnesstester,mumbai
6	Uv	Labindiauv3000+
7	Dissolutionapparatus	Electrolabtdt-08l
8	Vernier calipers	Cd-6”cs

RESULTS AND DISCUSSION

Construction of standard calibration curve of tinidazole in 0.1N HCl

The absorbance of the solution was measured at 275nm, using uv spectrometer with 0.1n HCl as blank. The values are shown in table. A graph of absorbance vs concentration was plotted which indicated in compliance to beer's law in the concentration range 5to 25µg/ml

Table 4: Standard calibration graph values of Tinidazole 0.1N HCl

Concentration (µg/ml)	Absorbance
0	0
5	0.065
10	0.131
15	0.193
20	0.259
25	0.323

The standard plot of tinidazole plotted by taking absorbance on y–axis and concentration (µg/ml) on x – axis, the plot is shown figure.

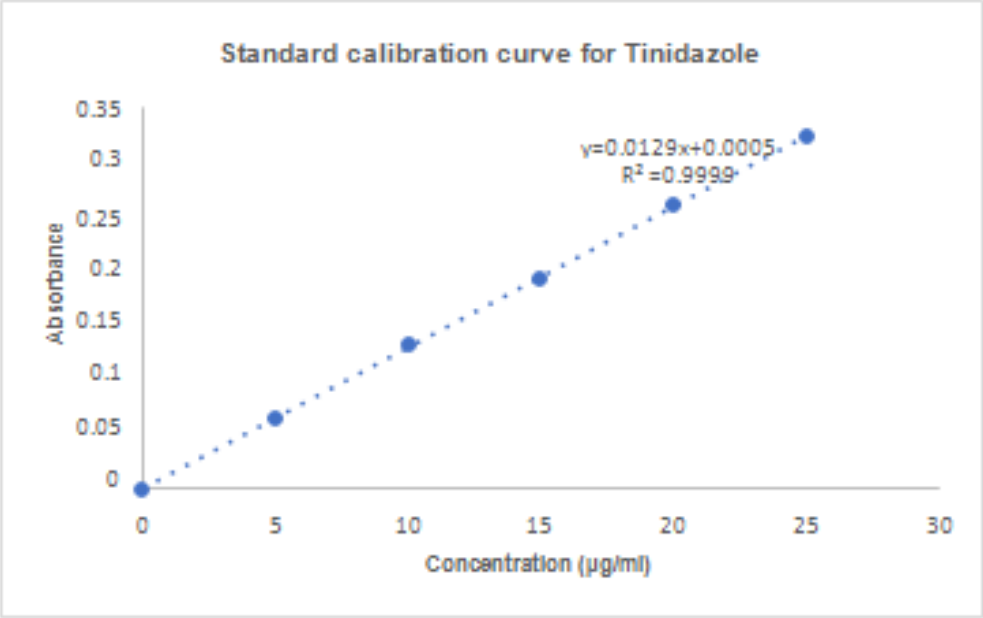

Fig. 10: standard calibration curve of Tinidazole in 0.1nhcl

Inference

The standard calibration curve of tinidazole in 0.1n HCl showed good correlation with regression value of 0.99%

Table 5: EVALUATION OF TABLETS
Precompression studies of tinidazole floating tablets

Formulation Code	Bulk density (kg/cm^3)	Tapped density (kg/cm^3)	Cars index	Hausners ratio	Angle of repose()
F1	0.43	0.52	17.3	1.41	25.62
F2	0.40	0.46	13.0	1.5	31.29
F3	0.50	0.58	13	1.16	29.58
F4	0.44	0.51	13.7	1.25	26.29
F5	0.39	0.47	17.0	1.56	25.23
F6	0.42	0.52	19.2	1.45	25.24
F7	0.36	0.39	7.6	1.0	28.03
F8	0.41	0.50	18	1.5	24.4
F9	0.39	0.48	18	1.23	29.96

Inference

- The tinidazole floting tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in table: 5.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The carr's index and hausner's ratio were found to be in the range of ≤18 and 1.0 to 1.23 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be in the range of 9.92-12.73˚ which indicating passable flow (i.e. Incorporation of glidant will enhance its flow).

Table 6: post compression studies
of tinidazole floating tablets

Formulation code	%weight variation	Thickness (mm)	%friability	%drug content	Hardness (kg/cm^2)
F1	Pass	5.06±0.11	0.142	101.3±1.2	5.56±0.057
F2	Pass	5.06±0.15	0.151	102.3±1.7	5.03±0.115
F3	Pass	5.03±0.057	0.62	100.1±1.2	5.01±0.1
F4	Pass	5.1±0.1	0.154	100.7±1.1	5.63±0.05
F5	Pass	5.03±0.05	0.132	99.6±1.5	5.63±0.03
F6	Pass	5.03±0.15	0.143	98.9±2.3	5.5 ±0.05
F7	Pass	4.93±0.05	0.110	100.2±1.7	5.7±0.1
F8	Pass	5.1±0.1	0.133	100.5±1.4	5.53±0.04
F9	Pass	5.02±0.2	0.13	99.2±1.1	5.69±0.05

*test for friability was performed on single batch of 20tablets

Inference

- The variation in weight was within the limit.
- The thickness of tablets was found to be between 4.9-5.2 mm.
- The hardness for different formulations was found to be between 5.01 to 5.69 kg/cm^2, indicating satisfactory mechanical strength.
- The friability was<1.0%w/w for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 to 102 %.

Table 7: Invitro buoyancy studies of tinidazole floating tablets

Formulation code	Floating Lag Time (sec) N=3	Total floating time N=3	Matrix integrity upto 12hrs. N=3
F1	20±0.51	Up to12	+
F2	40±0.21	Up to12	+
F3	80±0.61	Up to12	+
F4	20±0.71	Up to10	-
F5	30±0.81	Up to12	+
F6	35±0.51	Up to12	+
F7	24±0.31	Up to10	-
F8	20±0.81	Up to12	+
F9	36±0.71	Up to12	+

Table 8: concentration of drug

Time (hrs)	% drug released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	**0**	0	0	0	0	0	0	0
1	34	**27**	19	46	39	47	55	43	31
2	49	**35**	37	67	57	59	67	57	44
4	60	**47**	45	85	69	71	82	69	57
6	77	**61**	56	97	87	86	98	82	67
8	89	**72**	62	100	96	98	100	93	78
10	100	**89**	77	100	100	100	100	100	86
12	100	**100**	86	100	100	100	100	100	100

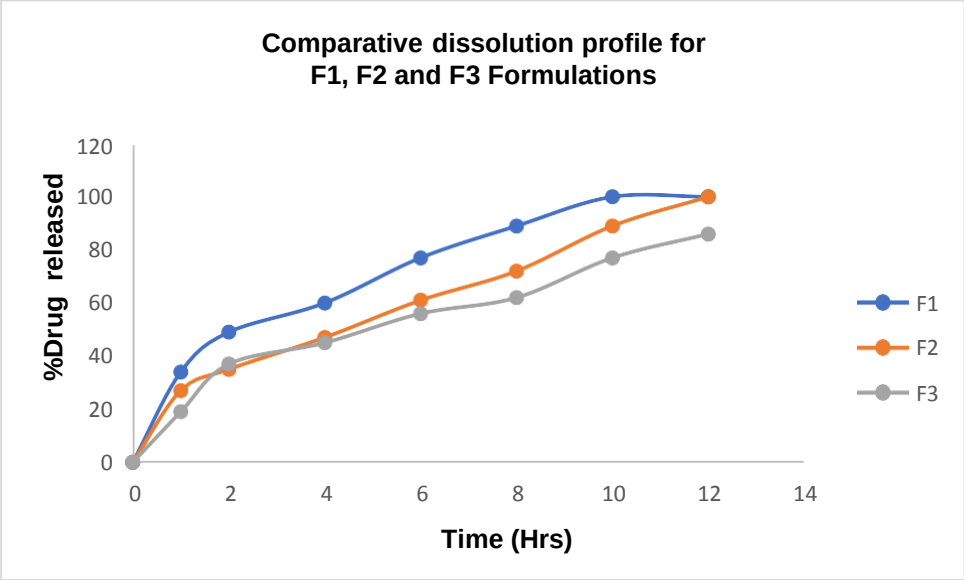

Fig. 11: Comparative dissolution profile for f1, f2 and f3 formulation

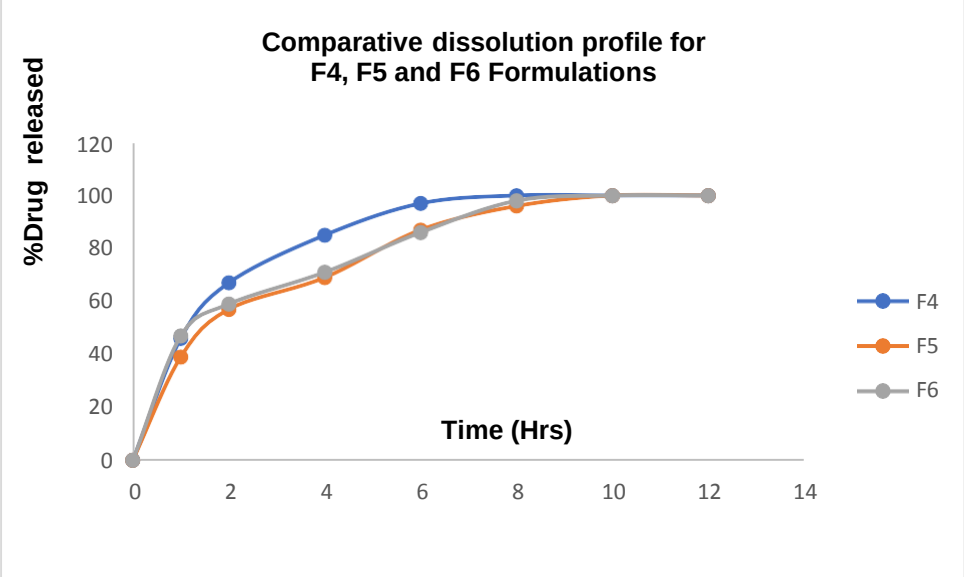

Fig. 12: Comparative dissolution profile for f4, f5 and f6 formulations

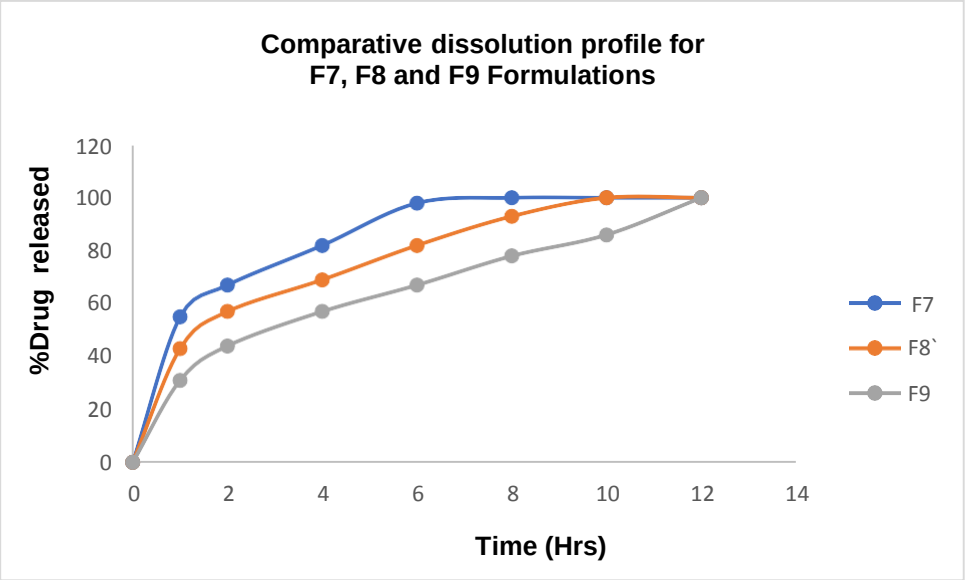

Fig. 13: Comparative dissolution profile for f7, f8 and f9 formulations

Table 9: r^2value and n result table

Formulation code	R2 value				"n" value
	Zero order	First order	Higuchi	Peppas	
F2	0.962	0.795	0.982	0.978	0.527

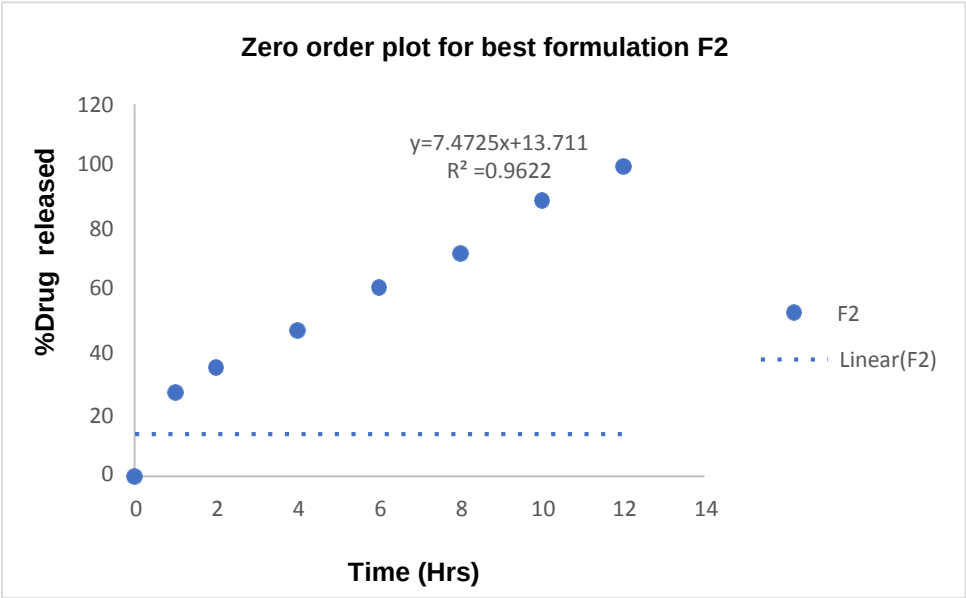

Fig. 14: Zero order plot for best formulation f2

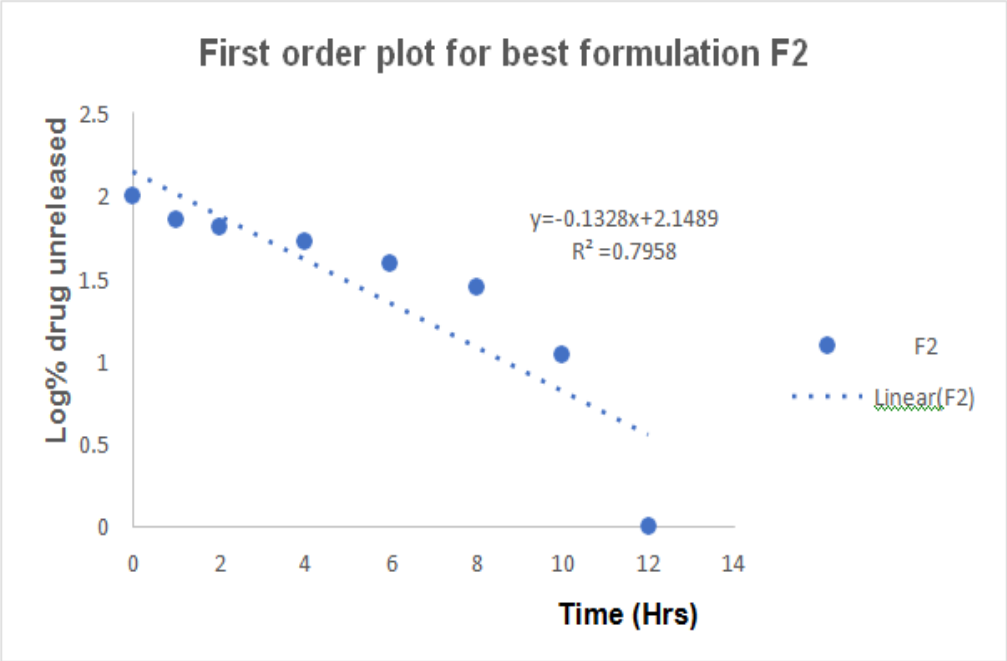

Fig. 15: First order plot for best formulation f2

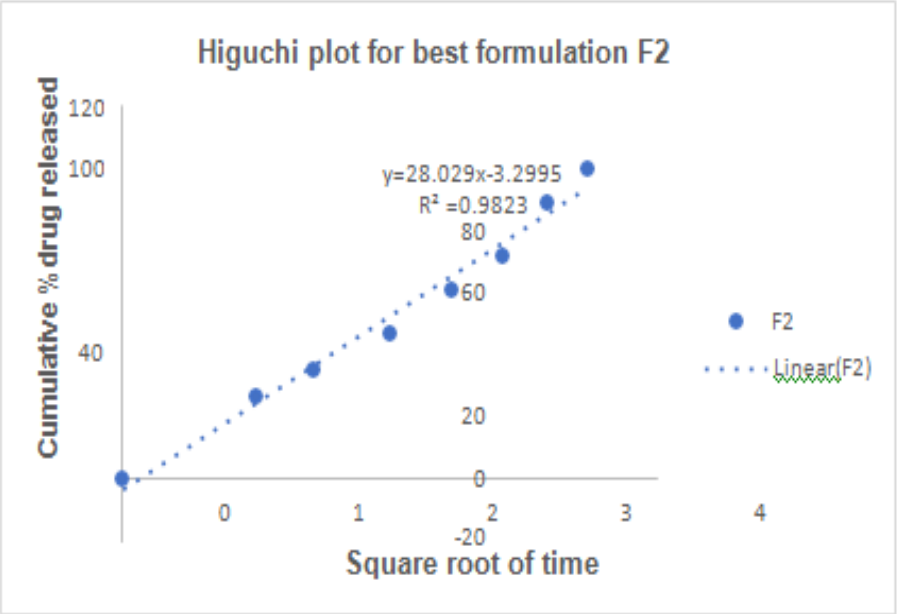

Fig. 16: Higuchi plot for best formulation f2

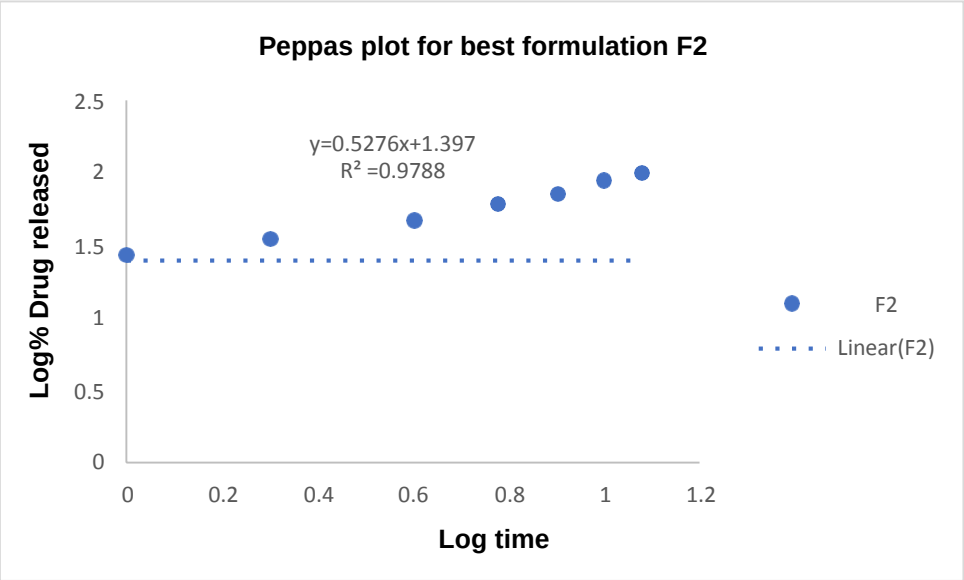

Fig. 17: Peppas plot for best formulation f2

- Among the different control release polymers, carbopol was showing highest drug release retarding capacity
- F2 was showing the satisfactory results.
- F or f2 formulation diffusion exponent n value is in between 0.45 to 0.89 so they are following non ficki ananmolous diffusion model

SUMMARY AND CONCLUSION

From the experimental data, it can be concluded that

- Floating tablets of tinidazole are formulated to increase gastric residence time and there by improve its therapeutic efficacy.
- Carbopol was respectively showed better sustained drug release of tinidazole.
- Synthetic polymers were showing more rate retarding drug release and matrix integrity.
- When drug : polymer concentration increases the release rate decreases this is because of reason when the concentration of polymer increases the diffusion path length increases
- Formulated tablets showed satisfactory results for various post compression evaluation parameters like: tablet thickness, hardness, weight variation, floating lag time, total floating time, content uniformity and *invitro* drug release.
- Formulation f2 gave better-controlled drug release and floating properties in comparison to the other formulations.
- The release pattern of the f2 formulations was best fitted to korsmeyer-peppas model, higuchi and first-order model.
- The most probable mechanism for the drug release pattern from the formulation was non-fickian diffusion or anomalous diffusion.

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