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Interplay Of Hydrophilic And Hydrophobic Polymers: Optimizing Floating Tablets

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Abstract: ***This research work deals with the design, fabrication and evaluation study of floating tablets using hydrophilic and hydrophobic based polymers, Hydroxy Propyl Methyl Cellulose (HPMC K4M), a hydrophilic polymer and ethyl cellulose a hydrophobic polymer. Xanthane gum was used as a swelling agent and sodium bicarbonate & citric acid at various compositions were used as a gas forming agent by wet granulation techniques. Metronidazole (MZ) was used as an antibiotic, amebicide, and antiprotozoal as a standard drug. The invitro dissolution study of Metronidazole floating tablets was carried out by USP Type- II dissolution test apparatus in 0.1N HCl at 37°C±0.5°C at 50 rpm for 12 hours. All prepared tablets were undergone compatibility study using Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetric (DSC). No significant change in MZ drug and combination of drug and other excipients were detected. The percentage of drug dissolved in floating tablet was found to be 98.67 % at the end of 12 hrs. The kinetic release data were analyzed which showed zero order kinetic and is best fit with Higuchi model. The optimized formulation of tablet was formulated by combination of HPMC K4 M and Ethyl Cellulose gives floating lag time and sustained drug release characteristics. The novelty behind the hydrophilic-hydrophobic polymers combined formulations resulted controlled drug release duration reduced the dose frequency and prolonged the retention time of stomach.***

Keywords: ***Hydrophobic and, hydrophilic polymer, Floating tablets, Metronidazole, Release kinetics, Buoyancy***

1. Introduction

The oral course is considered as the most proper course of medication conveyance framework. The desired characteristics of an ideal drug are absorb quickly from the absorption site and should arrive at the site of action rapidly and remain for sufficient duration of time, be removed from the site of action eventually not get distributed to any other tissue and have large therapeutic index and easily eliminated from of drug delivery systems which helps for maximizing therapeutic effect and reduction in side effects [1, 2]. The Floating medication conveyance frameworks (FDDS) are measurements structures which drift over the gastric substance and light in the stomach without influencing the gastric exhausting rate. It is to control the gastric home time. This measurement structure drawn out and controlled exhausting time which exists in the stomach for a more extended timeframe than traditional dose structures [3, 4]. The ideal characteristics of drug delivery systems, which is narrow absorption window in (GIT) and absorbed from stomach and upper portion

of GIT. Metronidazole is BCS Class-I and the primary decision for a nitro imidazole anti-toxin, sedate choosen as model medication and which would stay in stomach or potentially upper segment of GIT for delayed timeframe accordingly augmenting the medication discharge. The objective of ebb and flow investigate work is to build up a gliding drug conveyance framework for Metronidazole which expands the gastric living arrangement time, limits the issues related with oral continued discharge dose structures [5, 6]. The coasting tablets of MZ by with HPMC K4M and Xanthan gum as polymers so as to upgrade the retention pursued by improving bioavailability was completed in this work.

2. Materials and Methods

The samples of Metronidazole and Microcrystalline cellulose were collected from Arathi Pharmaceuticals, Mumbai, polymer samples HPMC K4M from Rubicon pharmaceutical Pvt Ltd., Xanthane gum, Talc magnesium stearate purchased from S.S. Chemicals, Chennai. All chemicals and reagents required for the present experimental work are of analytical grade.

2.1 Preparation of Metronidazole floating tablets

The composition of different formulation of Metronidazole floating tablets is shown in Table-1. The MZ floating tablets are prepared by wet granulation method. Accurately weighed all excipients and drugs are passed through sieve No. 24# and No. 66# size. In the first stage active ingredient, MZ, HPMC, Avicel, Ethyl cellulose/Xanthane gum, sodium bicarbonate, citric acid were mixed together except magnesium stearate and Talc. The second stage is preparation of binding solution with the help of PVPK 30 and IPA. Third stage is preparation of wet mass. Then, the wet mass is passed through 24 mesh size. All wet granules are passed through 24 mesh size and at that point dry the granules in customary tourist oven at 45 ^{0}C. The fine items were compacted, pounded and sieved through sifter no. 22# and 66# size. The cycle of compaction, processing, and sieving was rehashed until the granules and fines were gotten in the proportion of about 60:40. The granules continued till the sample reaches a loss on drying (LOD) less than 2%. Then finally mix the magnesium stearate and talc and the final mixture was compressed by using of multi-tooling compression machine by using 9 mm flat punches.

Table 1. Formulation of MZ Floating tablets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Metronidazole	200	200	200	200	200	200	200	200	200
HPMC K4M	185	185	175	165	155	145	135	135	185
AVICEL	35	25	15	15	50	50	55	45	35
Ethyl cellulose	*	*	*	*	70	80	90	100	*
Xanthane Gum	70	80	90	100	*	*	*	*	70
Sodium Bicarbonate	30	30	40	40	45	45	40	40	30
Citric acid	10	10	10	10	10	10	10	10	10
PVP K30	8	8	8	8	8	8	8	8	8
Magnesium stearate	8	8	8	8	8	8	8	8	8
	4	4	4	4	4	4	4	4	4
	550	550	550	550	550	550	550	550	550

3. Experimental results

3.1 Drug Excipients Compatibility Studies

Precisely measured quantity of 1 mg of MZ and physical blend containing a similar measure of medications were investigated in a programmed warm analyzer. The temperature adjustments were performed by utilizing indium as standard. A vacant container fixed similarly as the example was utilized as a kind of perspective. The whole examples were run at a filtering pace of 10 °C/min from 50-200 °C. DSC was performed and thermograms were compared and results were shown in Figure 1 and Figure 2. The exothermic peak of pure drug was obtained at 170 °C with a heat release of 599.57 MJ and polymer powder mixture was obtained at 169.37 °C with a heat release of 99.75 MJ.

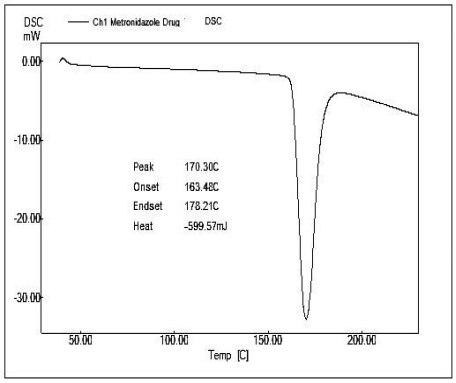


Figure 1 DSC of Metronidazole pure drug

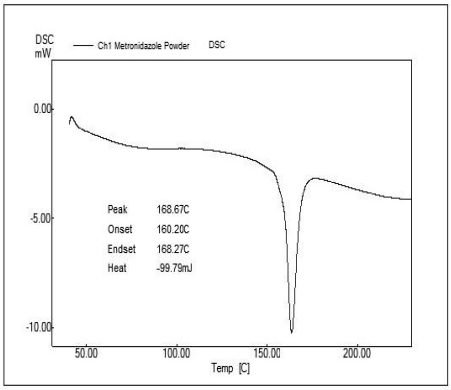
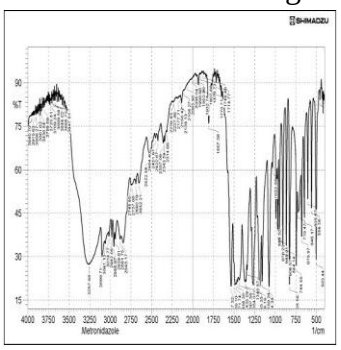
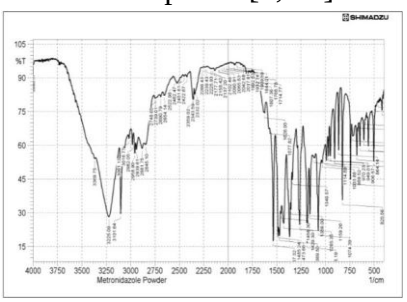


Figure 2. DSC of drug and Physical mixture

Fourier change Intra red investigation (FT-IR) estimation of unadulterated medication and medication with polymers stacked coasting definitions were acquired utilizing a model name BX Perkinelmer framework 200 FT-IR Spectrophotometer. The physical blend was set up on KBr press under water driven tension of 150 kg/cm2 at surrounding temperature. The spectra of different functional groups of pure drug and physical mixture are found to be within the spectral range which indicates that there are no interactions between the drug and the excipients as shown in the Figure 3 and Figure 4 respectively. The region of C-H aromatic is stretching 3100-3000 cm^{-1}, region of O-H, N-O stretching 1385-1345 $cm-^{1}$, and aliphatic C-H stretching at 3000-2850 cm^{-1} [7, 8]. All peaks have appeared in API and the optimized formulation F9 indicating no chemical interaction between MZ and excipients [9, 10].





Flow properties	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Angle of repose	24.14 ±0.02	24.45 ±0.01	24.66 ±0.04	25.66 ±0.04	26.72 ±0.012	2312 ±0.02	24.1 ±0.02	23.9 ±0.02	24.14 ±0.02
Bulk density	0.462 ±0.01	0.466 ±0.02	0.459 ±0.01	0.477 ±0.02	0.445 ±0.02	0.45 ±0.01	0.487 ±0.02	0.477 ±0.01	0.462 ±0.01
Tap density	0.554 ±0.01	0.561 ±0.02	0.556 ±0.01	0.558 ±0.01	0.53 ±0.01	0.56 ±0.01	0.578 ±0.02	0.548 ±0.02	0.554 ±0.01
Carr's index	16.61	16.93	17.4	14.51	16.037	19.64	15.74	12.95	16.61
Hauser's ratio	1.2	1.2	1.21	1.17	1.19	1.24	1.19	1.15	1.2
Bulkiness	2.16	2.14	2.17	2.09	2.24	2.22	2.05	2.09	2.16

Figure 3. FTIR of Pure drug

Figure 4. FTIR of drug and Physical mixture

3. 2. Pre-formulation studies

For completing the pre-definition contemplates, different parameters like point of rest, mass thickness, tapped thickness, and compressibility record and Hausner's ratio proportion, and so forth were resolved and the outcomes appeared in Table 2.

Table 2. Preformulation study of Metronidazole granule (F1-F9)

3.3 Post-compression studies

For completing the post pressure considers, different parameters like outward presentation, size, shape, thickness, weight variety, hardness, friability, and medication content, drifting property study, expanding the study, In Vitro Buoyancy Studies were resolved and the outcomes appeared in Table 3. For deciding the test based on the difference in weight, randomly some tablets were chosen from each group and independently gauged utilizing an electronic parity. The normal weight and rate deviation of 20 tablets were determined. Find out the deviation according to IP limit [11-13]. Hardness of tablets can be determined by Monsanto hardness tester. Tablet was placed in a hardness tester between two anvils. The force (kg) was gradually increases in order to get exact reading for breaking. The hardness tests were performed for each batch of prepared tablets in triplicate manner. The average hardness and standard deviation was determined. Hardness of ±5 kg/cm^2 and was results were reported [11]. For the Friability test, ten tablets haphazardly looked over the group, were cleaned with a material and weighed at first (W_0) and put in the Roche friability

Time(hrs)	Diameter (mm)	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Drug Content (%)	Swelling (%)	Floating Lag time (Sec)	Total Floating time (hr)

mechanical assembly that was turned at 25 rpm for 4 minutes. After unrests, the tablets were again deducted and reweighed (W) after fruition of 100 upsets. The watched worth ought not to be more than 1% at a separation of 6 creeps with every insurgency, worked for 100 unrests. The tablets were cleaned and rate friability was determined utilizing the accompanying equation [13-16].

$$\% \text{ Friability} = [W_0 - W/W_0] \times 100$$

Where W_0 is the initial weight of all tablets taken for the test, W is the weight after 100 revolutions of Tablets. For verifying the drug content, five tablets for each batch were taken and triturated. The powder equal to 100 mg were gauged and moved to 100 ml container and afterward, 0.01N HCl was included and it was then shaken for 5 minutes lastly 0.01N HCl was added to make the volume up to 100 ml and arrangement was then sonicated for 15 minutes and sifted through a Whatman channel paper. At long last, an answer was weakened reasonably and the absorbance of resultant arrangement was estimated spectrophotometrically at 203 nm utilizing UV/Visible spectrophotometer 0.01N HCl clear. For the skimming property study, time taken for the dose structure to develop on the outside of the disintegration medium is called lightness slack time (BLT). Span of time by which the measurements structure continually develops on surface of medium is called absolute coasting time (TF) and the time the tablets stayed drifting on the disintegration medium surface (gliding length) were reviewed outwardly with 0.1 N HCl, pH 1.2, at 37 ± 0.5 °C and the time taken for tablet to skim was noted down as BLT and the all-out time tablet skimmed was noted down as TFT. The outcomes were enrolled as a normal of three redundancies [17, 18]. By utilizing the Swelling study, the growing properties of details were controlled by setting the tablet frameworks in the disintegration test mechanical assembly, in 900 ml of 0.1 N HCl at 37± 0.5 ^{o}C. The tablets were expelled intermittently from the disintegration medium and in the wake of emptying free out of the water by blotching paper, these were estimated for weight gain. The percentage swelling can be calculated using the given formula [19],

$$\% \text{ Swelling} = \left\{ \frac{\text{Weight of tablet at time, t - Initial weight of tablet}}{\text{Initial weight of the tablets}} \right\} \times 100$$

Towards the end, In Vitro Buoyancy Studies, lightness test was performed utilizing the information from skimming slack time. The tablets were set in a 100 ml measuring utencil containing pH 1.2 supports. The time required for the tablet to ascend to the surface and buoy was resolved as skimming slack time. This test was performed on 3 tablets from each group [1].

Table 3. Post formulation study of Metronidazole blend granule (F1-F9)

Sl. No	Concentration (µg/ml)		Absorbance					
1	10.1 ±0.02	3.9 ±0.03	535 ±0.01	4.1 ±0.01	0.43±0.01	98.7±0.11	97.12±0.01	75	>7
2	10.0 ±0.03	4.0 ± 0.02	541 ±0.02	4.3±0.01	0.52±0.11	98.9±0.19	97.56±0.01	45	>8
3	10.2 ±0.01	4.2 ± 0.02	543 ±0.02	4.3±0.02	0.52±0.02	99.1±0.18	98.72±0.02	15	>12
4	10.0 ±0.01	4.1 ± 0.02	548 ±0.01	4.2 ±0.01	0.42±0.01	98,2±0.17	99.62±0.01	43	>12
5	10.2 ±0.01	4.0 ± 0.02	557 ±0.01	5.1± 0.01	0.56±0.01	98.2±0.16	96.67±0.10	40	>12
6	10.0 ±0.02	4.0 ± 0.01	550 ±0.01	5.0± 0.01	0.49±0.01	99.2±0.15	98.19±0.05	39	>12
7	10.1 ±0.02	3.9 ± 0.02	549 ±0.02	4.9± 0.01	0.51±0.01	99.4±0.14	98.22±0.02	31	>12
8	10.2 ±0.03	4.1 ± 0.01	552 ±0.02	5.2± 0.01	0.42±0.01	99.9±0.13	97.89±0.2	24	>12
9	10.2 ±0.01	4.1 ± 0.01	578 ±0.01	5.2± 0.02	0.42±0.01	98.7±0.12	98.78±0.1	20	>12
F1									
F2									
F3									
F4									
F5									
F6									
F7									
F8									
F9									

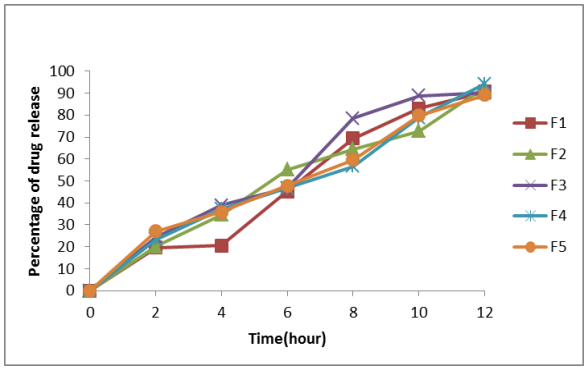
3.4 Preparation of Standard Curve of Metronidazole

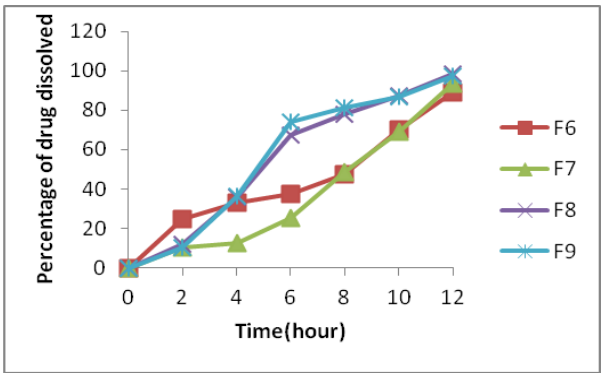
100 mg of MZ was decisively checked and separated in a 0.1 N HCl in a 100 ml volumetric container then the volume was made up to 100 ml with 0.1 N HCl. This was a basic stock course of action containing 1000 µg/ml. From this basic stock game plan, 1 ml was pipetted out and moved into a 100 ml volumetric cup and volume was made up to 100 ml with 0.1 N HCl which contained the centralization of 10 µg/ml (Second stock course of action). From the second stock course of action aliquots indistinguishable from 2-10 µg (2, 4, 6, 8, 10) were pipetted out into a movement of 10 ml volumetric container and volume was made up to 10 ml with 0.1 N HCl. The absorbance of these game plans was evaluated against the 0.1 N HCl as clear at 277 nm using a UV-Visible twofold bar spectrophotometer. By plotted a graph between a concentration in µg/ml on the X-axis and absorbance on Y-axis, shows a linear line obtained .By this linear line slope can be determined.

Table 4. Standard curve of Metronidazole

3.5 In-vitro Dissolution studies:

The disintegration of MZ skimming tablets were controlled by utilizing USP disintegration test contraption II (bin type) by utilizing 0.1 N HCl as disintegration medium at temperature of 37±0.5°C at 50 rpm 1 ml of the example was pulled back at an hour interim as long as 12 hours and supplanted with a similar volume of crisp disintegration medium. The pulled back examples were weakened to 10 ml utilizing 0.1 N HCl. The absorbance of these models was assessed at 276 nm using an UV Visible spectrophotometer [18-20]. The combined rate medicate discharge was plotted against time to decide the discharge profile and the outcomes were plotted in Figure 5.(a) and 5(b)





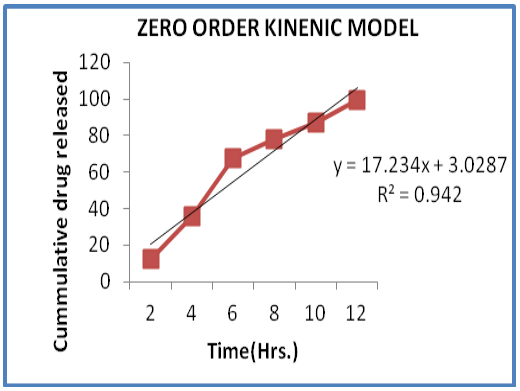
(a)

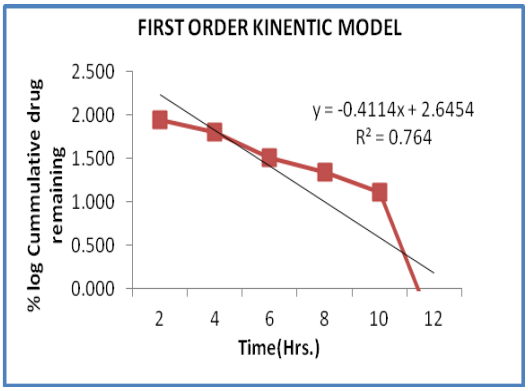
(b)

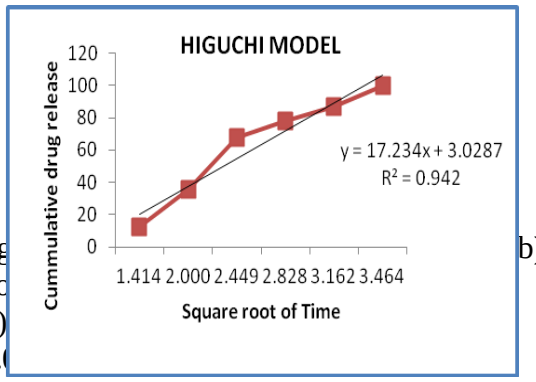
Figure 5 (a) Invitro dissolution of MZ tablets (F1-F5) (b) Invitro dissolution MZ tablets (F6-F9).

4. 0 Kinetic release Studies

The model that best fits the release data is picked subject to the association coefficient (R) regard in various models. The model with high R^2 regard was thought as the best qualified for the discharge information. The disintegration information was of a considerable number of groups were fitted to different dynamic models like zero request, first request, Higuchi and Korsmeyer-Peppas model to find out a precise system of medication discharge and the outcomes were plotted in figure 6.







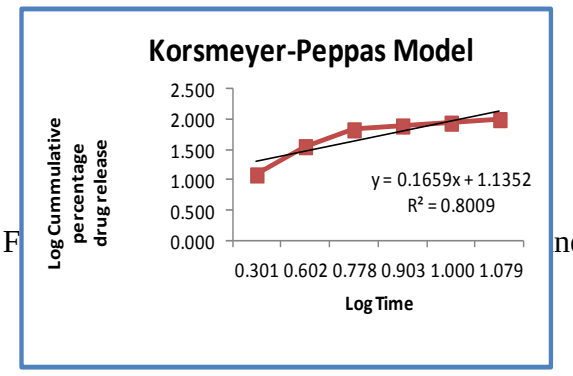


Fig b) F netic mo (d)

5.

The streamlined skimming tablet of MZ (F9) was set up by wet granulation technique by utilizing the medication, polymer (HPMC K4 M), Ethylcellulose) were expected to accomplish the improvement in tranquilizing discharge. There is no variety of medication

and physical blend by similarity thinks about. The stream properties of a physical blend are in the range. The expanding properties are basic in coasting and deciding the medication discharge rate and lesser skimming slack time and a gliding time could be accomplished by fluctuating the measure of HPMC K4 M and Xanthan gum. The upgraded definition (F9) shows a gliding length (>12hrs) having a controlled discharge trademark and the in vitro disintegration was completed by for 12 hrs (98.67 %). It was indicated zero-request dynamic discharge and best fit with the Higuchi model. So the coasting tablets of metronidazole defended adequate medication discharge for delayed activity and polymer is the key factor for enhancing the detailing.

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