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Development and Characterization of Gastroretentive Drug Delivery System of Hydrochlorothiazide

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Abstract The objective of the study was to develop an optimized gastro retentive drug delivery system of Hydrochlorothiazide. The tablets were formulated by direct compression using HPMC K15M, HPMC K4M, Carbopol 934P and PVP K30. Sodium bicarbonate was used as the gas generating agent to reduce the floating lag time. The drug-polymer interaction was evaluated by Fourier Transform Infrared Spectroscopy (FTIR) and DSC study. The FTIR and DSC study indicated the lack of drug-polymer interaction. The formulated tablets were evaluated for hardness, weight variation, thickness, floating capacity, swelling index, drug content, *in vitro* dissolution study. Formulations were following nonfickian (anamalous) diffusion as the release mechanism from all the floating tablets prepared with various polymers.

Keywords Gastroretentive drug delivery system, Anti-hypertensive, Hydrochlorothiazide, HPMC K15M, HPMC K4M, Carbopol 934P, PVP K30

INTRODUCTION

Various forms of oral controlled release formulations have been developed to increase the therapeutic effectiveness and patient compliance of medications with limited half-lives [1-5]. These formulas are made to produce medications at a predetermined pace under a variety of conditions and over varying lengths of time [6-7]. Over the last few decades, a variety of methodologies have been followed to increase the retention of an oral dosage form in the upper part of stomach, e.g. floating drug delivery system (FDDS) expanding and swelling systems, high density system modified shape system, bioadhesive system and other delayed gastric empting device [8-12]. Exhaustive studies on controlled drug delivery system described that, FDDS is a gastroretentive dosage from (GRDF), that is considerably relaxed and rational method to delay the gastric residence time (GRT) in achieving an optimum drug bioavailability [13-16]. In the case of floating drug delivery systems based on pathways, two separate technologies are

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attempted to unleash drug: effervescent FDDS and non-effervescent FDDS [17-18]. When a drug enters the stomach through an effervescent mechanism, CO_2 is released by the acidity of the gastric material and entrapped in a jellified hydro colloid [19-20]. As the liberated gas is expelled from the dosage material, it produces pores into which water can quickly flow and aids in the wetting of the polymers by maintaining the drug release. Non-effervescent floating dosage formulations, on the other hand, are created with gel-forming or swellable cellulose hydrocolloids, polysaccharides, and matrix-forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystryrene [21-24].

Hydrochlorothiazide is a bezothiadiazine diuretic that has shown to be effective in the treatment of mild to severe hypertension [25-26]. Hydrochlorothiazide controls hypertension in part by inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na^+-Cl^- symporter [25-28]. It is a poorly water soluble drug having oral bioavailability is 70% and plasma half-life of 6-8 hours. It is absorbed mostly from the upper portion of the duodenum, and if it crosses this absorption site for whatever reason, no absorption occurs [29-33].

The aim of this research was to create an improved Gastroretentive Drug Delivery System (GRDDS) using Hydrochlorothiazide as a model drug in order to increase absorption and oral bioavailability. The effect of polymer (HPMC K15M, HPMC K4M, Carbopol 934P, and PVP K30) on drug release activity and buoyancy properties of prepared formulations was investigated in the current research.

MATERIAL AND METHODS

All the chemicals were procured from Department of Pharmaceutics, BN College of Pharmacy and were of analytical grade.

Assay of hydrochlorothiazide

20 mg of hydrochlorothiazide was accurately weighed and was dissolved in 50 ml of 0.1 M sodium hydroxide. The solution was shaken for 20 minutes and diluted to 100 ml with 0.1 M sodium hydroxide solution. The solution was filtered and 5 ml of filtrate was taken in 100 ml of volumetric flask and volume was make up to the mark. Then absorbance of the solution was

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noted at wavelength at 273 nm. The concentration of hydrochlorothiazide was determined taking 520 as the specific absorbance [34].

Infra Red Spectroscopy

The IR analysis of the sample was carried out for qualitative compound identification. Fourier transform-infrared spectroscopy (FTIR) was performed by using ATR sampling technique on Tensor bruker. The sample scanned at wavelength 4000 – 667 cm^{-1} [34].

Preparation of hydrochlorothiazide tablets

All the polymers and drug were passed through sieve no 18 separately. Accurately weighted quantity of drug, polymer and excipients were thoroughly mixed in a glass motor in the presence of chloroform to form wet mass. The chloroform was evaporated at room temperature. The wet mass was then passed through the sieve no 22 to get granules. The granules were dried in hot air oven at 45°C. The dried granules were then mixed properly with magnesium stearate and talc [35]. The granules was then punched with the help of 10 station rotatory automatic tablet punching machine to get desired hardness, shape and size [35].

Table 1: Composition of Tablet of Hydrochlorothiazide

Hydrochlorothiazide (mg)	50	50	50	50	50	50	50	50
HPMC K15M (mg)	80	100	120	140	---	---	---	---
HPMC K4M (mg)	---	---	---	---	80	100	120	140
Carbopol 934P (mg)	100	80	60	40	100	80	60	40
PVP K30 (mg)	20	20	20	20	20	20	20	20
Sodium bicarbonate (mg)	40	40	40	40	40	40	40	40
MCC (mg)	80	80	80	80	80	80	80	80
Magnesium stearate (mg)	10	10	10	10	10	10	10	10
Talc (mg)	5	5	5	5	5	5	5	5
Citric acid (mg)	15	15	15	15	15	15	15	15
Total weight (mg)	400	400	400	400	400	400	400	400

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Evaluation Hydrochlorothiazide tablets

Pre-compression parameters

Tablets were prepared by wet granulation methods. Prepared granule was subjected to various characterization viz. angle of repose, bulk density, tapped density, compressibility index and Hausners ratio [34].

Angle of Repose

Angle of Repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula [36-37].

$$\tan\theta = \frac{h}{r}$$

Bulk Density

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk density was calculated using the formula

$$Bulk\ density = \frac{M}{V_b}$$

Whereas, M is the weight of the powder and V_b is the bulk volume of powder [36-37].

Tapped Density

The measuring cylinder containing a known mass of blend was tapped for a 100 times using density apparatus. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the formula [34-37]

$$Tapped\ density = \frac{M}{V_t}$$

Hausner ratio

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Compressibility Index

$$Compressibility\ Index = \frac{Tapped\ density\ - Bulk\ density}{Tapped\ density}$$

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DSC study

The possibility of drug–excipient interaction was investigated by differential scanning calorimetry. The DSC thermograms of pure drug, Hydrochlorothiazide, and formulation were recorded. The DSC analysis was carried out over 50-250°C at 5°C/ min., using duplicate samples of 5 mg in crimped aluminum pans. Indium samples were used to calibrate the DSC instruments [34-37].

Drug Polymer incompatibility studies

Physical mixtures of the formulation (1:1) was prepared and scanned using ATR sampling technique. Similarly, the IR spectra of Hydrochlorothiazide was also recorded. Physical appearance of the samples and appearance /disappearance of peaks in the spectra were observed to assess any possible physical and chemical interactions [34-37].

Determination of λ_{max} of hydrochlorothiazide

A standard solution of hydrochlorothiazide having a conc. of 0.01 mg/ml was prepared by dissolving hydrochlorothiazide in 1/10 N HCl. This solution was scanned in UV Visible spectrophotometer in the wavelength range of 200 – 400nm [38].

Calibration curve of hydrochlorothiazide

An accurately weighed amount of hydrochlorothiazide corresponding to 100 mg was dissolved in a small amount of 0.1 N HCl in 100 ml volumetric flask and volume made up to 100 ml with the same 0.1 N HCl. Further 10 ml of prepared solution was made up to 100 ml with 0.1 N HCl. From this stock's solution, 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml and 10 ml were withdrawn and diluted up to 10 ml with the 0.1 N HCl in 10ml volumetric flask to get concentration of 1 µg, 2 µg, 3 µg, 4 µg, 5 µg, 6 µg, 7 µg, 8 µg, 9 µg and 10 µg respectively. The optical density of every solution was calculated by UV-Visible Spectrophotometer at 272 nm, using 0.1 N HCl as blank [38].

Hardness

Randomly sampled five tablets from each batch of formulations were used for the determination of hardness with the help of Monsanto type hardness tester. The sample mean and standard deviation were reported for each batch [39].

Weight Variation

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Ten tablets selected at a random were weighed accurately and the average weights of the tablets were calculated. Then the deviation of individual weight from the average weight and the standard deviation were calculated [40].

Thickness

The individual crown-to-crown thicknesses of ten tablets were determined using screw gauge micrometer for each batch. The sample mean and standard deviation of each tablet were calculated [41].

Measurement of Floating Capacity

Three individual tablets were put in individual flask containing 400ml of 0.1 (N) HCl solutions. Then the time in min for each tablet to go from the bottom to the top of the flask (floating lag time) and the timetables constantly float on the water surface (duration of floating) were measured. The sample mean and standard deviation were calculated [42].

Swelling Index

Hydrochlorothiazide tablets were weighed individually (W_0) and placed in 900ml of dissolution medium (0.1 N HCl). The temperature was maintained at 37°C. At regular intervals, the samples were removed using a small basket and swollen weight (W_t) of each tablet was determined at predefined time intervals. The swelling index was calculated by the following equation [43]

$$Swelling\ Index = \frac{W_t - W_0}{W_0} \times 100$$

Where W_0 is the initial weight of tablet, and W_t is the weight of tablet at time t [43]

Drug Content

Three tablets from each batch was selected randomly and transfer to a 100ml volumetric flask, and the flask were filled with distilled water and 0.1(N) HCl respectively, kept it for 48hr. Then, 1ml from each of the volumetric flask was transferred to the test tubes. Sample was then filtered, suitably diluted and analyzed spectrometrically at 272 nm [38, 43].

***In vitro* Dissolution**

USP-II type dissolution apparatus (paddle type) was used to study the release characteristic of floating systems. The release study was performed at 50 rpm in 900ml-distilled water and 0.1(N) HCl. 1ml of sample were withdrawn at a predetermined intervals and the volume of dissolution medium was maintained by adding the same volume of fresh dissolution medium. The absorbance of withdrawn sample was measured spectrometrically with suitable dilution and the

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corresponding concentrations were determined from the respective calibration curve. All the studies were performed in triplicate, and the temperature was maintained at 37 ± 0.5°C throughout the studies [35-37].

RESULTS AND DISCUSSION

Percentage purity of hydrochlorothiazide was performed by UV spectrophotometry and the drug was found to be 98.2 % pure.

The IR analysis of the sample was carried out for qualitative compound identification. Infrared study was performed by using ATR sampling technique on Tensor bruker. The sample scanned at wavelength 4000 – 667 cm^{-1}.

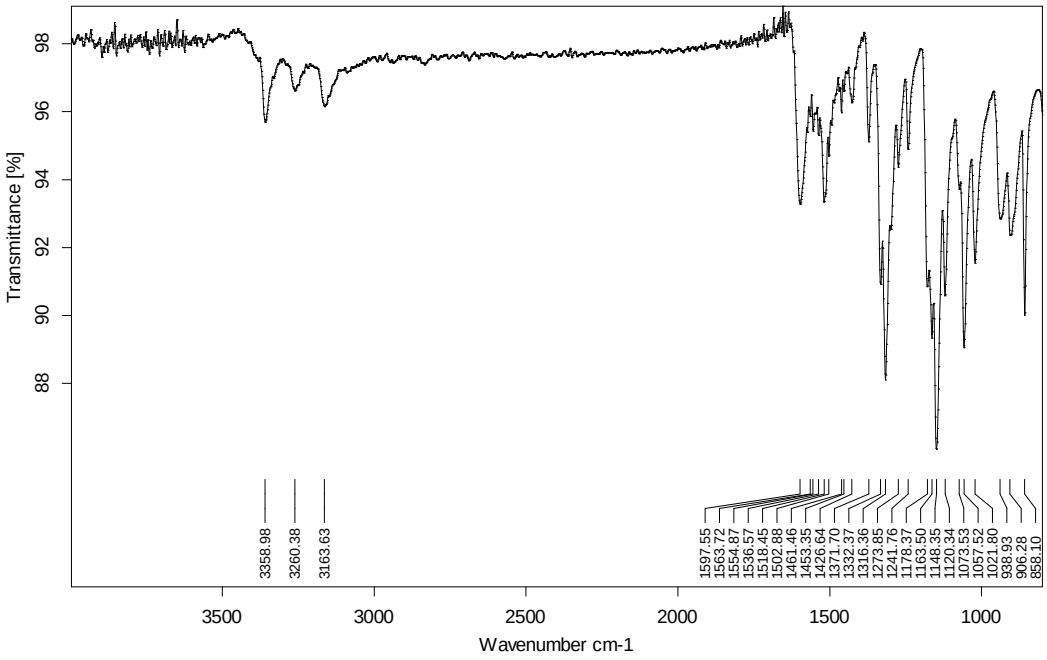

Figure 1: IR spectra of pure hydrochlorothiazide

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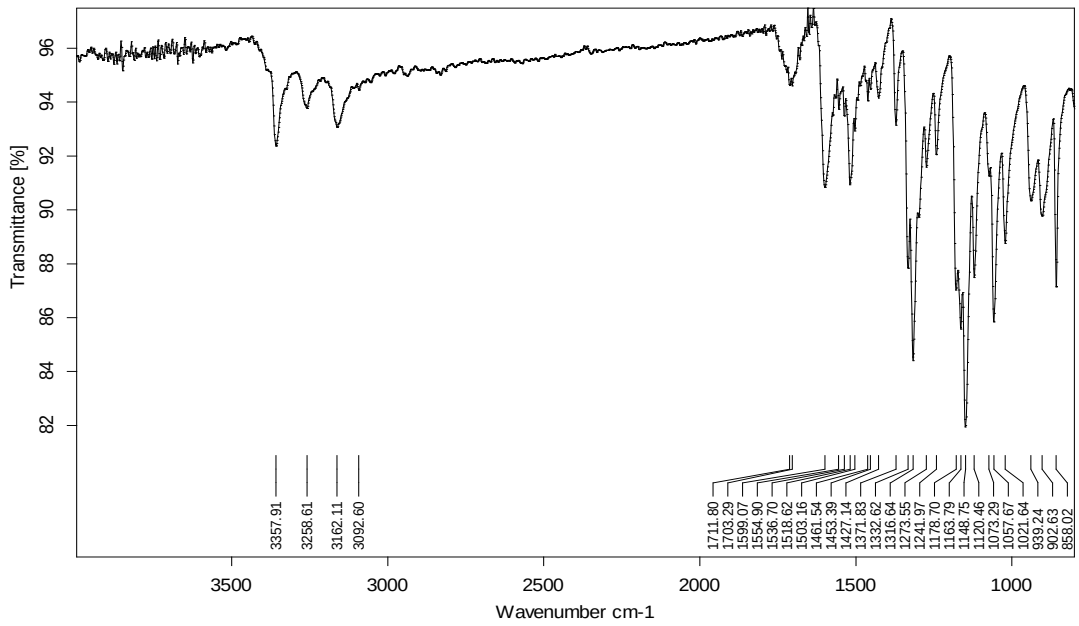

Figure 2: IR spectra of mixture of hydrochlorothiazide and excipients

Table 2: IR spectra of pure hydrochlorothiazide

Wave number (cm^{-1})	**Interaction**
3358.98	NH stretch
3260.38	SO_2–NH_2
1597.55	C=C stretch
1502.88	S=O stretch
1316.36, 1273.85	SO_2 stretch
1241.76	C-H bend

The characteristic peaks are reported for Hydrochlorothiazide (Figure 1) in table 2 respectively and these peaks were not affected and appeared in the spectra with excipients (Figure 2). Characteristic peaks of excipients were also retained and it is indicted that there is no incompatibility was found between Hydrochlorothiazide and excipients.

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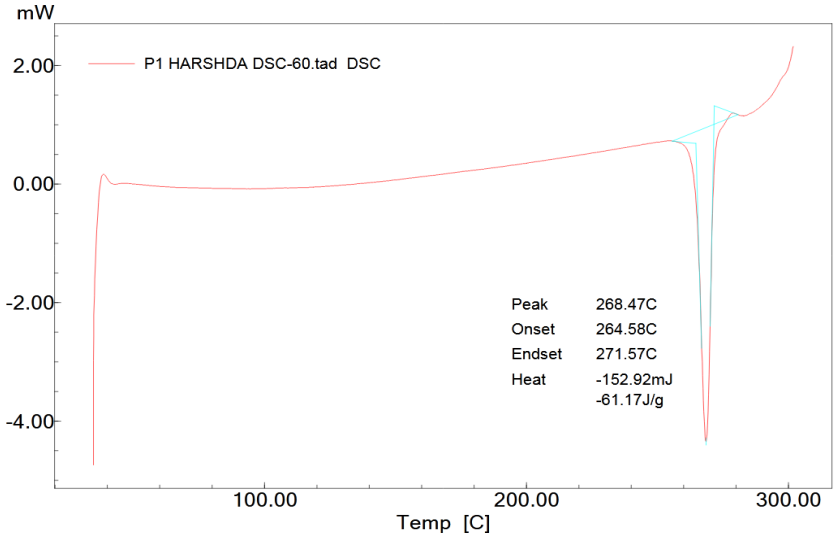

Figure 3: DSC of pure hydrochlorothiazide

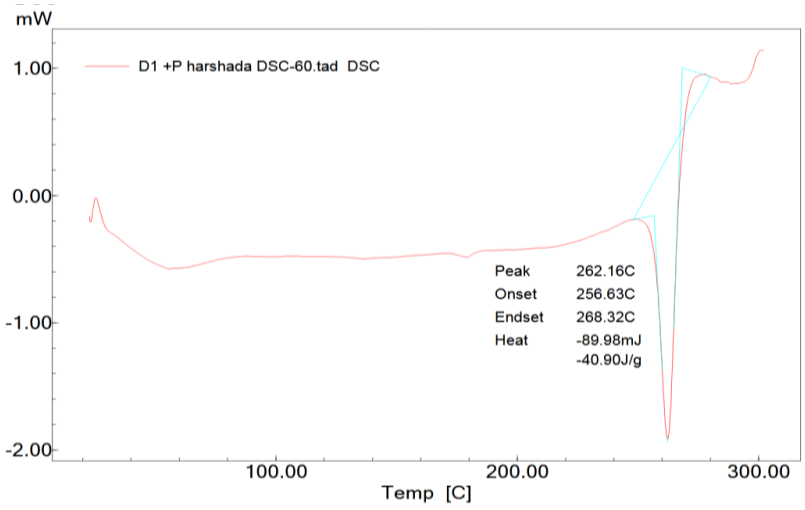

Figure 4: DSC of mixture of hydrochlorothiazide and excipients

Pure Hydrochlorothiazide displays sharp peaks corresponding to its melting point of pure drug suggested that there is no interaction between the Hydrochlorothiazide and polymers (Figure 3-4).

For preparing tablets of hydrochlorothiazide, quantities of Carbopol 934P was varied. In first four formulation, F1 – F4, HPMC K15M was added and its quantity was varied, whereas, in formulation, F5 – F8, HPMC K4M was added and its quantity was varied. Quantities of PVPK30 and MCC was common in all the formulation. For gas formation to make tablet float, $NaHCO_3$ and citric acid were added into the formulation.

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Tablets were made from blends by direct compression, dry granulation and wet granulation methods. 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 step and all these can affect the characteristics of blend produced. The characterization of mixed blend done for the flow property of powder that are bulk density, tapped density, Hausners ratio, Compressibility index, angle of repose [34-37].

Table 3: Result of evaluation of precompression parameters of hydrochlorothiazide tablets

Formulations	Angle of Repose	Bulk density (g/cm^3)	Tap density (g/cm^3)	Compresibility Index (%)	Hausner's Ratio
F1	23.21±0.34	0.39± 0.23	0.52 ±0.45	16.56	1.16
F2	22.11±0.46	0.37±0.41	0.58±0.34	17.67	1.19
F3	24.23±0.52	0.42±0.37	0.63±0.46	16.73	1.23
F4	25.42±0.38	0.47±0.46	0.58±0.54	18.44	1.27
F5	26.54±0.67	0.45±0.51	0.66±0.72	18.98	1.14
F6	25.63±0.44	0.43±0.48	0.72±0.32	19.11	1.25
F7	28.44±0.58	0.50±0.39	0.77±0.55	18.76	1.21
F8	27.37±0.62	0.51±0.56	0.78±0.51	17.57	1.17

Values are mean ± S.D.

Angle of repose for hydrochlorothiazide granules was found in the ranges from 22.11±0.46 – 28.44±0.58 and when compared with standard values available [194-195] shows that angle of repose of granules ranges from good to excellent resulting in flow property of good to excellent nature. Bulk density of hydrochlorothiazide granules found to be from 0.37±0.41 – 0.51±0.56 whereas tapped density was found to be from 0.52 ±0.45 – 0.78±0.51. Compressibility index and Hausner's ratio of hydrochlorothiazide granules were found to be 16.56–19.11 and 1.14–1.27

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respectively (Table 3). Compressibility index and Hausner's ratio of both the set of formulation indicates better to excellent flow properties.

Table 4: Properties of compressed tablets of hydrochlorothiazide

Batch code	Thickness* (mm)	Deviation in Weight Variation† (%)	Drug Content* (%)	Hardness* (kg/cm^2)	Friability† (%)
F1	4.36±0.04	2.89±0.18	94.39±0.03	6.5±0.26	0.54±0.02
F2	4.64±0.05	2.14±0.24	96.44±0.02	6.6±0.19	0.67±0.04
F3	4.33±0.03	1.98±0.21	97.29±0.02	6.6±0.22	0.48±0.07
F4	4.28±0.02	2.16±0.09	97.67±0.03	6.5±0.23	0.39±0.04
F5	4.76±0.04	2.23±0.19	97.58±0.05	6.8±0.25	0.67±0.03
F6	4.37±0.01	2.26±0.11	98.26±0.09	6.7±0.46	0.51±0.03
F7	4.87±0.03	2.87±0.34	97.67±0.04	6.5±0.27	0.28±0.07
F8	4.48±0.02	2.68±0.17	98.62±0.11	6.6±0.42	0.36±0.10

* All values are expressed as mean ± SE, n = 5

† All values are expressed as mean ± SE, n = 20

Thickness of hydrochlorothiazide tablet was found to be in the range of 4.28±0.02 to 4.87±0.03. Deviation of weight variation of hydrochlorothiazide was found to be in the range of 1.98±0.21 to 2.89±0.18. Weight variation was well within the limit as reported in United State Pharmacopoeia. Drug content was found to be from 94.39±0.03 to 98.62±0.11 which is well accepted. Hardness of tablet was found to be from 6.5±0.23 to 6.8±0.25 (Table 4). Friability was found to be from 0.28±0.07 to 0.67±0.04. Friability of all formulation is well within accepted limit of 1%.

Standard calibration curve of hydrochlorothiazide was prepared for determining the unknown concentration of drug. Standard calibration curve was prepared in 0.1 (N) hydrochloric acid (HCl) solution.

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Table 5: Absorbance by Hydrochlorothiazide drug at different concentration in 0.1 N HCl

Conc. (µg/ml)	Absorbance (272 nm)
1	0.019
2	0.034
3	0.048
4	0.065
5	0.087
6	0.102
7	0.114
8	0.126
9	0.146
10	0.178

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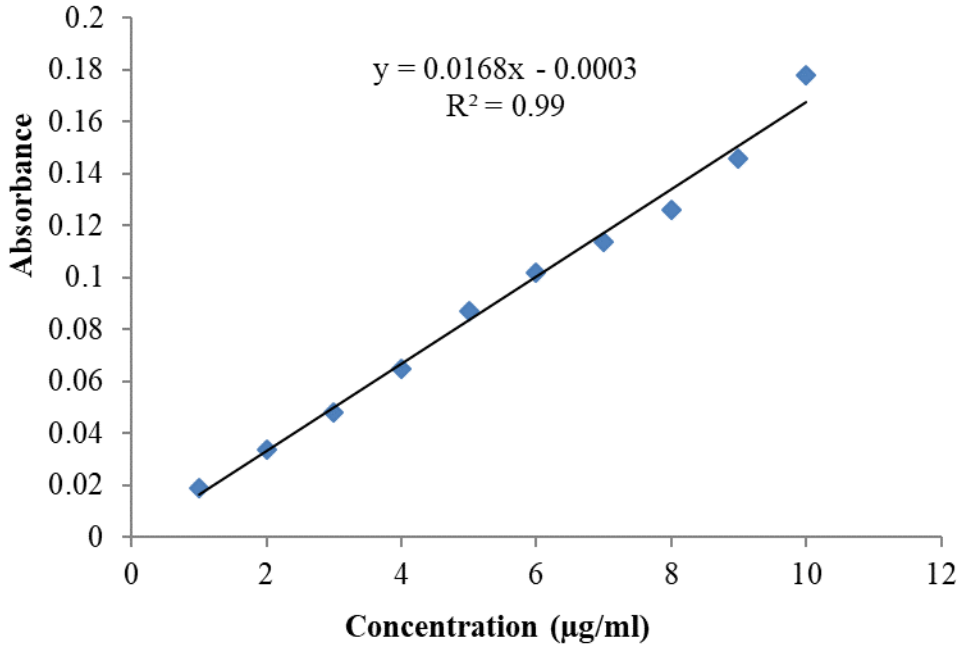

Figure 5: Calibration curve of Hydrochlorothiazide drug

Table 6: Result of Validation parameters of hydrochlorothiazide standard calibration curve

Parameters	**Drug**
Detection wavelength	272 nm
Linearity range	1-10 µg/ml
Slope	0.0168
Intercept	0.0003
Correlation coefficient	0.99
Regression equation	Y= 0.0168x - 0.0003

On engagement in 0.1 N HCl solution at 37±0.5 °C, all formulation of hydrochlorothiazide floating tablets floated immediately and remained buoyant up to 12 hours without disintegration. Sodium bicarbonate was added as a gas-generating agent which induced carbon dioxide in the

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presence of dissolution medium (0.1 N HCl). Floating characteristics of various matrix tablets formulated are given in Table 7. Hydrochlorothiazide tablets shows buoyancy lag time in the range of 25.4±0.22 to 41.7±0.51 seconds. This indicate that the tablets were taking very lesser time to initiate gas formation that enables floating of tablets. All the formulations were found to display short floating lag times in the presence of citric acid and sodium bicarbonate.

Table 7: Buoyancy Lag Time and total floating time of hydrochlorothiazide tablets

Formulations	Buoyancy lag time (sec)	Total Floating time (hr)
F1	41.7±0.51	>12
F2	37.2±0.64	>12
F3	33.5±0.92	>12
F4	28.1±0.17	>12
F5	38.2±0.43	>12
F6	32.6±0.29	>12
F7	29.1±0.38	>12
F8	25.4±0.22	>12

Values are mean ± S.D.

Table 8: Swelling index of hydrochlorothiazide tablets

Formulations	Swelling index (%)
F1	72.5±0.37
F2	78.9±0.82
F3	84.1±0.48
F4	93.5±0.27
F5	76.7±0.56
F6	85.6±0.63

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F7	96.3±0.37
F8	105.6±0.74

Values are mean ± S.D.

The swelling of the formulations of hydrochlorothiazide using polymers (carbopol 934p, HPMC K15M, HPMC K4M, PVP K30) were determined by water uptake of the tablet and represented in Table 8. Swelling index of formulations containing combination of HPMC K15 M and Carbopol 934P was found to be in the range of 72.5±0.37 to 93.5±0.27 whereas formulations containing combination of HPMC K4M with Carbopol 934P was found to be in the range of 76.7±0.56 to 105.6±0.74. It can be stated from the result obtained that the formulation with combination of HPMC K4M and carbopol 93P was showing more swelling capacity when compared to formulations containing combination of HPMC K15M and carbopol 934P.

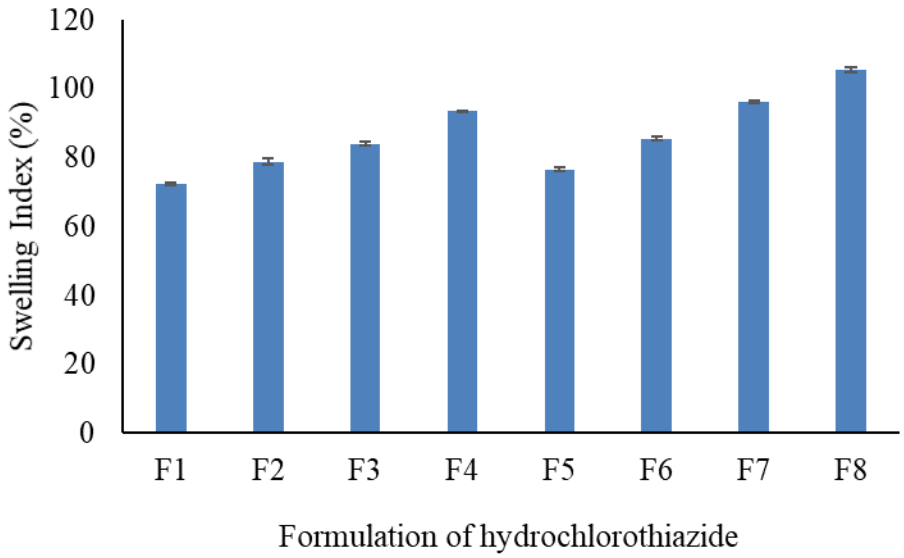

Figure 6: Swelling index of formulation of hydrochlorothiazide

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Table 9: Cumulative % Drug release of hydrochlorothiazide floating tablets

Time in hr	Cumulative percentage drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
1	28.42±0.67	23.63±0.39	16.31±0.47	29.27±0.51	21.37±0.16	26.39±0.86	28.38±0.27	21.66±0.53
2	44.31±0.25	34.35±0.85	22.38±0.11	43.36±0.48	29.84±0.49	39.76±0.14	38.22±0.49	30.49±0.36
3	62.15±0.21	47.51±0.49	32.44±0.52	54.72±0.38	44.53±0.27	46.58±0.61	47.41±0.87	39.93±0.73
4	76.52±0.76	53.82±0.32	39.55±0.86	68.55±0.74	51.33±0.18	51.92±0.48	56.39±0.56	46.38±0.13
5	82.34±0.94	61.32±0.71	42.61±0.92	74.33±0.21	57.49±0.36	58.28±0.18	63.47±0.28	52.73±0.76
6	91.71±0.31	71.48±0.58	53.18±0.37	81.34±0.83	68.38±0.82	69.39±0.58	73.51±0.11	60.27±0.45
7	99.59±0.53	80.23±0.33	60.56±0.26	90.45±0.47	73.43±0.31	77.88±0.71	79.78±0.73	69.92±0.29
8		88.34±0.28	67.23±0.71	99.18±0.42	79.67±0.64	80.38±0.32	85.38±0.25	75.59±0.12
9		98.11±0.61	74.46±0.45		87.24±0.52	88.78±0.63	90.62±0.58	79.21±0.79
10			83.98±0.49		91.45±0.74	90.67±0.78	98.43±0.19	86.56±0.57
11			97.56±0.23		98.79±0.13	96.86±0.45		91.88±0.42
12								97.21±0.82

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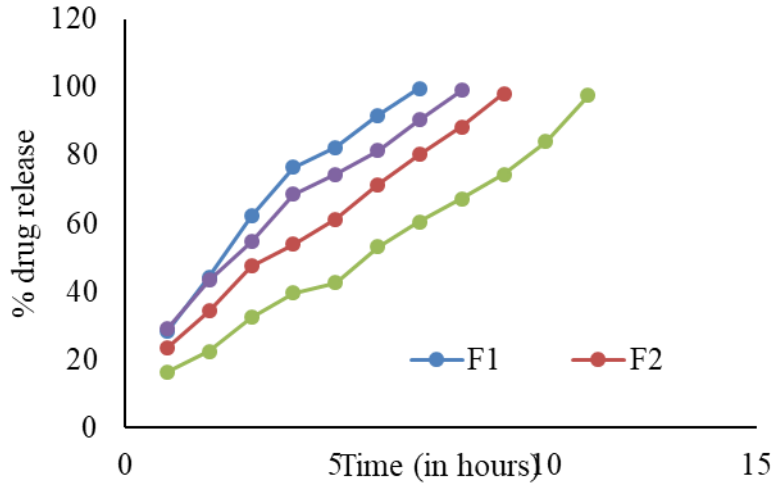

Figure 7: % Drug release of hydrochlorothiazide floating tablets, F1 – F4

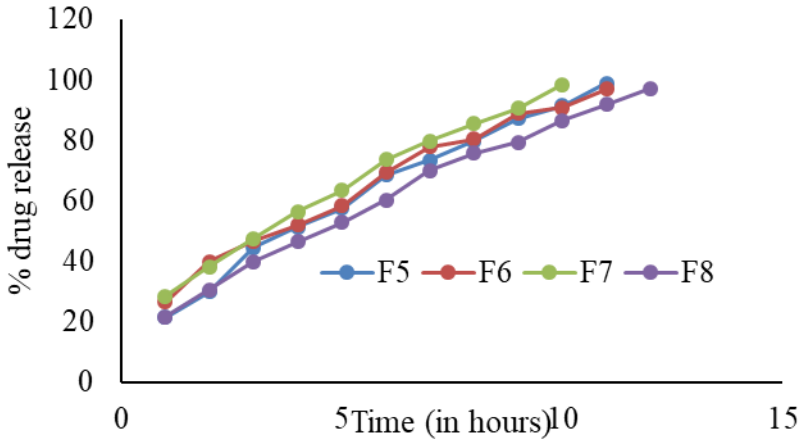

Figure 8: % Drug release of hydrochlorothiazide floating tablets, F5 – F8

Release of hydrochlorothiazide from formulated tables was studied in 1/10 N HCl. The release data is shown in Table 9.

Formulation F1, release drug till 7 hours only and could not sustain the release of drug beyond 7 hours where formulation F2, sustains the release of drug till 9 hours. However, formulation F3 could sustain the release of drug till 11 hours only. Formulation F4 can only sustain the release of drug till 8 hours. Formulation F5 and F6 could sustain the release of drug till 11 hours. Formulation F7 could sustain the drug till 10 hours. Formulation F8 was only a formulation that could sustain the release of drug till 12 hours.

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Table 10: Release kinetics of hydrochlorothiazide tablets

Formulation	Zero Order model		First order model		Higuchi model		Korsmeyer Peppas Equation	
F1	R^2	0.993	R^2	0.930	R^2	0.993	R^2	0.992
	K (mg/h^{-1})	11.732	K (hr^{-1})	0.420	K_H ($h^{-1/2}$)	43.956	n	0.447
F2	R^2	0.996	R^2	0.790	R^2	0.987	R^2	0.984
	K (mg/h^{-1})	9.050	K (hr^{-1})	0.374	K_H ($h^{-1/2}$)	36.843	n	0.493
F3	R^2	0.991	R^2	0.719	R^2	0.956	R^2	0.975
	K (mg/h^{-1})	7.746	K (hr^{-1})	0.259	K_H ($h^{-1/2}$)	33.838	n	0.617
F4	R^2	0.983	R^2	0.964	R^2	0.996	R^2	0.992
	K (mg/h^{-1})	9.648	K (hr^{-1})	0.314	K_H ($h^{-1/2}$)	37.857	n	0.421
F5	R^2	0.985	R^2	0.804	R^2	0.995	R^2	0.995
	K (mg/h^{-1})	7.584	K (hr^{-1})	0.327	K_H ($h^{-1/2}$)	33.910	n	0.508
F6	R^2	0.983	R^2	0.906	R^2	0.990	R^2	0.963
	K (mg/h^{-1})	6.901	K (hr^{-1})	0.276	K_H ($h^{-1/2}$)	30.811	n	0.412
F7	R^2	0.991	R^2	0.821	R^2	0.994	R^2	0.989
	K (mg/h^{-1})	7.681	K (hr^{-1})	0.343	K_H ($h^{-1/2}$)	32.877	n	0.438
F8	R^2	0.992	R^2	0.876	R^2	0.992	R^2	0.987
	K (mg/h^{-1})	6.826	K (hr^{-1})	0.257	K_H ($h^{-1/2}$)	31.506	n	0.497

The release data found after dissolution studies was fitted into different kinetic models viz. zero order kinetics, first order kinetics, Higuchi model and Krosmeyer Peppas equation model. The correlation coefficient (R^2) values in various models are given in Table 10.

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When the release data were analyzed as per zero and first order models, the 'R^2' values (Table 10) of zero order kinetics was in the range of 0.983 – 0.996 whereas R^2 values of first order kinetics was found to be in the range of 0.719 – 0.964. The R^2 values were relatively higher in zero order model with all the floating tablets formulated indicating that the drug release from all these tablets (F1 to F8) followed zero order kinetics. Values of zero order rate constant for formulation F1 – F8, ranges from, 6.826 – 11.732 whereas first release rate constant ranges from 0.257 – 0..

Release data of hydrochlorothiazide floating tablets obeyed Higuchi and Peppas equation models with R^2 values greater than 0.956. When cumulative percent drug release was plotted against square root of time, linear regressions with 'R^2' > 0.956 were observed with all the floating tablets prepared indicating that the drug release from all these tablets was diffusion controlled.

When the release data were analyzed as per Korsmeyer Peppas equation, the release exponent 'n' was found in the range 0.421 to 0.617. Formulation, F1, F4, F6 and F7 was following fickian drug release where formulation, F2, F3, F5 and F8 were following nonfickian (anamalous) diffusion as the release mechanism from all the floating tablets prepared with various polymers.

CONCLUSION

In the present work floating tablets of Hydrochlorothiazide were prepared by direct compression. The tablets were formulated by direct compression using HPMC K15M, HPMC K4M, Carbopol 934P and PVP K30. Sodium bicarbonate was used as the gas generating agent to reduce the floating lag time. The drug-polymer interaction was evaluated by Fourier Transform Infrared Spectroscopy (FTIR) and DSC study. The FTIR and DSC study indicated the lack of drug-polymer interaction. The formulated tablets were evaluated for hardness, weight variation, thickness, floating capacity, swelling index, drug content, *in vitro* dissolution study. In Hydrochlorothiazide tablet, formulation with combination of HPMC K4M and carbopol 93P was showing more swelling capacity when compared to formulations containing combination of HPMC K15M and carbopol 934P. Among all the formulations F2, F3, F5 and F8 were showing non ficikan drug release mechanism.

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REFERENCES

[1]. Chen, X., Wen, H., & Park, K. (2010). Challenges and new technologies of oral controlled release. Oral controlled release formulation design and drug delivery: Theory to Practice, 16, 257-277.

[2]. Thombre, A. G. (2005). Assessment of the feasibility of oral controlled release in an exploratory development setting. Drug discovery today, 10(17), 1159-1166.

[3]. Ummadi, S., Shravani, B., Rao, N. R., Reddy, M. S., & Sanjeev, B. (2013). Overview on controlled release dosage form. System, 7(8), 51-60.

[4]. Lee, P. I., & Li, J. X. (2010). Evolution of oral controlled release dosage forms. Oral Controlled Release Formulation Design and Drug Delivery, John Wiley & Sons, Inc., Hoboken, NJ, 21-31.

[5]. Flack, J. M., Novikov, S. V., & Ferrario, C. M. (1996). Benefits of adherence to anti-hypertensive drug therapy. European Heart Journal, 17(suppl_A), 16-20.

[6]. Kamaly, N., Yameen, B., Wu, J., & Farokhzad, O. C. (2016). Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. Chemical reviews, 116(4), 2602-2663.

[7]. Kumar, S., Jeet, K., & Baldi, A. (2015). Recent technological advancements in multiparticulate formulations: The smart drug delivery systems. Asian J Pharm, 9, S13-25.

[8]. Shah, S. H., Patel, J. K., & Patel, N. V. (2009). Stomach specific floating drug delivery system: A review. Int J Pharm Tech Res, 1(3), 623-33.

[9]. Dixit, N. (2011). Floating drug delivery system. Journal of current pharmaceutical research, 7(1), 6-20.

[10]. Patel, N., Nagesh, C., Chandrashekhar, S., Jinal, P., & Devdatt, J. (2012). Floating drug delivery system: an innovative acceptable approach in gastro retentive drug delivery. Asian J. Pharm. Res, 2(1), 07-18.

[11]. Shaha, S. H., Patel, J. K., Pundarikakshudu, K., & Patel, N. V. (2009). An overview of a gastro-retentive floating drug delivery system. Asian journal of pharmaceutical sciences, 4(1), 65-80.

[12]. Gopalakrishnan, S., & Chenthilnathan, A. (2011). Floating drug delivery systems: A Review. Journal of Pharmaceutical Science and Technology, 3(2), 548-554.

[13]. Kotreka, U., & Adeyeye, M. C. (2011). Gastroretentive floating drug-delivery systems: a critical review. Critical Reviews™ in Therapeutic Drug Carrier Systems, 28(1).

[14]. Sharma, N., Agarwal, D., Gupta, M. K., & Khinchi, M. (2011). A comprehensive review on floating drug delivery system. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2(2), 428-441.

[15]. Prabha, K., Sunil, S., & Kumar, A. V. (2013). Approaches to increase the gastric residence time: floating drug delivery systems-a review. Asian J Pharm Clin Res, 6(3), 1-9.

[16]. Kumar, M., & Kaushik, D. (2018). An overview on various approaches and recent patents on gastroretentive drug delivery systems. Recent patents on drug delivery & formulation, 12(2), 84-92.

[17]. Arunachalam, A., Karthikeyan, M., Konam, K., Prasad, H. P., Sethuraman, S., Ashutoshkumar, S., & Manidipa, S. (2011). Floating drug delivery systems: A review. Int. J. Res. Pharm. Sci, 2(1), 76-83.

[18]. Gupta, P., Gnanarajan, P. K., & Kothiyal, P. (2015). Floating drug delivery system: a review. International Journal of Pharma Research & Review, 4(8), 37-44.

[19]. Patel, S. G., & Siddaiah, M. (2018). Formulation and evaluation of effervescent tablets: a review. Journal of Drug Delivery and Therapeutics, 8(6), 296-303.

[20]. Singh, P., Chaudhari, V. K., Verma, P. K., Singh, A. K., & Yadav, V. K. (2015). Multiunit floating drug delivery system a significant tool for the treatment of peptic ulcer disease. International Journal of Pharmaceutical Sciences and Research, 6(4), 1351.

[21]. Varma, M. V., Kaushal, A. M., Garg, A., & Garg, S. (2004). Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. American Journal of drug delivery, 2(1), 43-57.

[22]. Makwana, A., Sameja, K., Parekh, H., & Pandya, Y. (2012). Advancements in controlled release gastroretentive drug delivery system: A review. Journal of Drug Delivery and Therapeutics, 2(3).

[23]. Ayalasomayajula, L. U., Navya, K., Earle, R. R., & Pravallika, A. A. (2020). Review on Non Effervescent Gastro Retentive Drug Delivery Systems-Microballons. Asian Journal of Pharmaceutical Research, 10(4), 312-318.

[24]. Rajak, P., Bhattacharya, A., Sharma, N., Kataki, M. S., & Rajkumari, A. (2011). Gastro-retentive floating drug delivery system-an approach in gastroretentive drug delivery. Int J Pharm Pharm Sci, 3(suppl 4), 9-16.

[25]. Burnier, M., Bakris, G., & Williams, B. (2019). Redefining diuretics use in hypertension: why select a thiazide-like diuretic?. Journal of hypertension, 37(8), 1574.

[26]. Ernst, M. E., & Moser, M. (2009). Use of diuretics in patients with hypertension. New England Journal of Medicine, 361(22), 2153-2164.

[27]. Flatman, P. W. (2007). Cotransporters, WNKs and hypertension: important leads from the study of monogenetic disorders of blood pressure regulation. Clinical science, 112(4), 203-216.

[28]. César, K. R., & Magaldi, A. J. (1999). Thiazide induces water absorption in the inner medullary collecting duct of normal and Brattleboro rats. American Journal of Physiology-Renal Physiology, 277(5), F756-F760.

[29]. Patel, R. B., Patel, U. R., Rogge, M. C., Selen, A., Welling, P. G., Shah, V. P., & Prasad, V. K. (1984). Bioavailability of hydrochlorothiazide from tablets and suspensions. Journal of pharmaceutical sciences, 73(3), 359-361.

[30]. Barbhaiya, R. H., Craig, W. A., Corrick-West, H. P., & Welling, P. G. (1982). Pharmacokinetics of hydrochlorothiazide in fasted and nonfasted subjects: a comparison of plasma level and urinary excretion methods. Journal of pharmaceutical sciences, 71(2), 245-248.

[31]. Beermann, B., Groschinsky-Grind, M., & Rosén, A. (1976). Absorption, metabolism, and excretion of hydrochlorothiazide. Clinical Pharmacology & Therapeutics, 19(5part1), 531-537.

[32]. Fuchs, M., Mallin, S. R., Irie, S., Hernando, L., & Moyer, J. H. (1960). A review of the pharmacology and clinical observations of hydrochlorothiazide. AMA Archives of Internal Medicine, 105(1), 39-50.

[33]. Simpson, H. W. (1979). Hydrochlorothiazide Diuresis in Healthy Man: Review of the Orcadian Mediation. Nephron, 23(2-3), 98-105.

[34]. Government of India, Ministry of Health. Pharmacopoeia of India: (the Indian Pharmacopoeia). Delhi: Manager of Publications, 2010.

[35]. Bahadur, S., Roy, A., Chanda, R., Baghel, P., Saha, S., & Choudhury, A. (2016). Assessment of Some Phytochemcial and Physicochemical Properties of Fenugreek Seed Mucilage. Research Journal of Pharmacy and Technology, 9(9), 1261–1264.

[36]. Strübing, S., Metz, H., & Mäder, K. (2008). Characterization of poly (vinyl acetate) based floating matrix tablets. Journal of controlled release, 126(2), 149-155.

[37]. Nerurkar, J., Jun, H. W., Price, J. C., & Park, M. O. (2005). Controlled-release matrix tablets of ibuprofen using cellulose ethers and carrageenans: effect of formulation factors on dissolution rates. European journal of pharmaceutics and biopharmaceutics, 61(1-2), 56-68.

[38]. Devanaboyina, N., Satyanarayana, T., & Rao, B. G. (2012). Simultaneous determination of olmesartan and hydrochlorothiazide in combined pharmaceutical dosage form by RP-HPLC method. Int J Pharm Biosci, 3(2), 107-15.

[39]. Beckert, T. E., Lehmann, K., & Schmidt, P. C. (1996). Compression of enteric-coated pellets to disintegrating tablets. International Journal of Pharmaceutics, 143(1), 13-23.

[40]. Stops, F., Fell, J. T., Collett, J. H., Martini, L. G., Sharma, H. L., & Smith, A. M. (2006). Citric acid prolongs the gastro-retention of a floating dosage form and increases bioavailability of riboflavin in the fasted state. International Journal of Pharmaceutics, 308(1-2), 14-24.

[41]. Rahman, Z., Ali, M., & Khar, R. K. (2006). Design and evaluation of bilayer floating tablets of captopril. Acta Pharmaceutica, 56(1), 49-57.

[42]. Sungthongjeen, S., Sriamornsak, P., & Puttipipatkhachorn, S. (2008). Design and evaluation of floating multi-layer coated tablets based on gas formation. European Journal of Pharmaceutics and Biopharmaceutics, 69(1), 255-263.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 5435 - 5458

Received 16 February 2021; Accepted 08 March 2021.

[43]. Narendra, C., Srinath, M. S., & Babu, G. (2006). Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. AAPS pharmSciTech, 7(2), E23-E29.