European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 07, Issue 11, 2020

DEVELOPMENT AND EVALUATION OF FLOATING IN SITU GELLING SYSTEMS OF HYDROCHLOROTHIAZIDE.

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ABSTRACT

This study aimed to develop a new in situ floating gel system that prevents oedema, congestive heart failures, and hypertension using hydrochlorothiazide. Sodium alginate solutions with a concentration of 0.25, 0.5, 1.0, and 1.5% (w/v) were formed by stirring alginate into ultra-pure water, with 0.25 percent (w/v) sodium citrate and 0.075 percent (w/v) calcium chlorine and heating up to 60 /v, then dissolved into 10 mL (pH 1.2) solution of 0.1N hydrochloride. Using 0.1N sodium hydroxide, the solvent was neutralized. A 1% (w/v) control solution was formed by dissolving hydrochlorothiazide into a 0.6% (w/v) solution of aqueous sodium alginate. Ultra-pure water provided a 1% (w/v) solution of hydrochlorothiazide. The resulting in situ alginate gel hydrochlorothiazide solution for viscosity and gelling proprieties was tested. The resulting gel was tested for in-vivo gelation and estimation of viscosity, physical appearance and drug content, in-vitro drug release, and gel water absorption measurement and was found to be compatible with the results discussed. This study shows that oral administration of aqueous solutions containing sodium alginate contributes to in situ stomach gel growth. The complete 32 factorial design findings indicate that sodium alginate concentration and calcium chloride concentration greatly influenced dependent variables such as viscosity, the content of medicinal products, Q50 and Q80.

KEYWORDS: Floating In Situ Gelling System, Hydrochlorothiazide.

1. INTRODUCTION

Hydrochlorothiazide is a diuretic medication frequently used to treat high blood pressure and swelling due to fluid buildup. Other uses take account of treating renal tubular acidosis and diabetes insipidus and to reduce the risk of kidney stones in those with a high calcium level in the urine. The bioavailability of hydrochlorothiazide was enhanced when given with food by delaying gastric emptying in both cases. If the drug's absorption window is in the stomach and formulations stay in for a long time would be better. The above information supports the theory that hydrochlorothiazide has an absorption window, making it a good candidate for an intragastric floating drug delivery system [1].

Gastro-retentive dosage forms (GRDFs) are designed to be retained the dosage forms in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs, for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and their therapeutic outcome [2]. It has been reported that the oral treatment of gastric dis-orders with an H2 receptor antagonist like hydrochlorothiazide used in combination with antacids promotes local de-livery of such drugs to the receptor of the parietal cell wall. Lo-cal delivery in the upper part of the stomach also increases the stomach wall receptor site bioavailability and increases drugs' efficacy to decrease acid secretion. For this reason, the same principle may be applied for improving systemic as well as local delivery of hydrochlorothiazide by floating delivery in the stomach, which would efficiently reduce gastric acid secretion [3].

Some approaches can be used to prolong gastric retention time of dosage forms, like floating drug delivery systems, swelling and expandable drug delivery system, bioadhesive/mucoadhesive systems, in-situ gelling systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices [4-10]. A floating drug delivery system is a lesser amount dense than gastric juice due to incorporating at least one porous structural element was described11. Many researchers have been used effervescent type drug delivery system for hydrochlorothiazide [12-14].

In-situ forming gels are formulations, useful as a solution, which undergoes gelation after instillation due to physicochemical changes like ion activation or pH dependent inbuilt to the biological fluids. In this fashion, the polymers, which show sol-gel phase transition and thus trigger drug release in response to external stimuli, are the most investigated. In-situ hydrogels provide such 'sensor' properties and can undergo reversible sol-gel phase transitions upon changes in the environmental situation. These "intelligent" or "smart" polymers play an important role in drug delivery since they may read out not only where a drug is delivered but also when and with which interval it is released [15-16].

The proposed deacetylated gellan gum and alginate-based floating in-situ gelling systems of hydrochlorothiazide would have the advantage of the ease of administration, as being a liquid in soft gelatin and is more patient compliance.

2. MATERIALS AND METHODS

Materials

Hydrochlorothiazide was received as a gift sample from Torrent Research Center, Ahmedabad, India. Gellan gum, calcium chloride, sodium citrate and sodium alginate were purchased from the local chemical supplier. All other chemicals used were of HPLC or analytical grade.

Methods

Estimation of hydrochlorothiazide

Ultraviolet absorption in the range 200 to 400nm of 50 μg/mL solution in artificial simulated gastric fluid (pH 1.2) was determined and found sharp peak at 271 nm.

Preparation of standard curve of hydrochlorothiazide in artificial simulated gastric fluid (pH 1.2)

100mg of Hydrochlorothiazide was weighed accurately and dissolved in artificial simulated gastric fluid (pH 1.2) in a 100 mL of volumetric flask, and volume was made up to the mark with the synthetic, simulated gastric juice (pH 1.2). From this stock solution, different dilution were prepared. The absorbance of these solutions was measured at 271 nm against a blank artificial simulated gastric fluid (pH 1.2). The absorbance v/s concentration (µg/mL) was plotted, and data were subjected to linear regression analysis in software (Microsoft Excel). The calibration curve is shown in Figure 1.

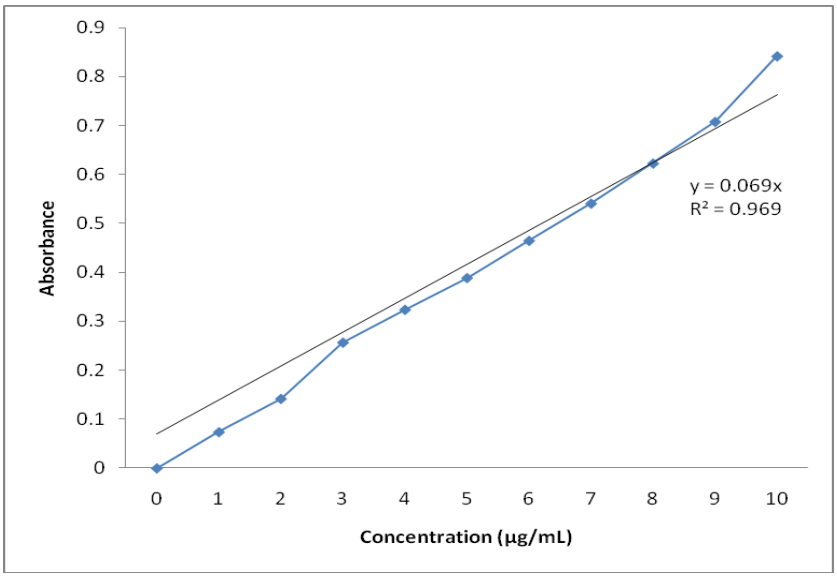

Figure 1. Calibration curve of hydrochlorothiazide in artificial simulated gastric fluid (pH 1.2) at 271nm.

Preparation of in-situ gelling solution

Gellan gum gels of concentrations between 0.4 and 1.0% (*w*/*w*) were prepared by slowly adding a weighed amount of the deacetylated gellan gum to cold purified water with continuous stirring high-speed stirrer for 30 min. Alginate solutions (0.25–1.5%, *w*/*w*) with calcium chloride (0.2 % w/v) and sodium citrate (1.0 % w/v) were prepared by gradually adding a weighed amount of the alginate to cold purified water with constant stirring with a high-speed stirrer for 30 min. The solutions were stored overnight at eight °C to ensure complete soluble, and hydrochlorothiazide (40mg) was added and dispersed well with constant stirring at 4000 rpm for 2 hours. The resulting in-situ gel solution containing the drug was evaluated for viscosity, gelling property and drug content. Finally, in-situ gel solutions were stored in glass bottles until more use. In the formulation batches R1 to R12 the concentration of calcium chloride (0.2 % w/v) and sodium citrate (1.0 % w/v) were kept constant. The deacetylated gellan gum concentration was between 0.4 and 1.0% (*w*/*w*), and the amount of alginate was diverse in batches R1 to R12 from 0.25–1.5% *w*/*w*. The effects of different concentration and amount of the gellan gum and sodium alginate-based in-situ gel of hydrochlorothiazide on characteristics are summarized in Table 2a and 2b.

EVALUATION OF *IN-SITU GEL*

Physical appearance and pH

All the formulated batches of deacetylated gellan gum/alginate-based in-situ solutions of hydrochlorothiazide were evaluated for their transparency and the time necessary for gel formation. The pH was calculated of in-situ solutions of hydrochlorothiazide using a calibrated digital pH meter at 25°C. All measurements of pH were made in triplicate, and the results are given in Table 2a.

Viscosity of in-situ gels

The deacetylated gellan gum/sodium alginate solution's viscosity either in solution or in gel completed with artificial simulated gastric fluid was determined with a Brookfield viscometer using a 20 mL aliquot of the sample. Viscosity was performed using different spindle number at 250 rpm, and the temperature was maintained at 25±1°C. The viscosity was read directly from the viscometer display. Gelation was also evaluated in artificial simulated gastric fluid (pH 1.2). All measurements were made in triplicate, and the results are given in Table 2a and 2b.

Determination of drug content

Precisely, 0.5 mL of in-situ gelling solution (equivalent to 20 mg of hydrochlorothiazide) was added to 20 mL of artificial simulated gastric fluid (pH 1.2) with proper dilution the UV absorbance of the sample was determined at a wavelength of 271nm using a spectrophotometer (UV-1800, Shimadzu, Japan). The drug content for batches R1 to R12 and D1 to D9 are depicted in Tables 2a, 2b and Figure 3.

Swelling Index

A gel (after 5 min gelation) of 100 mg was weighed accurately (W1). It was kept in a petri dish, and 50 mL of artificial simulated gastric fluid (pH 1.2) was added. The petri dish was kept sideways for 8 hr. The weight of swollen matrix gel (W2) was measured and was calculated using the following formula:

$$\text{Swelling index} = W2 - W1 / W1 \times 100 \quad \text{---Formula 1}$$

The Swelling Index for batches R1 to R12 is depicted in Table 2a.

In-vitro gelation study

Hydrochlorothiazide in-situ solution (2 mL) was added in and 100 mL artificial simulated gastric fluid (pH 1.2). Gelation was observed by visual examination, and the time of gelation was observed. The gelation times for batches D1 to D9 are depicted in Table 3 and Figure 4.

In-vitro floating study

In vitro floating study was carried out in 500 mL of artificial simulated gastric fluid (pH 1.2) in a beaker. Precisely measured 5 mL of in-situ solution was added to synthetic, simulated gastric juice. Time requires engaging on the surface after adding solution (floating lag time), and total floating time was considered. The floating time for batches D1 to D9 is depicted in Table 2b and Figure 5. Simultaneously, the floating time after 2 sec and 8 hr for batches D5 is illustrated in Figure 6.

In vitro drug release

The release of hydrochlorothiazide from floating in-situ gel was determined as mentioned by Zatz and Woodford [17] with some modification using the dialysis Cassettes (10000 MWCO, Thermo Scientific). A dialysis Cassettes previously soaked overnight in the artificial simulated gastric fluid. A defined amount of floating in-situ gel containing 20mg hydrochlorothiazide was accurately inserted using a syringe into dialysis Cassettes. The dialysis Cassettes was suspended in the USP dissolution test apparatus (USP 24) with a paddle stirrer at 50 rpm, and the temperature was maintained at 37± 0.5oC. 900 mL of artificial simulated gastric fluid (pH 1.2) were used as a dissolution medium. At every time gap, a precisely measured sample of the dissolution medium was withdrawn and replaced with a pre-warmed (37°C) new dissolution medium. Samples were diluted suitably and analyzed spectrophotometrically at 271nm. The amount of drug released at 4 hr (Q50) and 8 hr (Q80) was calculated [18-19]. The in vitro drug release results for batches D1 to D9 are depicted in Tables 3-4 and Figures 7 and 8. The average value of Q50 and Q80 for batches D1 to D9 is mentioned in Table 2b and Figures 9 and 10.

Stability studies

Stability studies of hydrochlorothiazide containing floating in-situ gel were carried out according to ICH (International Conference on Harmonization) guidelines. 10 mL optimized formulation (D5) in glass bottles was stored at 40±2oC/75±5% RH in Temperature/Humidity Control Chamber for four months. The drug content residual and the viscosity of in-situ gel were measured at a fixed time interval. The physical stability of gel was also observed periodically in the occurrence of turbidity or gelation. The results of the stability study for the selected batch of the in-situ formulation is given in Figure 11.

In-situ formulation in soft gelatin capsules

Hydrochlorothiazide containing floating in-situ gel was filled in soft gelatin capsules. Empty soft gelatin capsules were stored at 40°C for 10 minutes to remove moisture in use up by the capsules throughout storage. Each oval-shaped soft gelatin capsule of size 20 equal to 1.25 mL was in use for filling. Each capsule was filled by insertion with 1.0 mL of each of the formulation containing 40 mg hydrochlorothiazide. Each capsule should be filled up to 80 per cent of its total volume. Using a glass syringe, the gel solution fill was injected into the capsule, which was then sealed by a heat process.

Comparison of dissolution of drug release profile

The similarity of the drug release profiles, specifically dissolution test conditions assessed using the similarity factor (*f*2). It is the mathematical comparison among the drug release profiles of marketed preparation and an optimized batch of both the drugs. Similarity factor (*f*2) calculated as below:

$$f_2 = 50 * \text{Log} [1+ (1/n)\sum [Rt-Tt]^2] -0.5*100 \quad \text{---Formula 2}$$

Where,

n stands for the sample number,

Rt and Tt are the % release of optimized batch (D5) and soft gelatin capsules (hydrochlorothiazide containing floating in-situ gel of D5) at different time intervals up to 8 hr.

The value of *f*2 between 50 and 100 is suggestive of the similarity among the two release profiles. The value of *f*2 of more than 50 ensures a similarity or equivalence between the two curves. The FDA, as a satisfactory and favoured system for dissolution profile comparison, endorses this factor. The comparison of dissolution of drug release profile for the selected batch of an in-situ formulation is given in Table 5 and Figure 12.

Fit to kinetic models

Through fitting the experimental concentration-time consequences to theoretical curves, diffusion coefficients were found out acquired from the applied different kinetics models like Zero-order, First-order, Higuchi and Korsmeyer-Peppas. The results are shown in Table 6 and Figures 12 to 15.

3. RESULTS AND DISCUSSION

The floating in-situ gels of hydrochlorothiazide were prepared by ion activation technique, deacetylated gellan gum of concentrations between 0.4 and 1.0% (*w*/*w*) alginate solutions 0.25–1.5%, (*w*/*w*) with calcium chloride (0.2 % w/v) and sodium citrate (1.0 % w/v) were used. In groundwork trial batches of R1 to R12 (Table 5.2) were prepared using different concentration and amount of deacetylated gellan gum and sodium alginate to see the pH, effect on the viscosity of the solution, drug content, swelling index and the physical properties of the gel in simulated gastric fluid (pH 1.2). The concentration of deacetylated gellan gum and sodium alginate was varied from 0.4 to 1.0% *w*/*w* and 0.25 to 1.5 % *w*/*w*, respectively. In the batches, R1 to R3 improper gelation was observed means gel were not formed. In the batches, R4 to R6 proper gelation was observed after a few minutes. While batches R7 to R9 found good gel formation in 2 sec and batches R10 to R12, found high viscous formation. The swelling index of all batches was found satisfactory. With increasing the concentration of polymers, drug content was found increasing. Batches containing 0.6 to 1.0 w/w of deacetylated gellan gum and 1.0 to 1.5 w/w of alginate found more than 90% drug content. Based on preliminary trials, 0.6 to 0.8 w/w of deacetylated gellan gum and 1.0 to 1.25 w/w of alginate in different ration were utilized for further study. Calcium chloride (0.1 to 0.2 % w/v) and sodium citrate (0.5 to 1.0 % w/v) were used. Batches D1 to D9 were studied for viscosity, drug content, gelling and floating time. Batch (D5) containing 0.8:1.0 w/w of deacetylated gellan gum: alginate with calcium chloride:sodium citrate ratio of 0.2:0.5 % w/v found, 445 cp viscosity, 99.44% drug content, 1.2 min gelling time and floating lag time was 1 sec. The gel was floated for more than 8 hours. a Drug release study found sustain for all bathes. % drug release Q50 and Q80 of batch D5 found 66.07 and 99.28, respectively.

Table 2a. Evaluation results of formulation batches*

Batch No.	Concentration (%) *w*/*w*		pH	Viscosity (cp)	Drug content (%)	Swelling Index (%)	Attribute of In-situ gels
	Deacetylated gellan gum	Sodium alginate					
R1	0.4	0.25	7.1	99	84.29	42.72	Gel is not form
R2	0.6	0.25	7.2	104	85.27	57.88	

R3	0.4	0.50	7.1	102	89.38	60.18	properly
R4	0.6	0.50	6.9	156	93.94	52.74	Gel formation after few minutes
R5	0.4	0.75	6.9	168	95.26	60.36	
R6	0.6	0.75	7.0	174	94.22	70.55	
R7	0.6	1.0	7.1	441	98.81	60.21	Good gel formation
R8	0.8	1.0	7.0	445	99.44	42.36	
R9	0.8	1.25	7.2	440	97.65	45.32	
R10	1.0	1.25	7.0	1022	97.66	56.87	High viscous gel formation
R11	0.8	1.5	6.8	1532	97.26	52.38	
R12	1.0	1.5	7.1	1624	98.16	64.21	

*In all the batches 0.2 % (w/v) calcium chloride and 1.0% (w/v) sodium citrate were kept constant

Table 2b. Results of formulation batches*

Batch No.	**Concentration (%) *w/w***		**Viscosity (cp)**	**Drug content (%)**	**Gelling time (min)**	**Total Floating Time (hr)**	**% Drug release (Q_{50})**	**% Drug release (Q_{80})**
	Gellan gum: Sodium alginate	**Calcium chloride: Sodium citrate**						
D1	0.6:1.0	0.1:0.5	112	91.14	5.1	≤4.5	66.04	76.47
D2	0.8:1.0	0.1:0.5	1046	92.41	5.2	≤8.0	61.63	87.38
D3	0.8:1.25	0.1:0.5	988	95.88	4.6	≥6.5	66.62	96.77
D4	0.6:1.0	0.2:0.5	208	96.22	2.6	≥8.5	71.33	100.1
D5	0.8:1.0	0.2:0.5	445	99.44	1.2	≥8.0	66.07	99.28
D6	0.8:1.25	0.2:0.5	878	97.28	1.5	≥8.0	56.90	87.22
D7	0.6:1.0	0.1:1.0	326	97.29	1.5	≥8.0	68.47	95.56
D8	0.8:1.0	0.1:1.0	885	98.02	2.0	≥9.0	78.98	99.61
D9	0.8:1.25	0.1:1.0	1002	97.55	2.5	≥10.0	87.59	100.62

*All the batches were prepared using 40 mg hydrochlorothiazide; viscosity was measured at 250 rpm.

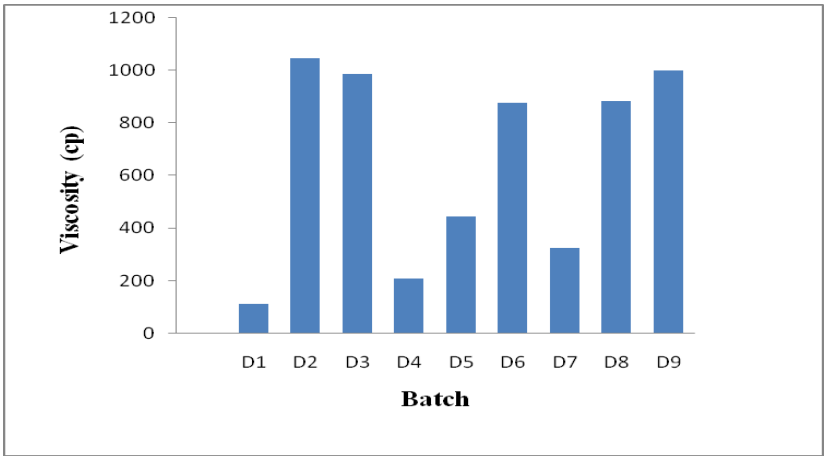

Figure 2. Viscosity of hydrochlorothiazide containing floating in-situ gel batches D1-D9

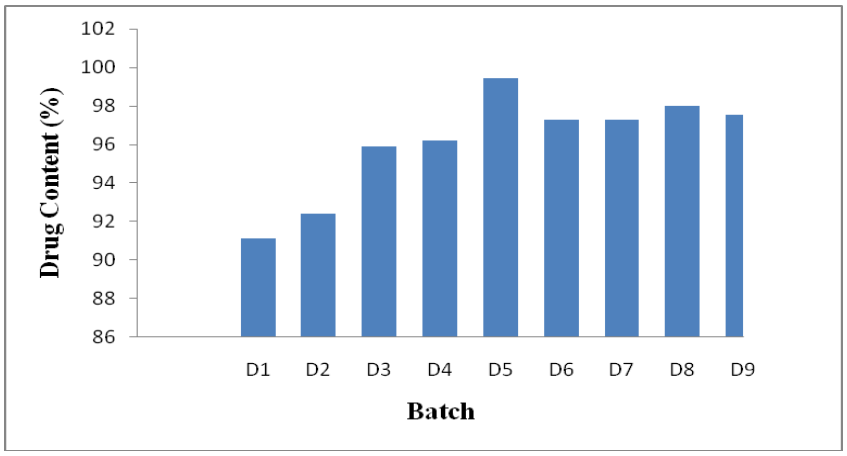

Figure 3. % drug content of hydrochlorothiazide containing floating in-situ gel batches D1-D9

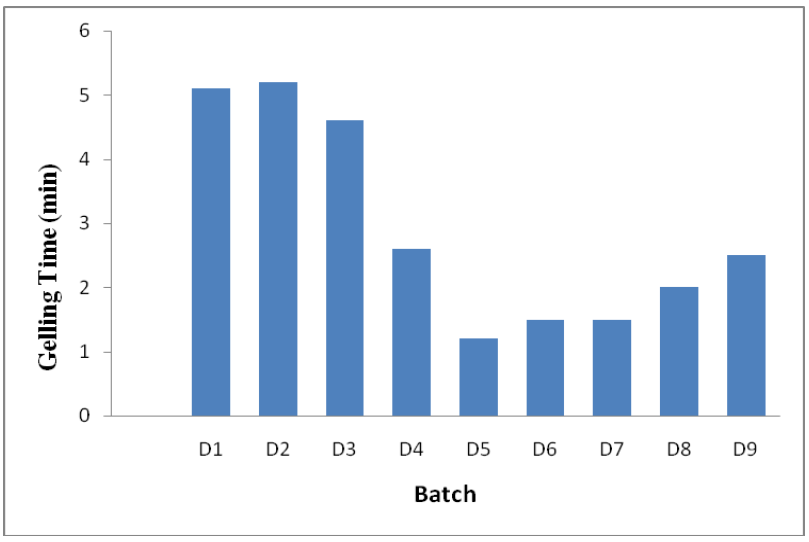

Figure 4. Gelling time (min) of hydrochlorothiazide containing floating in-situ gel batches D1-D9.

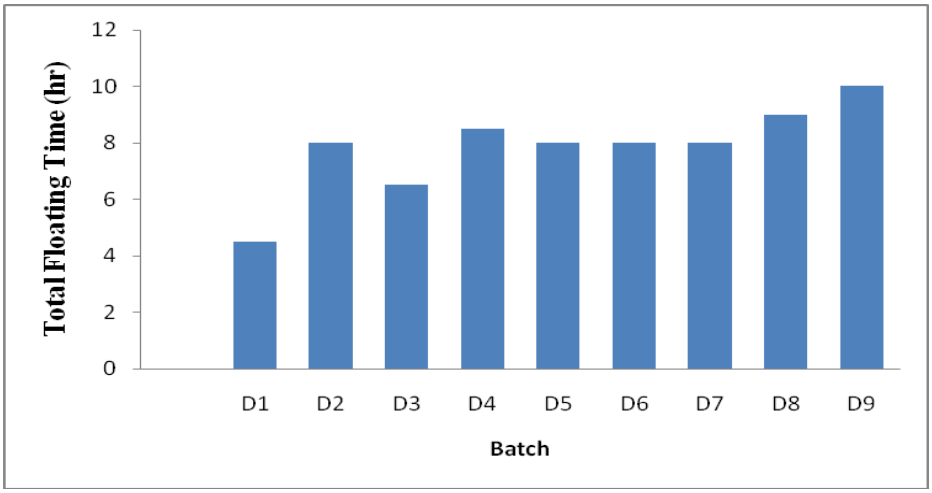

Figure 5. Total floating time (hr) of hydrochlorothiazide containing floating in-situ gel batches D1-D9.

(A) After 2 sec **(B) After 8 hr**

(C) Top view

Figure 6. Gel formation of in-situ gel in simulated gastric fluid (batch D5).

Table 3. Cumulative % drug release of trial batches D1-D5.

Time (hr)	D1	D2	D3	D4	D5
0	0	0	0	0	0
1	17.08±0.78	19.85±1.2	28.15±0.71	31.85±1.72	18.69±0.92
2	30.40±0.87	39.34±0.93	36.62±0.8	51.79±1.41	45.89±0.91
3	43.59±0.76	50.02±0.89	46.97±0.83	56.79±0.87	54.81±0.71
4	57.58±0.91	61.63±2.08	66.62±0.93	71.33±0.78	66.07±0.78
5	66.04±0.79	77.85±0.81	77.75±0.89	84.16±1.92	81.34±0.93
6	70.56±3.02	80.75±1.14	81.75±1.19	91.56±0.92	85.44±1.93
7	72.86±2.75	84.15±2.52	87.75±2.45	94.56±0.92	90.32±0.98
8	76.47±0.98	87.38±0.99	96.77±0.91	100.1±1.23	99.28±0.87

Table 4. Cumulative % drug release of trial batches D6-D9.

Time (hr)	D6	D7	D8	D9
0	0	0	0	0
1	21.62±0.78	27.08±0.89	32.92±0.7	48.30±0.19
2	38.75±0.87	40.33±0.78	59.15±0.7	65.44±0.98
3	44.61±0.76	51.40±0.78	68.54±0.89	81.00±1.22
4	56.90±0.91	68.47±0.87	78.98±0.67	87.59±1.18
5	66.54±1.54	76.74±1.45	93.71±0.77	90.07±0.98
6	71.58±1.65	80.14±2.45	95.77±1.23	92.12±2.18
7	76.54±2.14	82.74±2.80	98.21±2.53	98.14±4.08
8	87.22±0.91	95.56±0.70	99.61±0.89	100.62±0.89

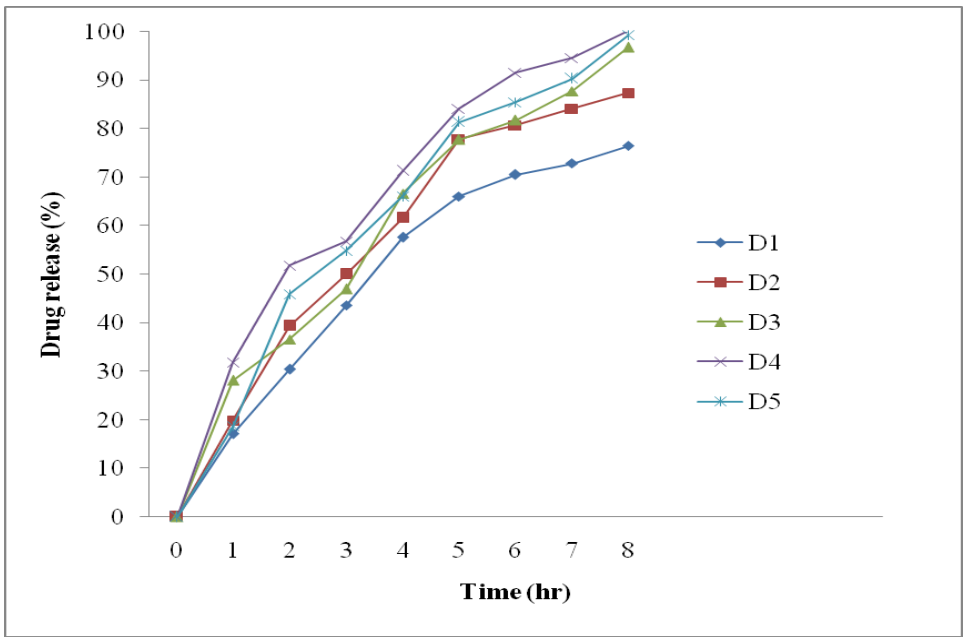

Figure 7. % drug release from in-situ gel batches D1-D5.

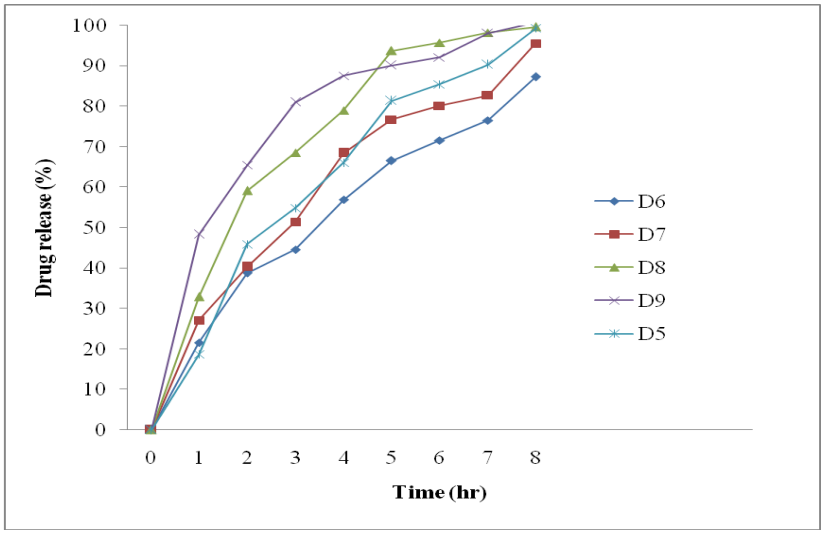

Figure 8. % drug release from in-situ gel batches D6-D9.

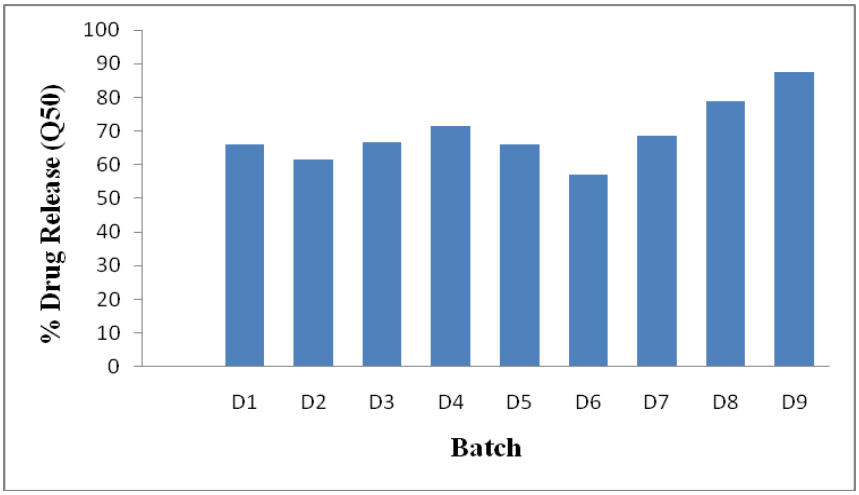

Figure 9. The average value of % drug release (Q50) for batches D1 to D9.

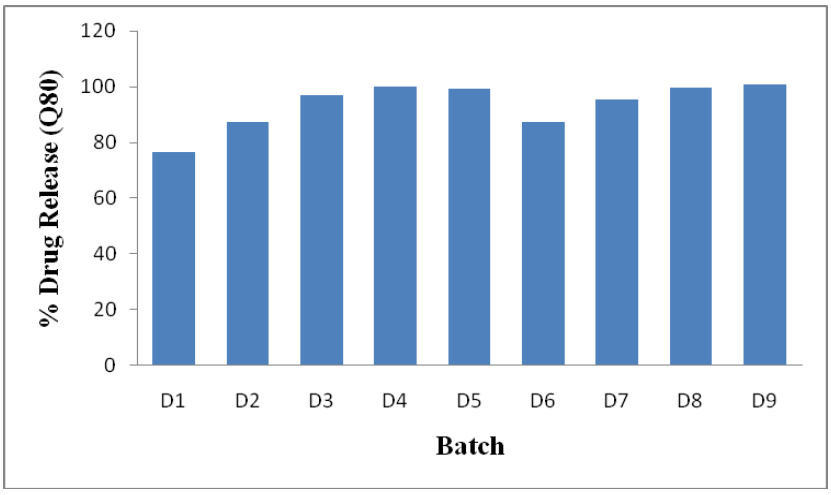

Figure 10. The average value of % drug release (Q80) for batches D1 to D9.

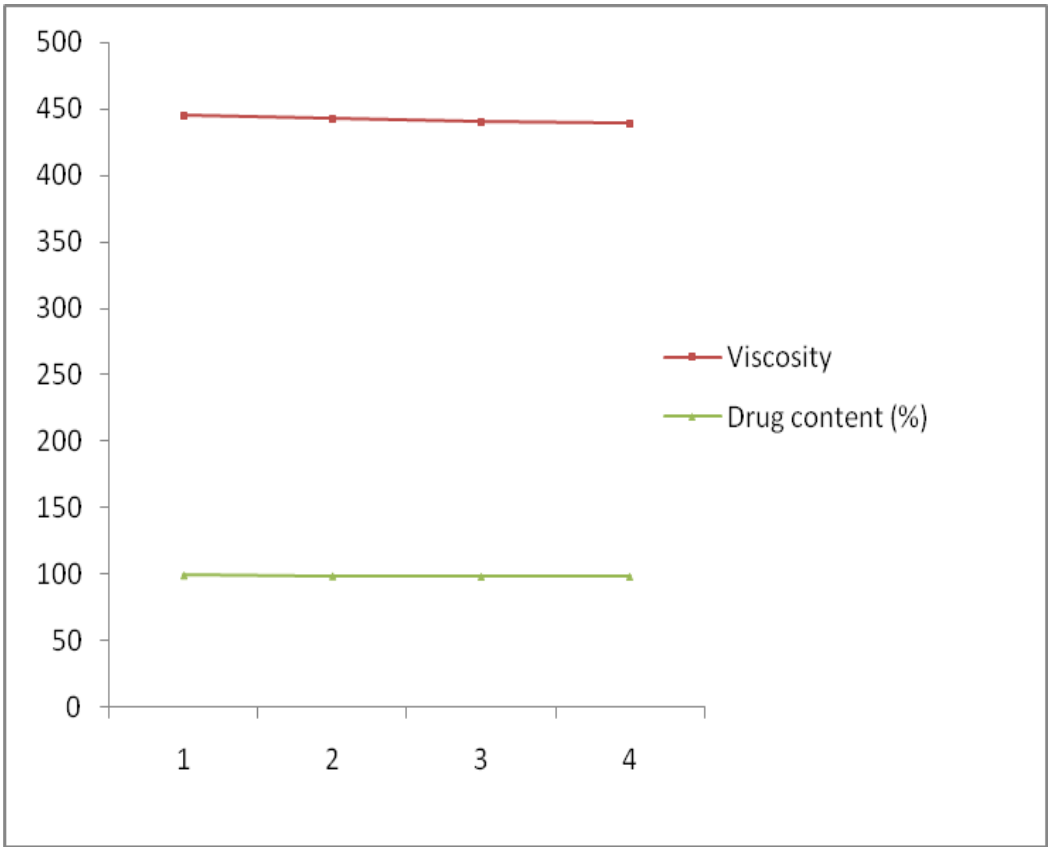

Figure 11. Stability study of hydrochlorothiazide in-situ gel

Based on the visual detection results, the in-situ gel has remained liquid for more than four months without the incidence of turbidity or gelation at 40±2oC. As per Figure 11, the gel's viscosity shows a slightly decreased was 445 cp at zero months and found 439 cp after 4th months. The work of drug content was found 1.0 % decreased after four months but was within the limit.

Table 5. Calculation of similarity factor.

Time (hr)	Optimized batch (D5)	Soft gelatin capsules (hydrochlorothiazide containing floating in-situ gel of D5)	Rt-Tt	(Rt-Tt)^2
0	0	0	0.00	0.00
1	18.69±0.92	15.28±1.32	3.41	11.63
2	45.89±0.91	37.52±2.35	8.37	70.06
3	54.81±0.71	52.78±4.52	2.03	4.12
4	66.07±0.78	63.37±2.15	2.70	7.29
5	81.34±0.93	78.56±1.32	2.78	7.73

6	85.44±1.93	83.22±1.97	2.22	4.93
7	90.32±0.98	91.42±2.53	-1.10	1.21
8	99.28±0.87	98.88±1.88	0.40	0.16
			Total =	107.12
*f*2=75.07				

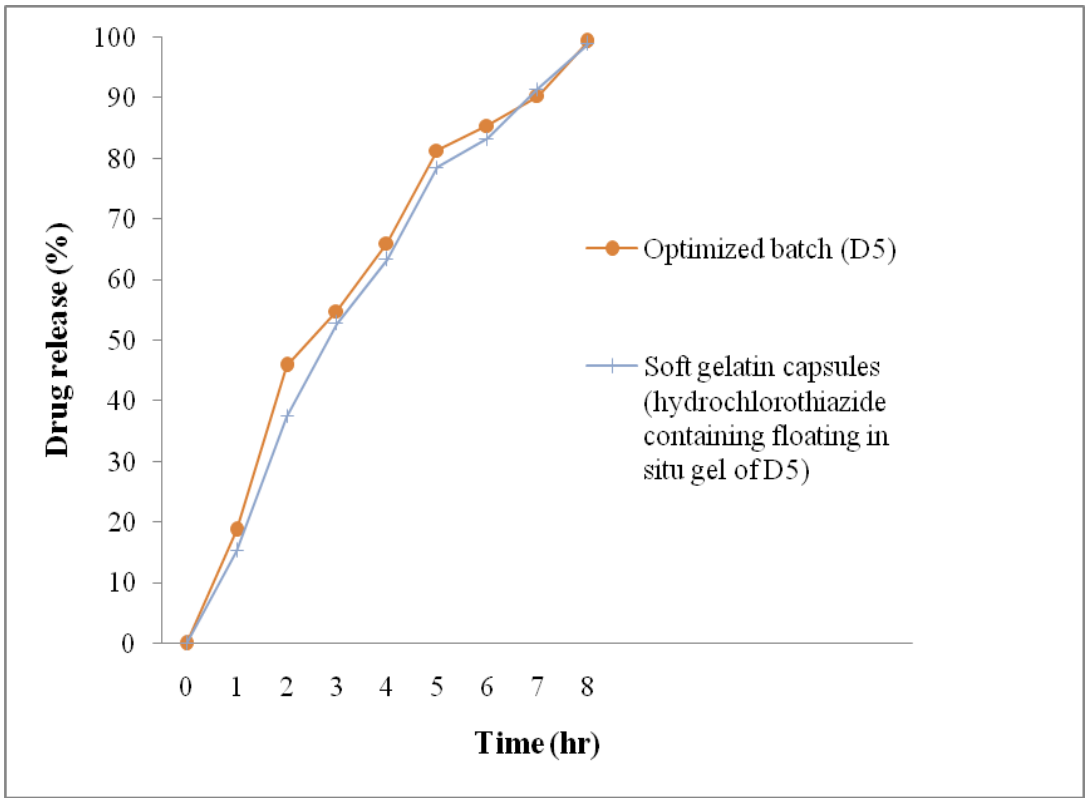

Figure 12. Comparison of dissolution of drug release profile.

The *f*2 value of 75.07 suggests the similarity between the two release profiles. There was no significant difference in % drug release between optimized batch and soft gelatin capsules (hydrochlorothiazide containing floating in-situ gel of D5). In the initial 30 min, soft gelatin capsules show lower release because time was required for dissolved the soft gelatin capsules.

Table 6. Kinetic model fitting.

Kinetic Model	L_1 Formulation	
	R^2	Equation
Zero-order	0.939	11.96x+12.36
First-order	0.596	6.179x+0.870
Higuchi	0.975	37.15x-7.109

Korsmeyer-Peppas	0.649	1.486x+0.826

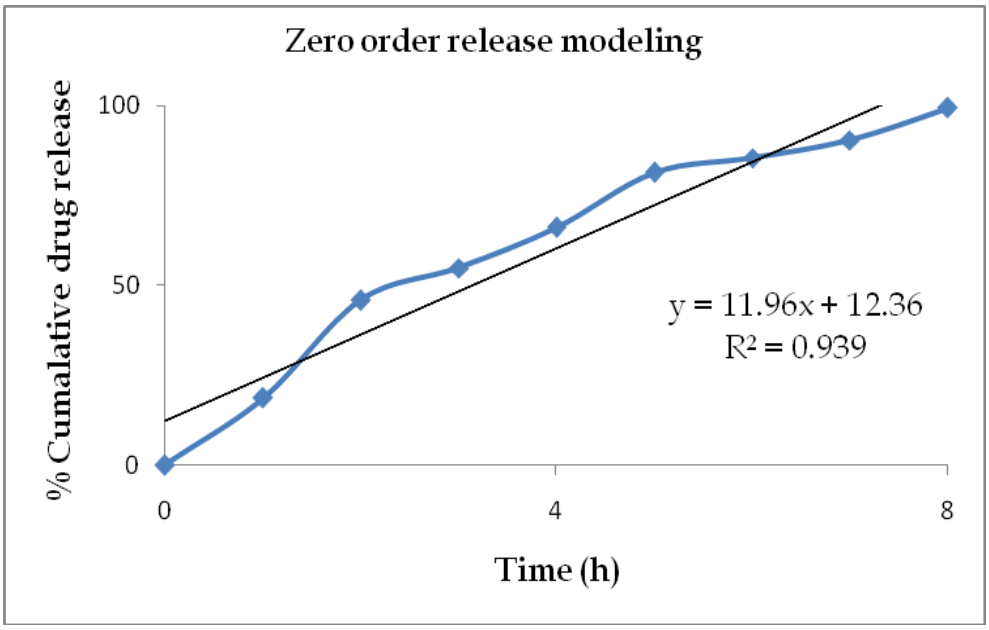

Figure 12. Zero order release modeling.

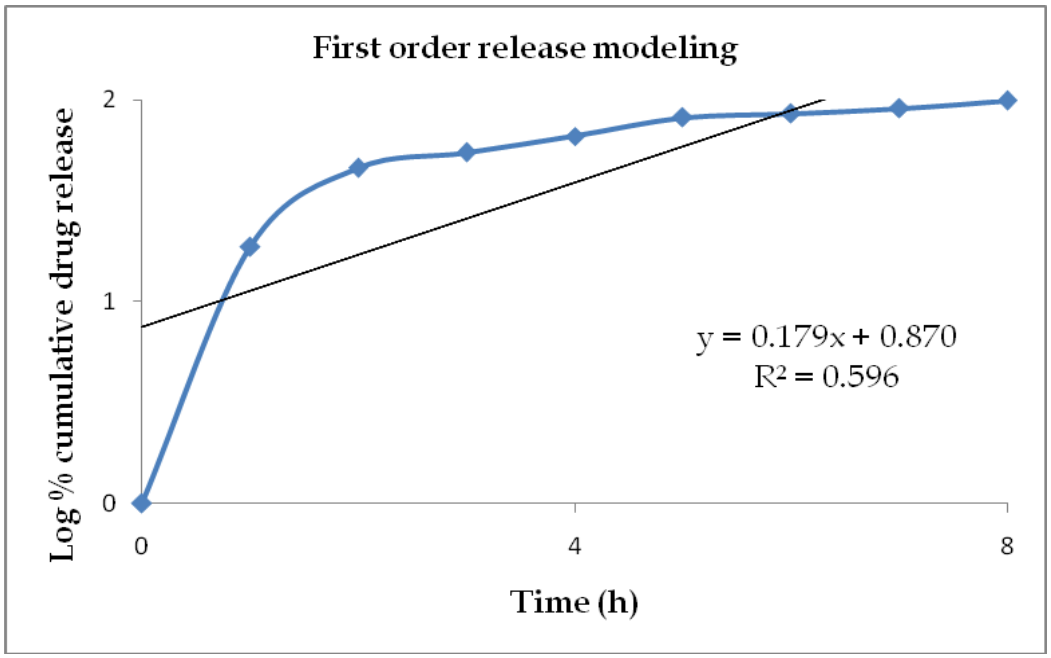

Figure 13. First order release modeling.

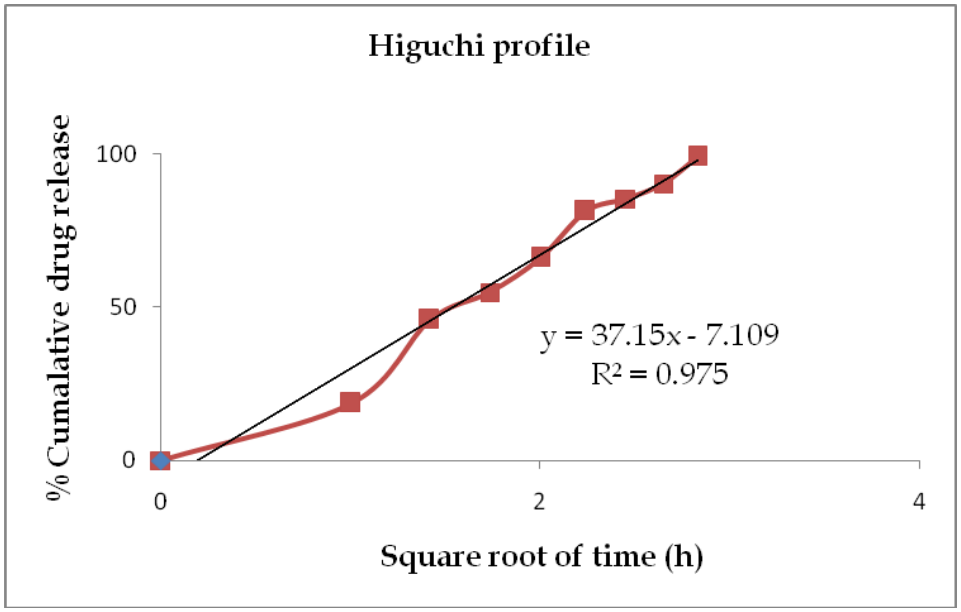

Figure 14. Higuchi profile release modeling.

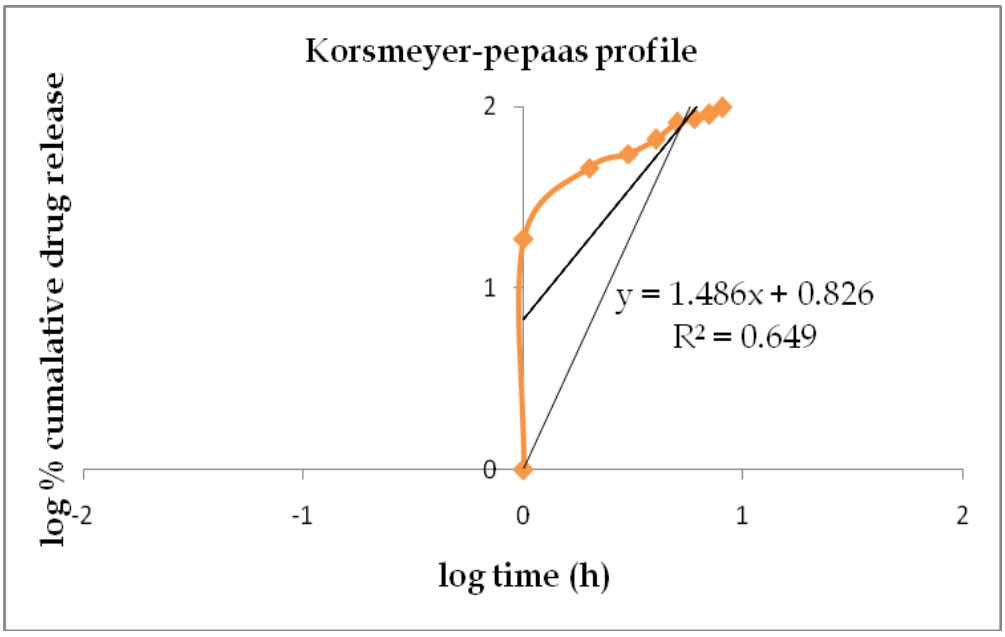

Figure 15. Korsmeyer-Peppas profile release modeling.

A typical Higuchi profile release modeling (R^2 0.975) pattern had been followed by the drug transport in the solution.

4. CONCLUSION

This study demonstrates that oral administration of soft gelatin capsules containing gel-forming hydrochlorothiazide solutions is formed in-situ gel at the stomach site. The amount and concentration of polymers have affected formulation and its properties. The gel was floated for more than 8 hr and give sustain drug release up to 8 hr. The proposed deacetylated gellan gum and alginate-based floating in-situ gelling systems of hydrochlorothiazide would

benefit the ease of administration, as being a liquid in soft gelatin and is more patient compliance.

5. CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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