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Development and Evaluation of Floating Drug Delivery System of Chlorothiazide

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ABSTRACT

Objective- Formulation of floating tablet which would remain in stomach for prolonged period of time thereby maximizing the drug release at the desired site for stipulated time. Chlorothiazide is having half life 45-120 min; to improve its half life by using excipient like HPMC K4M, HPMC K100M and gellan gum as natural polymer, Optimization using 3^2 full factorial design to study stability testing of optimized formulation according to ICH guidelines. **Method-** The tablet formulation prepared by direct compression method. Prepared formulation were evaluated in terms of their physical properties, hardness, % friability, weight variation, content uniformity, *in-vitro* release, floating properties and swelling index. The optimized formula was also confirmed by design expert 7.0 optimization software. The classical zero order release curve was found to be linear ($R^2 \geq 0.80$). For the Korsemeyer's Peppas release curves R^2 was found to be ≥ 0.90 for all 9 formulations. **Result-** FTIR and DSC studies showed no evidence of interactions between drug, polymers, and excipients. The best *in-vitro* drug release profile was achieved with the formulation F8 is 91.48% after 12 hr which contain 250 mg drug, 50 mg HPMC K4M and 20 mg Gellan gum. The floating lag time of formulation F8 was found to be 63 ±0.05 sec. to 118±0.04 sec. The *in-vitro* release kinetics studies reveal that all formulations show Zero order and anomalous or non-fickian diffusion. The stability study and no change in any physical characteristics and drug content over a 3 months period at 40±2°C. **Conclusion** –Study concluded that successful stable formulation of floating drug delivery system of chlorothiazide can be prepared to maximize drug release at desired site for stipulated time.

INTRODUCTION

The importance of controlled drug delivery system is that release drug over an extended period of time has long been recognized in the pharmaceutical field. Application of such controlled release technology to oral drug delivery system, however, has been limited because the actual time for effective drug delivery is restricted by gastrointestinal transit time. Gastric retention devices are designed to prolong the gastric residence time of oral controlled release dosage forms. They thus result in increased contact time for drugs that act locally, increased absorption of drugs that have absorption windows in upper part of gastrointestinal tract (GIT), and better absorption of drugs less soluble in the intestinal fluid [1]. Several approaches have been developed to achieve extended gastric residence time of the oral drug delivery systems such as bioadhesive system, swelling and expanding systems, floating systems and delayed gastric emptying devices. Amongst these methods, floating drug delivery system (FDDS) is preferred one that offers a simple and practical approach to achieve gastro-retention [2]. Floating dosage forms have a bulk density lower than that of gastric fluids and therefore remain buoyant on the stomach contents to prolong the gastric retention time [3-7].

These systems are also known as hydrodynamically balanced system. (HBS).They have a bulk density lower than gastric fluid[6].The specific gravity of gastric fluid is approximately 1.004–1.010 g/cm^3 and thus the FDDS remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. It is formulation of a drug and gel forming hydrocolloids meant to remain buoyant on stomach contents. This system not only prolongs GI residence time but also maximize the area at which the drug reaching its absorption site in solution and hence ready for absorption while the system is floating on the gastric contents. The drug is released slowly at a desired rate from the system, after the release of the drug the residual system is emptied from the stomach. Drug dissolved and released from the capsule/tablet, retained in stomach fluids for a desired period of time.

The HBS must comply with following three major criteria:-

- It must have sufficient structure to form cohesive gel barrier.
- It must maintain an overall specific density lower than that of gastric contents.

- It should dissolve slowly enough to serve as reservoir for the delivery system.

This study was conducted with an aim to develop floating gastro-retentive tablet formulation incorporating 250 mg Chlorothiazide into hydrophilic polymeric matrix which would release the drug in stomach and upper part of GIT in a controlled manner. Since Chlorothiazide has site-specific absorption from this regions, gastro-retention of the dosage form will improve its oral gastric residence time [8-10].

MATERIAL AND METHOD

Material:

Chlorothiazide was obtained as gift sample from Apothecon pharmaceutical, Baroda, Gujarat. HPMC K4M, HPMC K100M and Gellan gum Purchased from SD fine chemicals Mumbai. Other reagents and solvents used were of analytical grade.

Method:

Formulation of floating tablets

Direct compression method was employed to prepare floating tablet of Chlorothiazide using HPMC K4M, HPMC K100M and gellan gum.

Factorial design

A 3^2 full factorial design was constructed, where the amounts of HPMC K4M (X1) and Gellan gum (X2) selected as the independent factors. *In-vitro* drug released (Y1) and Floating lag time (Y2) were selected as dependent variables. The levels of the two factors were selected on the basis of studies carried out before implementing the experimental design.

Table 1: Summarizes the experimental runs, their factor combinations and the translation of the coded levels to the experimental units used in the study

Factor	Name	units	Low	Medium	High
			(-)	(0)	(+)
X_1	Gellan gum	mg	10	15	20
X_2	HPMC K4M	mg	40	50	60

Preparation of floating tablet of Chlorothiazide: [11]

It was planned to prepare floating tablet of Chlorothiazide with different polymers like gellan gum, HPMC K4M in various proportions. Various rheological characteristics of the powder bed like bulk density, compressibility index, and repose angle were evaluated and studied. Floating tablets were compressed on a 10 station pilot press using 8 mm flat faced punches (Karnavati India) and were all assessed for weight variation, hardness, thickness, floating lag time and *in-vitro* release of the drug into the simulated fluid using USP 8DL dissolution testing apparatus II using a paddle at 50 rpm. The optimized formula was also confirmed by design expert 7.0 optimization software. The classical zero order release curve was found to be linear ($R^2 \geq 0.80$). For the Korsemeyer's Peppas release curves, R^2 was found to be ≥ 0.90 for all 9 formulations. Further stability studies were also conducted at 40°C/ 75 % RH for period of 90 days for optimized formulation F8.

Table 2: Composition Chlorothiazide floating tablet

Formulation code Ingredient's	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlorothiazide	250	250	250	250	250	250	250	250	250
Gellan gum	10	10	10	15	15	15	20	20	20
HPMC K4M	40	50	60	40	50	60	40	50	60
HPMC K100M	10	10	10	10	10	10	10	10	10
$NAHCO_3$	40	40	40	40	40	40	40	40	40
Lactose	42	32	22	37	27	17	32	22	12
Talc	4	4	4	4	4	4	4	4	4
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Total Weight	400	400	400	400	400	400	400	400	400

All the weights are taken in mg, total weight of tablet is 400 mg.

Evaluation of Pre-compression parameters:[12, 13]

Bulk density

Bulk density of the powder was determined by pouring gently 10 grams of sample through a glass funnel into a 100ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density was calculated as follows:

$$BulkDensity = \frac{Weightofsamples \in grams}{volumeoccupiedbythesample}$$

Tapped Density:

10 grams of powder sample was poured gently through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained.

Volume occupied by the sample after tapping were recorded and tapped density was calculated as follows:

$$TappedDensity = \frac{Weightofsamples \in grams}{volumeoccupiedbythesample}$$

Carr's Index:

One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index (I), which is determined by the following equation:

$$I = \frac{TAPPEDDENSITY - BULKDENSITY}{TAPPEDDENSITY} * 100$$

Table 3: Percent Compressibility value

% Compressibility	Flow property
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Extremely poor

Hausner's ratio:

It is the ratio of tapped density to the bulk density. Hausner's ratio is an ease of powder flow, it is calculated by formula given below:

$$Hausner'sratio = \frac{TappedDensity}{BulkDensity}$$

7.4.5 Angle of Repose:

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The fixed amount of granule mass was allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of the granules from the funnel mouth forms a pile of granules at the surface this is continued until the pile touches the stem tip of the funnel. A rough circle is drawn around the pile base and the radius of the powder cone was measured. Angle of repose was then calculated by using following formula:

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

Where, θ= angle of repose

h= height of the pile

r = average radius of the powder cone

Table 4: Angle of repose (θ) and Flowability

Angle of repose (θ)	Flowability
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Evaluation of Post-compression characteristics of the tablets:

Weight variation [14]

The weight variation of the prepared floating tablet was done by weighing twenty tablets individually and the average weight was calculated. For the tablets to be accepted, the weight of not more than two tablets deviates from the average weight by no more than 7.5% and no tablet deviates by more than 15%.

Hardness [15]

The hardness (force required to break a tablet by diametrical compression) of all the prepared floating tablets (with and without Chlorothiazide). The test was down using manual Monsanto hardness tester in which the hardness was measured in terms of kg/cm2. Since the minimum practical hardness that provides adequate mechanical resistance is not less than 3 Kg/cm2.

Friability [16]

Twenty tablets were weighed and placed in the Roche friabilator. After this, the apparatus was rotated at 25 rpm for 4 minutes. After revolution the tablets were dusted and weighed. The friability is given by the formula:

$$F = (1-W/W_O) \times 100$$

Where Wo is weight of the tablet before test.

W is the weight of the tablets after test

Content uniformity [17]

This test was down for each formula that loaded with Chlorothiazide. Tablet was dissolved in 100 ml of distilled water and the absorbance of the final solution was measured at the maximum at 282 nm. This test is used to determine whether the individual contents are within limits set with references to the average contents of the sample. The preparation complies with the test if each individual content is 85 to 115 % of the average content.

In-vitro buoyancy studies [18]

The *in-vitro* buoyancy was determined by floating lag time (FLT) and total floating time (TFT) as the method described by Rosa et al. the tablets were placed in 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution media was noted as the total floating as the total floating time respectively (TFT) .

Determination of floating capacity[19, 20]

Three individual tablets from each formulation were put in an individual flask containing 400 ml of 0.1N HCl solutions. Then time in minutes for each tablet to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) were measured. The sample mean and standard deviation were calculated. (n=3)

RESULT AND DISCUSSION

Table 5: Evaluation of Pre-compression characteristics of the floating tablet of Chlorothiazide.

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ^o)	Compressibility index (%)	Hausner's ratio
F1	0.581±0.004	0.666±0.008	25.24±0.37	12.9±0.529	1.14±0.04
F2	0.588±0.006	0.684±0.005	21.83±0.34	14.03±0.471	1.16±0.09
F3	0.502±0.007	0.694±0.007	23.25±0.27	13.2±0.352	1.15±0.00
F4	0.568±0.008	0.675±0.006	26.72±0.37	13.85±0.648	1.18±0.00
F5	0.595±0.006	0.694±0.006	23.41±0.47	14.26±0.650	1.16±0.07
F6	0.581±0.007	0.684±0.007	25.65±0.23	12.05±0.210	1.17±0.07
F7	0.574±0.006	0.684±0.006	24.33±0.11	14.08±0.981	1.19±0.08
F8	0.561±0.009	0.666±0.004	25.65±0.17	13.76±0.468	1.18±0.02
F9	0.581±0.008	0.694±0.003	22.81±0.22	14.28±0.589	1.19±0.06

The angle of repose is an indicative parameter of powder flowability from hopper to die cavity. An angle of repose between 25^0 to 30^0 indicates excellent flowability of powder bed. In this work, the angle of repose was found to be varying between 22.81º and 26.72º when glidants were incorporated. These studies indicated that the powder beds of all formulations are easily flowable.

All the Pre-compression parameters were found to be within acceptable limits.

Table 6: Evaluation of Post-compression characteristics of the floating tablet of Chlorothiazide

Formulations Code	Hardness (kg/cm^2) n=3	Thickness (mm)	Friability %	Wt. Variation (mg) (mg) n=3
F1	3.46±0.12	9.08±0.072	0.03323±0.069	398.5±1.774
F2	3.49±0.13	9.10±0.097	0.03871±0.083	399.6±1.609
F3	3.48±0.10	9.08±0.129	0.04593±0.050	399.7±2.291
F4	3.63±0.12	9.09±0.125	0.02879±0.0096	400.6±1.446
F5	3.58±0.14	9.09±0.129	0.0343±0.0051	400.3±1.943
F6	3.89±0.12	9.08±0.126	0.02548±0.0083	399.2±2.026
F7	3.73±0.13	9.07±0.122	0.02773±0.0084	401.2±1.712
F8	3.86±0.11	9.09±0.130	0.02885±0.0051	399.4±2.161
F9	3.69±0.12	9.08±0.213	0.03101±0.050	398.6±2.026

Hardness of the tablets varied between 3.46 ± 0.12 Kg/cm^2 and 3.89 ± 0.12 Kg/cm^2 indicating good binding and satisfactory strength of tablets to withstand stress during transportation and also may offer good floating effect. The % friability was found in the range of 0.02548-0.4593 %. The weight variation ranges from 398.5 to 401.2 which passes the standard.

Table 7: Floating lag time (FLT) and Uniformity content of formulations of F1 to F9 formulations

Formulation Code	Floating Lag Time (sec.)	Floating time (hours)	Uniformity of Content (%) (% 9% (%)
F1	63 ±0.04	12	98.42±0.1178
F2	76 ±0.03	12	98.87±0.1178
F3	99 ±0.02	12	99.16±0.1027
F4	68 ±0.08	12	98.72±0.3171
F5	114 ±0.06	12	98.92±0.2041
F6	116 ±0.03	12	99.85±0.2357
F7	91 ±0.01	12	99.79±0.1471
F8	105 ±0.05	12	99.87±0.1178
F9	118 ±0.04	12	98.32±0.3118

Floating lag time (FLT), for all batches (F1 to F9) was found between 63 ±0.044 sec. to 118 ±0.04sec. These results indicate that the buoyancy lag time was found to be satisfactory.

Floating time was observed in all 9 formulations; all the 9 formulations showed the floating time for 12 hours which is sufficient to achieve sustained release action. It was observed that as polymer concentration increase floating lag time increase.

Tablets from each batch showed uniformity of content in the range 98.32% to 99.92% which is within pharmacopoeial specifications. All the formulations comply the test for uniformity of content as it found to be within the limit of 99- 110%.

***In-vitro* drug release:**

HPMC K4M and Gellan gum are hydrophilic polymers. When tablets containing these polymers come in contact with water, hydrophilic polymers allow gradual hydration of the tablet matrix, leading to swelling of the tablet. Drug release from matrix tablet is determined by drug characteristics, delivery system and destination (site of drug release). Maintaining sink condition is important during the dissolution experiment for consistent and accurate measurement of the dissolution rate. Sink conditions could be maintained throughout the dissolution study and drug

solubility could not be a factor responsible for retardation of drug release from the formulations studied. Hence retardation of drug release from the formulations could be attributed to the properties of polymers used in the formulations. % Cumulative drug release of all formulation are shown in Figure 1.

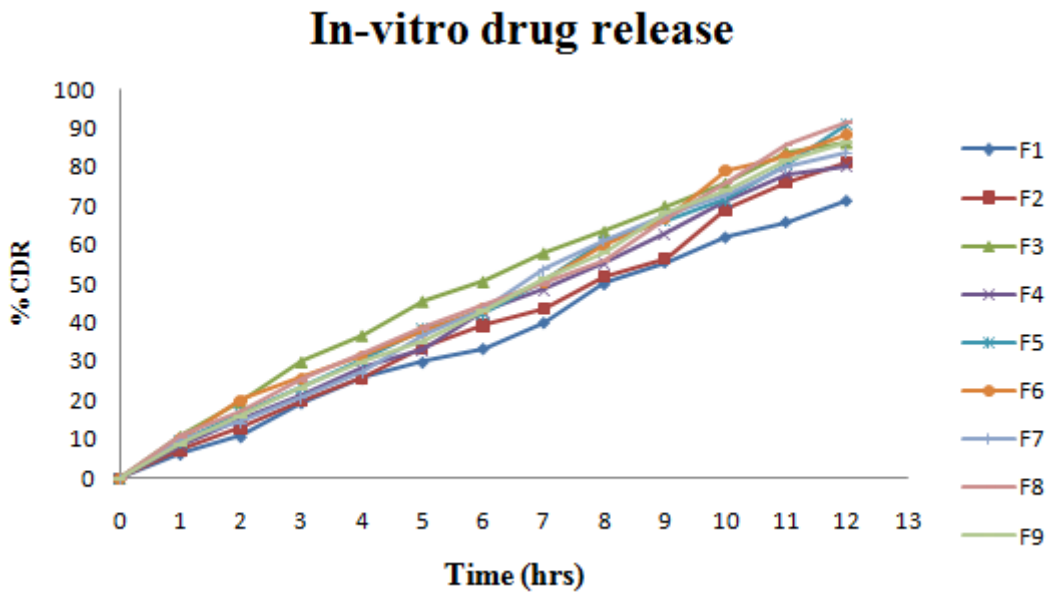

Figure 1: *In-Vitro* dissolution data of formulation F1-F9

The % drug release showed that as the concentration of polymer goes on increasing the drug release also goes on decreasing and as well as time for drug release will be more sustained or release time will also goes on increasing, but we want more and optimize release at 12 hrs., it was shown by a F8 batch 91.48% and later on drug release goes on decreasing. Hence F8 batch was taken as optimize batch due to highest drug release up to 12hrs, Hence F8 batch was used for further evaluation and stability study.

Kinetic Data: [21]

In the present study, the drug release was analyzed to study the kinetics of drug release mechanism. The results showed that the factorial design batches followed first order model kinetics, Higuchi model kinetics and Korsemeyer's Peppas model kinetics.

Table 8: Drug release kinetic of different formulation F1-F9

Formulation	Zero order	Korsemeyer- Peppas	
	R^2	R^2	n
F1	0.994	0.889	0.546
F2	0.994	0.866	0.616
F3	0.987	0.941	0.786
F4	0.996	0.888	0.577
F5	0.996	0.874	0.679
F6	0.993	0.876	0.837
F7	0.994	0.892	0.828
F8	0.993	0.866	0.731
F9	0.997	0.887	0.769

The classical zero order release curve was found to be linear ($R^2 \geq 0.80$). For the Korsemeyer's Peppas release curves R^2 was found to be ≥ 0.90 for all 9 formulations and n value was found to be ≥ 0.5 which indicates that all the formulations show non anomalous (non fickian release).The drug release occurs probably by diffusion with erosion and dissolution.

Optimization

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. The percentage of HPMC K4M (X_1) and Gellan gum(X_2) were selected as independent variables and the % drug release, swelling index and floating lag time was selected as dependent variables. The data obtained were treated using design expert version 7.0 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to study the effect of HPMC K4M (X_1) and Gellan gum (X_2) on dependent variables. Results showed that other statistical parameters for the dependent variable % drug release, for floating lag time, swelling index. The values of X_1 and X_2 were found to be significant at $p < 0.05$, hence it was confirmed that there is significant effect of both the variables on the selected responses. From this data optimum concentration of Gellan gum 20 mg and HPMC K4M 50 mg was found in F8.

Multiple regression analysis of 3^2 full factorial design batches for *in-vitro* drug release and floating lag time.

Surface response plots

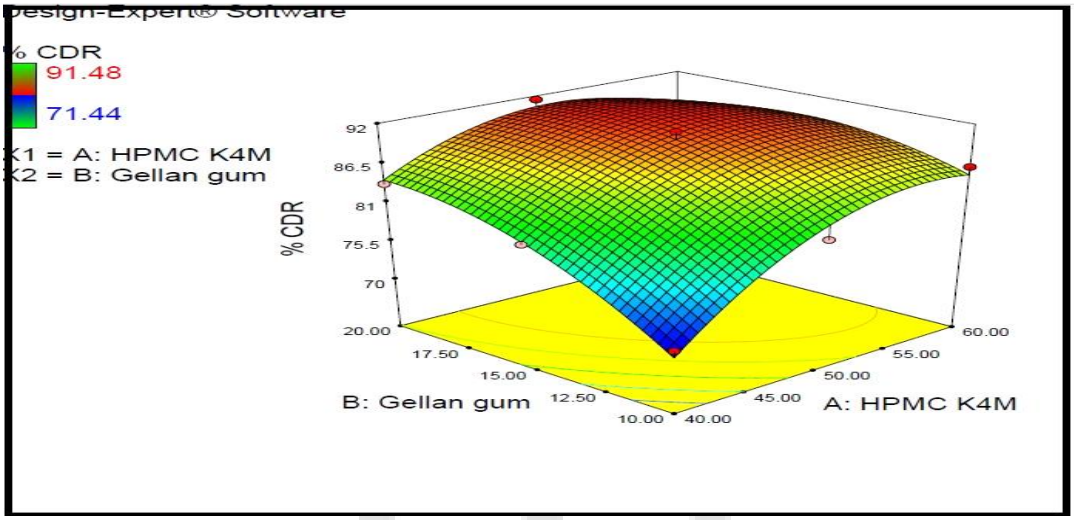

Figure 2: Surface response 3D plot showing effect of Gellan gum and HPMC K4M on % CDR

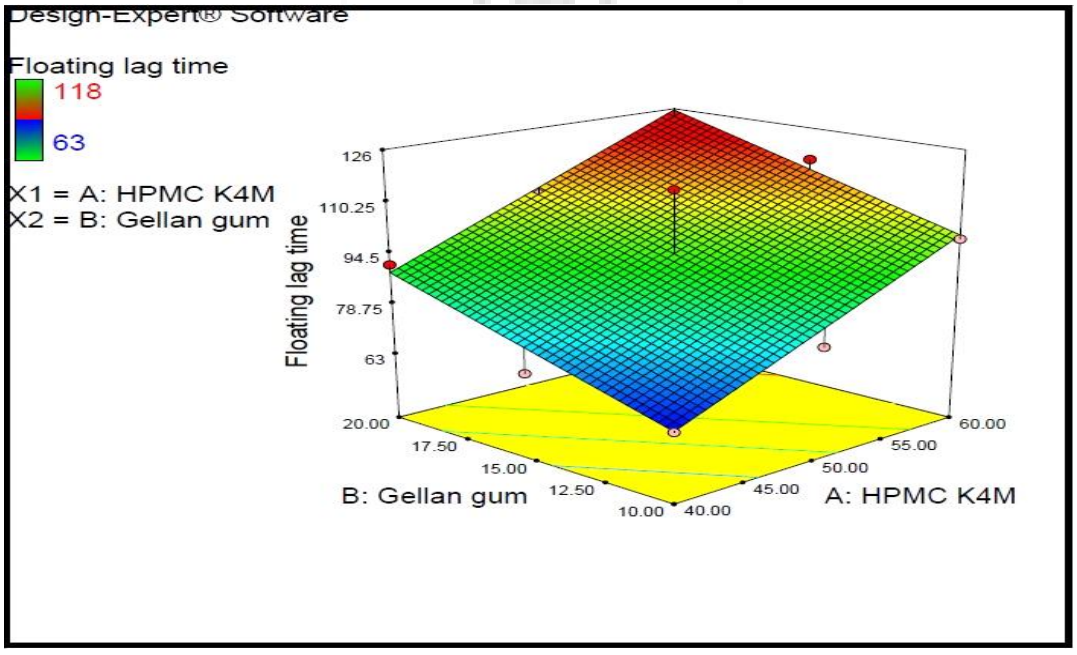

Figure 3: Surface response 3D plot showing effect of Gellan gum and HPMC K4M on floating lag time

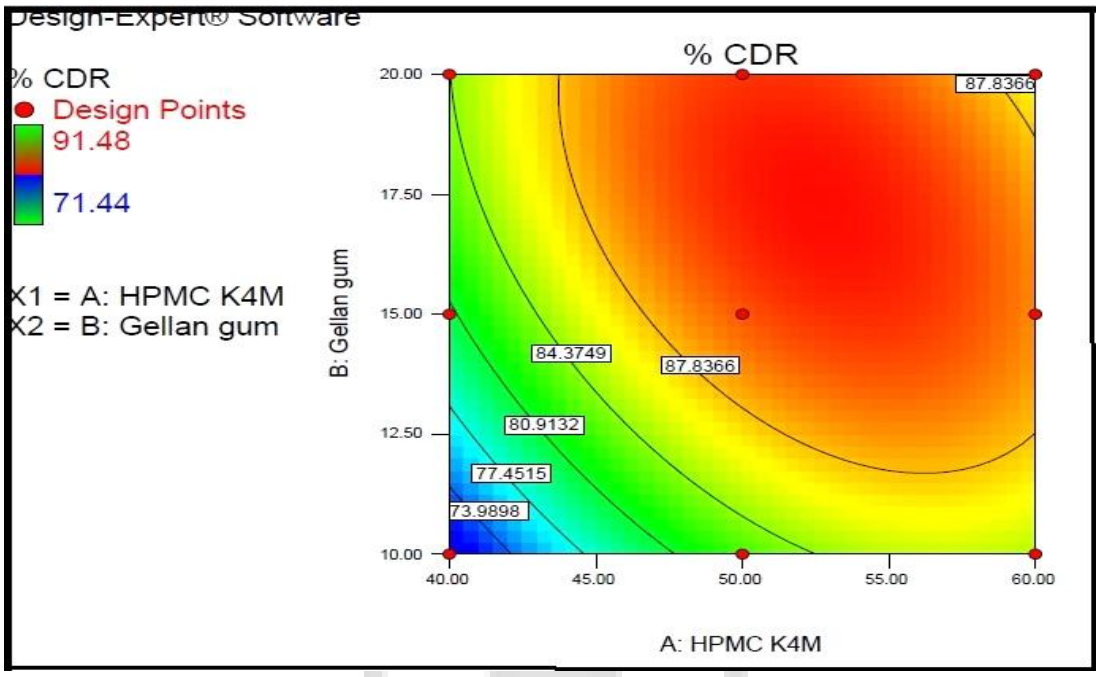

Figure 4: Contour plot showing effect of Gellan gum and HPMC K4M on drug release at 12hrs

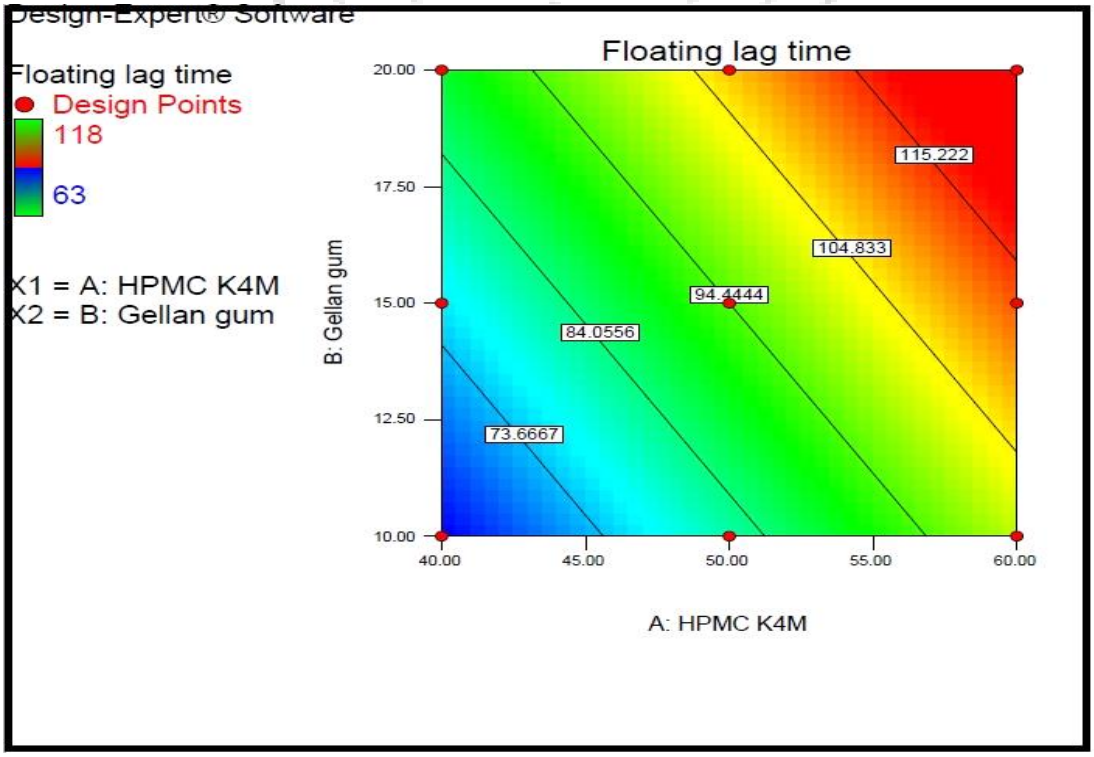

Figure 5: Contour plot showing effect of Gellan gum and HPMC K4M on floating lag time

Stability study:[22]

Table 9: Results of stability study

Sr. No.	Test	Before stability testing	After stability testing		
			1months	2 months	3 months
1	Colour	White	White	White	White
2	Thickness (mm)	9.09±0.126	9.09±0.013	9.08±0.013	9.08±0.011
3	Hardness (kg/cm^2)	3.8±0.12	3.8±0.123	3.7±0.12	3.7±0.17
4	Drug content	99.90±0.2357	99.87±0.0004	99.88±0.0002	99.89±0.0002

*(Mean ± S.D) *(n=3)

The optimized formulation F8 showed good stability and no change in any physical characteristics, drug content over a 3 months period at 40°C±5°C and 75%±2%.

CONCLUSION

Chlorothiazide was successfully formulated as controlled release floating tablet with a dose 250 mg that extends the drug release for 12 hrs. This dosage form was prepared by direct compression method.

Based on results, one can conclude the following points:

- Increasing HPMC K4M concentration increased the drug release from floating tablets, and increased the FLT.
- The floating lag time for all tablet formulations was found to be in between 63 ±0.044 sec. to 118±0.04 sec. for F1 to F9.
- Tablets from each batch showed uniformity of content in the range 98.32% to 99.92% which is within pharmacopoeial specifications. All the formulations comply the test for uniformity of content as it was found to be within the limit of 99-110%.
- The drug release results obtained indicated that formulation containing 20 mg gellan gum and 50 mg HPMC K4M showed highest release i.e.91.48 % after 12 hrs. which indicates that the F8 formulation have shown prolonged release. This optimized formula was also confirmed by

design expert 7.0 optimization software.

- The classical zero order release curve was found to be linear ($R^2 \geq 0.80$). For the Korsemeyer's Peppas release curves R^2 was found to be ≥ 0.90 for all 9 formulations and n value was found to be ≥ 0.5 which indicates that all the formulations showed non anomalous (non fickian release).The drug release occurs probably by diffusion with erosion and dissolution.
- For future work, one can make pre-clinical and clinical study to determine the pharmacokinetics parameters in order to confirm the results of *in-vitro* studies.

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REFERENCES

1. Moes AJ. Gastroretentive dosage forms. Crit Rev Ther Drug Carrier Syst 1993;10:143-195.
2. Baumgartner S, Kristl J, Vrecer F. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000;195:125-135.
3. Hoffman A. Pharmacodynamic aspects of sustained release preparations. Adv Drug Deliv Rev 1998;33:185-199.
4. Klausner EA, Lavy E, Friedman M, et al. Expandable gastroretentive dosage forms. J Control Release 2003;90:143-162.
5. Shaha SH, Patel JK, Pundarikakshudu K. An overview of a gastroretentive floating drug delivery system. Asian J Pharm Sci 2009;4:65-80.
6. Rouge N, Allemann E, Gex-Fabry M, et al. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high-density multiple-unit capsule and an immediate release tablet containing 25 mg atenolol. Pharm Acta Helv 1998;73:81-87.
7. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release 2000;63:235-239.
8. Cui Yue, Zhang Yu, Tang Xing. In vitro and in vivo evaluation of ofloxacin sustained release pellets. Int J Pharm 2008;360:47-52.
9. Timmermans J, Moes AJ. How well floating dosage do forms float Int J Pharm 1990;62:207-216.
10. Hwang SJ, Park H, Park K. Gastric retentive drug delivery systems. Crit Rev Ther Drug Carrier Syst 1998;15:243-284.
11. Birajdar SM., Darveshwar JD.Development And Evaluation Of Floating-Mucoadhesive Dipyridamole Tablet.AJPRHC. 2007; 4(3):78–79.
12. Niazi SK. Handbook of Preformulation. Informa Healthcare USA, New York. 2007. p. 57-276.
13. Lachman L, Liberman LA, Kanig JL. The theory and practice of industrial pharmacy. 3rded. Mumbai, India: Varghese Publishing House. 297-299.
14. Johns, Bengamin Onnoonay. Hydrophilic polymer viscosities on gastro retentive drug delivery systems of Gabapentin sustained release tablets. TUI 2010;354.

15. Ghassan Z A, Muthana F A, Chittneni M. Carbopol 934P, 940P, ultrez 10 as viscosity modifier of plan olein esters based nano-scaled emulsion containing ibuprofen. Pat. J Pharm Sci 2013;26 (1):75-83.
16. Jodupati Malakar, Amit Kumar Nayak, Floating bioadhesive matrix tablet of ondansetron HCL: optimization of hydrophilic polymer-blends. Asian J of Pharm 2013;7(4):174-83.
17. R Jacky Dias, S Shamling Sakhare, K Krishnal Mail. Design and development of mucoadhesive Acyclovir tablet. IJPR 2009;8(4):231-9.
18. M Mohan Varma, P Anita. Design and evaluation of gastro retentive floating drug delivery system of Metoprololtartrate. R Gutts J Pharm Sci 2012;2(Issue 2)
19. Mukhopadhyay S, Goswami L, Upadhyaya K.Formulation and Evaluation of Floating Bioadhesive Tablets of Ciprofloxacin Hydrochloride by Direct Compression Technique. International Journal of Pharmacy and Pharmaceutical Sciences. 2010; 2(3): 3–5.
20. Kumar PU, Ramakrishna G, Rao DS, Ramu S,Varun D.Design and In-vitro Assessment of Gastroselective Buoyant Tablets of Cefuroxime Axetil.International Journal of Pharmaceutical Chemistry and Science. 2014; 4(4): 1051–1060.
21. Korsemeyer RW, Gurny R, Doclker E, Buri P, Nikolas AP. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm. 1983; 15:25-35.
22. ICH Harmonized Tripartite Guideline, International Conference on Harmonisation.Stability Testing of New Drug Substances and Products Q1A(R_2) and Evaluation For Stability data Q1E. Current Step Version, 6 February 2003.