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Research Article

DEVELOPMENT OF NON-EFFERVESCENT FORMULATIONS OF FAMOTIDINE HYDROCHLORIDE AND EVALUATION OF PREPARED FORMULATIONS

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ABSTRACT

The present study was to devlop drug delivery systems for gastroretintive capabilities with non effervescent floating drug delivery systems. Formulations were prepared with different poymers and checked for compatability using FTIR and DSC. And prepared formulations are evaluated for different parameters like weight variation drug content and various physico chemical properties. Based on the in vitro evaluation data formulation G6 was considered as optimized formulation which controlled drug release for upto 12 h. Since the value of n calculated for Korsmeyer- Peppas equation was found to be less than 1.0, it indicated that the drug release followed anomaloustransport. Stability studies were carried out for Famotidine formulations and obtained positive results.

KEYWORDS: *Famotidine, Gastroretintive, Invitro and Invivo parametrs, FDDS.*

INTRODUCTION

Gastroretentive drug delivery system:

Gastroretentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically gastroretentive systems swells following ingestion and is retained in the stomach for a number of hours, while it continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or unstable in the medium of distal intestinal regions. They can also be used beneficially in the local therapy of the stomach [1, 2].

Drugs that would benefit from GRDDS:

1) CNS drugs (for Parkinson disease, epilepsy, alzheimer and migraine).
2) Anti-viral products (for HIV, herpes and hepatitis) and certain antibiotics.
3) Anti-hypertension drugs.
4) Anti-diabetic agents for Type 2 diabetes.
5) Drugs for local treatment of GI infections and gastric enzyme replacement.

MATERIALS AND METHODS

List of materials:

Famotidine HCl obtained from zyduscadila healthcare india. Accurel®MP1000, Karaya Gum, Chitosan, Lactose, Magnesium Stearate is Gift samples from danmed Pharmaceuticals, Hyderabad.

Drug-excipient compatibility studies:

Fourier Transform infra red spectroscopy (FT-IR): In order to evaluate the integrity and compatibility of the drug in the formulation, drug-excipient interaction studies were performed. Pure drug and optimized formulations were analyzed by Fourier transform infra-red (FTIR) spectroscopy. FTIR spectra of pure drug and its formulations were obtained by a FT-IR Shimadzu 8400S (Japan) spectrophotometer using the KBr pellet method. The samples were scanned from 400 to 4,000 cm^{-1} wave number [3-7].

Differential scanning calorimetry (DSC): Differential scanning calorimetry was performed on pure sample of drug and its formulation. Calorimetric measurements were made with empty cell (high purity alpha alumina discs) as the reference. The dynamic scans were taken in nitrogen Atmosphere at the heating rate of 10 °C min-1. The energy was measured as Joules per kilocalorie [8, 9].

Preformulation parameters:

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia [10-13].

a. Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan\theta = h / r \quad \theta = \text{Angle of repose}$$

h = Height of the cone, r = Radius of the cone base

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Table No. 1: Angle of repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

b. Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully levelled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample; V_o = apparent volume of powder

c. Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where,Tap= Tapped Density; M = Weight of sample; V= Tapped volume of powder

d. Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density; Tap = Tapped Density

Table No. 2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation of Non-Effervescent floating tablets:

Floating tablets were prepared by direct compression method. All the ingredients were blended together to get homogenous mixture. Accurel® MP1000 as low density polypropylene foam powder, karaya gum as release retardant, chitosan as swellable polymer, lactose as diluent and magnesium stearate as lubricant were used. Powder mass was compressed into tablets using a 10 station rotary tablet punching press with 12 mm punch and die set. Each tablet contained 10 mg of Famotidine HCl. Composition of each tablet is given in table 3.

Table No. 3: Formulation chart of non-effervescent floating Famotidine HCl Tablets

Ingredients (mg)	G-1	G-2	G-3	G-4	G-5	G-6	G-7	G-8	G-9
Famotidine HCl	10	10	10	10	10	10	10	10	10
Accurel®MP1000	150	150	150	150	150	150	150	150	150
Karaya Gum	40	50	60	40	50	60	40	50	60
Chitosan	20	30	40	30	40	20	40	20	30
Lactose	76.5	56.5	36.5	66.5	46.5	56.5	56.5	66.5	46.5
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total Weight	300	300	300	300	300	300	300	300	300

Post compression parameters:

A. Weight variation test: 20 tablets from each formulation were randomly picked up and weighed individually and the average weight was calculated. The individual weights were then compared with the average weight. For the tablets of average weight 350 mg, the % deviation allowed is ± 5 %.

$$\% \text{ deviation} = \frac{\text{Average weight of tablet} - \text{individual tablet weight}}{\text{Average weight of tablet}} * 100$$

B. Friability: Ten tablets were weighed and placed in a Roche friabilator and rotated at 25 rpm for 4 min. The tablets were taken out, dedusted, and reweighed. The percentage friability of the tablets was calculated using the equation:

$$\% F = \{1-(W_t/W)\} \times 100$$

Where, % F is percentage friability, W is the initial weight of tablet and W_t is the final weight of tablets after revolutions.
Compressed tablets with a loss of less than 1 % are generally considered acceptable.

C. Hardness: The hardness of core tablets was measured using Inweka hardness tester. A total of five tablets from each formulation were taken for the study and the average of the three is reported. It is expressed in kg.

D. Thickness and diameter: Thickness and diameter of the tablets were determined by using Mitutoyo micrometer screw gauge. The average of five tablets from each formulation was taken. It is expressed in mm.

E. Uniformity of drug content: Drug content uniformity was determined by randomly selecting 5 tablets were powdered. The quantity equivalent to single dose of the drug was dissolved in HCl buffer solution, pH 1.2 for 5 hours with occasional shaking and diluted to 100 ml with buffer. After filtration to remove insoluble residue, 1 ml of the filtrate was diluted to 10 ml with the buffer. The absorbance was measured at the required λ_{max} using a UV visible spectrophotometer. The experiments were carried out in triplicate for all formulations and average values were recorded.

The drug content was calculated using the following equation:

$$\% \text{ Drug content} = \text{conc. } (\mu g/ml) \times \text{Dilution factor} \times 100 / 50$$

G. In vitro floating studies: The in vitro buoyancy was characterized by floating lag time and total floating time. The test was performed using a USP dissolution apparatus type-II (basket) using 900 ml of 0.1 N HCl buffer solution at 100 rpm at 37 ± 0.5°C. The time required for the formulation to rise to the surface of the dissolution medium and the duration for which the formulation constantly floated on the dissolution medium were noted as floating lag time and total time, respectively.

H. Water uptake studies: The swelling of the polymers was measured by their ability to absorb water and swell. The water uptake study of the tablet was done using a USP dissolution apparatus type-II (basket) in 900 ml of pH 1.2 Hydrochloric acid buffer at 100 rpm. The medium was maintained at 37 ± 0.5°C throughout the study. At regular time intervals, the tablets were withdrawn, blotted to remove excess water, and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake (WU) as:

WU (%) =Weight of Swollen tablet- Initial weight of tablet X 100 Initial weight of tablet

% Drug entrapment efficiency = Calculated drug concentration × 100 Theoretical drug concentration

I. Invitro drug release: The dissolution conditions used for studying the drug release from the effervescent floating tablets of Famotidine HCl.

Apparatus	:	Dissolution test apparatus (USP XXIII)
Method	:	USP type 2 apparatus (paddle method)
Dissolution medium	:	0.1N HCl
Volume	:	900 ml
Temperature	:	37 + 0.5 °C
Speed	:	50 rpm
λ_{max}	:	265 nm

Procedure:

The *invitro* dissolution studies were performed for the formulated non efferevescent floating tablets of Famotidine HCl over a period of 12 hours, using USP dissolution test apparatus 2 (paddle method) at 50 rpm, [Electro lab , TDT – 082].A minimum of 3 tablets per each batch was tested. The dissolution medium consists of 900 ml of 0.1 N HCl and temp was maintained at 37 + 0.5 °C. The tablets were placed inside the dissolution vessel. An aliquot (5ml) of sample was withdrawn at specific time intervals of 30, 60, 120, 180, 240, 360, 480, 600 and 720 minutes. The volume of dissolution fluid adjusted to by replacing 5ml of dissolution medium after each sampling. Each sample was analyzed at 265 nm using double beam UV and Visible Spectrophotometer against reagent blank. The drug concentration was calculated using standard calibration curve.

RESULTS AND DISCUSSIONS

Fourier Transform Infrared spectroscopy (FT-IR):

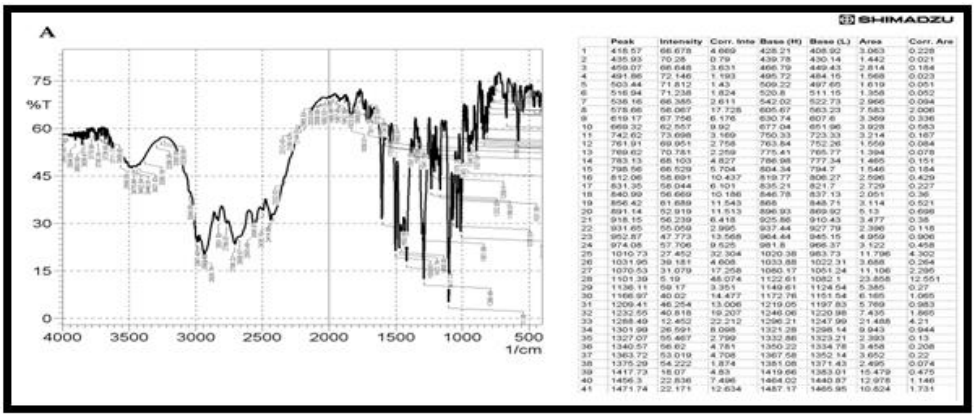

Fig. 1: Model drug Famotidine HCl

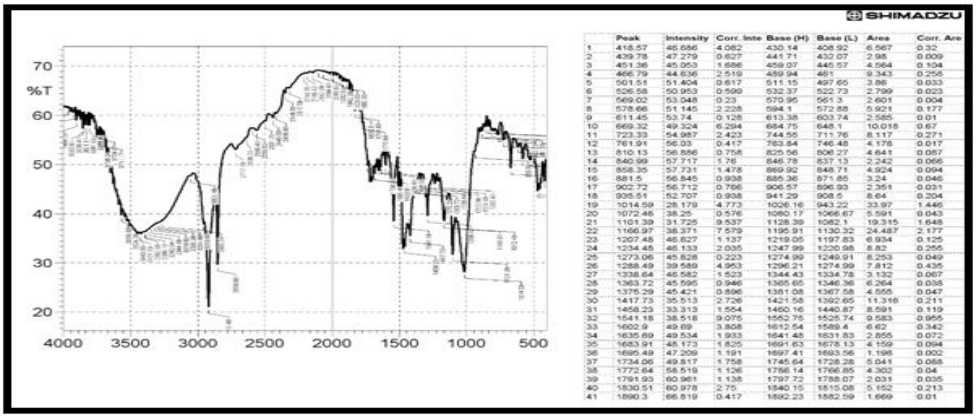

Fig. 2: FT-IR spectra of Famotidine HCl& its floating tablet formulation G6

Differential scanning calorimetric study (DSC):

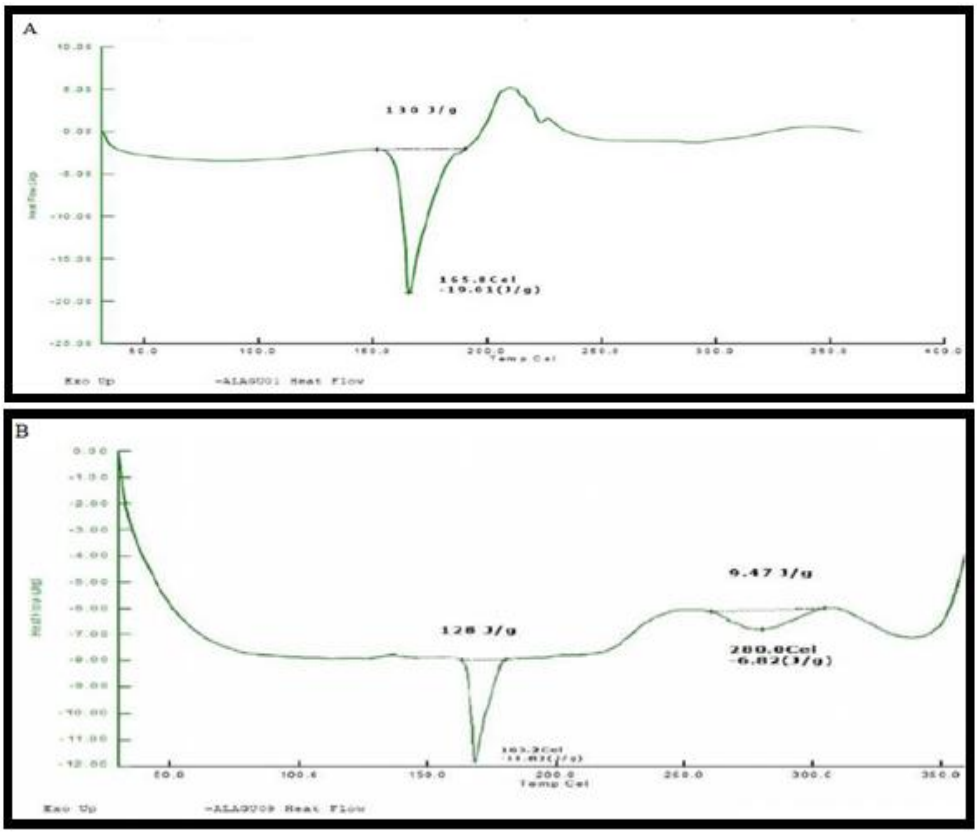

Fig. 3: DSC Thermograms of (A) Pure drug, (B) Drug +Polymer mix

Table No. 4: Pre compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
G1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
G2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
G3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
G4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
G5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
G6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
G7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
G8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
G9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Table No. 5: Physical properties of non-effervescent floating tablets of Famotidine HCl

Formulations	Diameter (mm)	Thickness (mm)	Friability (%)	Density (g/cm3)	Hardness (kg/cm2)	Weight variation (mg)	Drug content	Duration of buoyancy (hrs)
G1	12±0.04	2.86±0.08	0.45±0.07	0.881±0.06	4.56±0.04	299±0.06	99.01±0.01	>120.02
G2	12±0.02	2.89±0.04	0.68±0.06	0.885±0.07	4.35±0.06	302±0.04	99.05±0.02	>12
G3	12±0.06	3.12±0.02	0.78±0.04	0.882±0.06	4.95±0.08	301±0.02	99.65±0.04	>12
G4	12±0.08	2.87±0.07	0.59±0.02	0.883±0.04	4.85±0.02	300±0.04	99.35±0.06	>12
G5	12±0.07	2.93±0.06	0.65±0.01	0.884±0.02	4.59±0.04	299±0.06	99.48±0.08	>12
G6	12±0.06	2.65±0.01	0.37±0.02	0.881±0.04	4.68±0.02	298±0.04	99.48±0.02	>12
G7	12±0.01	2.78±0.02	0.48±0.04	0.882±0.06	4.62±0.08	297±0.02	98.65±0.04	>12
G8	12±0.07	3.15±0.07	0.42±0.02	0.881±0.04	4.84±0.02	300±0.04	99.47±0.02	>12
G9	12±0.09	3.45±0.06	0.36±0.07	0.882±0.02	4.68±0.04	299±0.07	99.65±0.07	>12

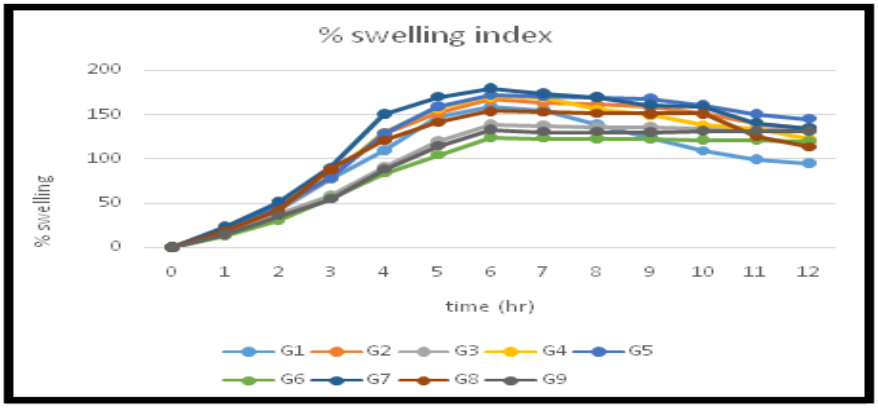

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Fig. 4: Swelling profile of floating tablet formulations in pH 1.2 HCl buffer

***In vitro* drug release studies:**

Table No. 6: *In vitro* release data of Famotidine HCl from Non Effervescent floating tablet formulations

Time (hr)	Cumulative percentage drug released (mean SD*)								
	G1	G2	G3	G4	G5	G6	G7	G8	G9
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
0.5	4.56±0.19	8.92±0.05	4.38±0.10	4.08±0.01	3.71±0.06	3.74±0.01	4.24±0.04	9.06±0.04	4.59±0.07
1	10.00±0.06	13.89±0.03	10.25±0.01	10.24±0.03	10.35±0.06	11.94±3.04	10.35±0.06	13.81±0.05	10.33±0.06
2	14.99±0.05	36.19±0.55	15.50±0.01	14.41±0.04	14.41±0.03	14.33±0.04	14.37±0.04	37.64±0.17	15.74±0.18
3	31.10±0.29	39.30±0.36	34.37±0.88	33.37±0.45	33.03±0.51	33.22±0.20	35.57±0.40	40.25±0.10	35.53±0.36
4	48.18±1.12	52.88±0.21	42.19±0.11	43.67±0.36	37.83±0.26	38.02±0.27	45.36±0.30	53.67±0.40	43.48±017
5	58.68±0.31	74.17±0.18	55.86±0.92	51.53±0.46	45.80±0.95	49.34±0.12	52.44±0.80	74.85±0.82	59.19±3.21
6	56.57±0.36	77.34±0.36	67.38±0.19	65.30±0.37	59.39±0.61	57.03±0.20	66.85±0.77	79.35±0.47	70.50±1.03
7	74.43±0.84	88.10±0.47	80.28±1.76	73.85±0.44	65.69±1.01	66.19±0.81	76.23±0.88	89.78±0.27	83.38±1.04
8	87.87±0.23	89.67±0.42	84.66±1.77	84.86±0.54	71.42±0.80	68.74±0.34	86.22±1.41	91.90±0.81	86.12±0.37
9	98.05±0.56	91.68±0.22	88.97±1.62	98.34±0.18	90.00±0.21	76.05±0.93	99.67±0.37	97.15±2.41	89.12±1.45
10	-	99.10±0.12	95.77±1.82	-	99.50±0.13	78.41±0.49	-	98.41±0.42	91.10±0.85
11	-	-	99.25±0.04	-	-	86.44±0.30	-	-	99.15±0.05
12	-	-	-	-	-	99.35±0.35	-	-	-

Standard deviation, n=3

Table No. 7: Stability studies for optimised formulation (G6) for drug release

S. No.	Optimised formulation (G6)duration	25⁰C(75%RH)	37⁰C(75%RH)
1	**1 MONTH**	99.12 ± 0.02	98.02 ± 0.85
2	**2 MONTH**	98.48 ± 0.15	98.20 ± 0.54
3	**3MONTH**	98.03 ± 0.75	98.00 ± 0.17

By observing the stability studies it is concluded that the optimised formulation is stable through the entire period of 3 months and the drug release profile is also intact throughout the time being.

Table No. 8: Kinetic data of optimized formulation

Cumulative (%) release q(g6)	Time (t)	root (t)	Log (%) release	log (t)	log (%) remain
0	0	0	0	0	2.000
3.7	0.5	0.000	0.568	0	1.984
11.94	1	0.707	1.077	-0.301	1.945
14.33	2	1.000	1.156	0.000	1.933
33.22	3	1.414	1.521	0.301	1.825
38.02	4	1.732	1.580	0.477	1.792
49.34	5	2.000	1.693	0.602	1.705
57.03	6	2.236	1.756	0.699	1.633
66.19	7	2.449	1.821	0.778	1.529
68.74	8	2.646	1.837	0.845	1.495
76.05	9	2.828	1.881	0.903	1.379
78.41	10	3.000	1.894	0.954	1.334
86.44	11	3.162	1.937	1.000	1.132
99.35	12	3.317	1.997	1.041	-0.187

CONCLUSION

The physical properties of tablets were found to be within Pharmacopoeial limits. Density of tablets was found to be less than that of gastric fluid (< 1.0 g/cm^3) indicating that the tablet floated in gastric fluid. The tablets floated immediately with floating lag time zero and remained buoyant for more than 12 hrs. Upon absorption of the gastric fluid the tablets got swollen and their size increased. Complete swelling was achieved by the end of 6h. From the FT-IR and DSC spectra, it was observed that characteristic peaks appeared with minor differences for both the drug and the formulation. Hence, it was confirmed that no chemical interaction has took place between the drug and the polymers used. Based on the *in vitro* evaluation data formulation G6 was considered as optimized formulation which controlled drug release for upto 12 h. Since the value of n calculated for Korsmeyer- Peppas equation was found to be less than 1.0, it indicated that the drug release followed anomalous transport.

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