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Development and Characterization of Verapamil Hydrochloride Hollow Microspheres

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Abstract:
The main objective of present study is to formulate and evaluate floating microspheres of Verapamil hydrochloride for treating hypertension. Verapamil hydrochloride is an effective antihypertensive drug but it undergoes hepatic first pass metabolism. Its half-life (t1/2) is 2-5 hrs and it should be administered 3-4 times to maintain plasma drug concentration. So, it requires control release of a drug. Hence an alternative drug delivery system is needed for increasing therapeutic efficacy, reducing the dosing frequency of drug and improving its half-life and bioavailability. Therefore, it is necessary to develop a newer formulation which releases the drug in a sustained release manner. Floating microspheres loaded with Verapamil hydrochloride were prepared using ionic gelation method using sodium alginate in different ratios. Sodium alginate as Microsphere core forming agent, calcium carbonate as Gas generating agent, and Calcium chloride as Cross inking agent were used for the formulation of Verapamil hydrochloride floating Microsphere. Preformulation studies like drug excipient compatibility studies, Particle size, particle shape, flow properties were carried out. Invitro buoyancy, Invitro dissolution studies, Entrapment efficiency and Drug content were performed. Preformulation studies for Verapamil hydrochloride loaded hollow microspheres demonstrated that all formulations exhibit good flow properties. SEM analysis demonstrated that the surface of hollow microspheres was smooth and spherical in shape. FTIR spectra studies displayed that there is no incompatibility between drug and excipients. Optimization of formulations done by maximum amount of drug release within 12h and buoyancy studies. Based on the results of invitro drug release studies it was found that F7 formulation has shown Sustained drug release for 12h with zero order drug release. Hence the optimized formulation (F7) of Verapamil hydrochloride hollow microspheres shows good potential for novel treatment of hypertension.

Keywords: Verapamil hydrochloride, Hollow microspheres, Ionic gelation method, sodium alginate, calcium carbonate.

INTRODUCTION

Over the last twenty years, oral drug delivery has been the predominant method for administering medications. To address the need for controlled release over time, researchers have developed

various oral delivery systems acting as drug reservoirs. However, challenges like rapid gastrointestinal transit and unpredictable emptying, lasting typically 8-12 hours, hinder consistent drug absorption. To counteract these challenges, researchers have devised systems to prolong drug retention in the stomach, exploit on the narrow absorption window of specific drugs in the upper gastrointestinal tract [1]

The researchers aim to develop a drug delivery system that sustains therapeutic drug concentrations in the bloodstream over prolonged durations, thereby decreasing dosing frequency and ensuring consistent plasma drug levels. This demands administering the drug in a controlled and regulated manner. Gastric retention systems are utilized to prolong drug residence time in the stomach, enhancing drug bioavailability. Additionally, this approach enhances the solubility of poorly soluble drugs in high pH environments and minimizes drug wastage [2].

Hollow microspheres" are vital to gastro-retentive drug delivery systems, acclaimed for their cost-effectiveness and exceptional buoyancy properties. These microspheres, distinguished by their hollow interior, are spherical particles ideally sized below 200 micrometers. Composed mainly of synthetic polymers or proteins, they evident as free-flowing powders, offering a versatile platform for controlled drug release [3]. The selection of plasticizer type, polymers, and solvents in floating microspheres fabrication plays a crucial role in determining drug release rate and buoyancy. Modification the polymer concentration and the polymer-to-plasticizer ratio is key to modulating the drug release profile. This optimization process ensures a controlled and desirable release rate of the drug from the microspheres, all while conserving their buoyancy properties.[4].

Verapamil, a calcium channel blocker belonging to the phenylalkylamine class, is prescribed for managing conditions like hypertension, cardiac arrhythmias, and angina. However, Verapamil hydrochloride falls into "BCS class II" due to its substantial presystemic metabolism, leading to low bioavailability (typically 20-30%) and poor solubility. Given the restricted absorption window of Verapamil hydrochloride in the upper gastrointestinal tract, the formulation of a gastric retention system becomes imperative to improve its efficacy and therapeutic outcomes. [5].

MATERIALS AND METHODS

Verapamil Hydrochloride was purchased from Dr. Reddy's laboratories Limited Hyderabad. Sodium alginate, calcium chloride and calcium carbonate. All the "chemicals are of Laboratory-grade and purchased from SD Fine Chemicals" Private Limited.

Formulation of floating hollow microspheres

Floating microspheres loaded with Verapamil hydrochloride were prepared using ionic gelation method using sodium alginate in different ratios. Sodium alginate as Microsphere core forming agent, calcium carbonate as Gas generating agent, and Calcium chloride as Cross linking agent were used for the formulation of Verapamil hydrochloride Microballoons. Microspheres containing Verapamil hydrochloride as a core material were formulated by ionotropic gelation method showed in Table 1. Initially, Sodium alginate solution was prepared by dissolving in distilled water at a concentration ranges from 0.5% to 4 % w/v then stirred thoroughly by using magnetic stirrer. Once complete clear solution is formed weighed quantities of Verapamil hydrochloride followed by calcium carbonate were added to the above dispersion. Then the above mixture was stirred at 500rpm, maintained room temperature. The mixture was sonicated for 30min to eliminate air bubbles that may have been formed during the stirring process. The homogenous dispersion was extruded using a 20G needle fitted with a 10 ml syringe into 100ml of 2% of calcium chloride solution containing,

being stirred at 100rpm for 10min into the gelation medium and set aside for1h for curing of microspheres. Then microspheres were collected, washed with distilled water and oven-dried at 60°C [6].

Table 1: Composition of Verapamil hydrochloride Microballoons

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Verapamil HCl	0.12gm	0.12gm	0.12gm	0.12gm	0.12gm	0.12gm	0.12gm	0.12gm
Sodium alginate	0.5gm	1gm	1.5gm	2gm	2.5gm	3gm	3.5gm	4gm
Calcium carbonate	1gm	1gm	1gm	1gm	1gm	1gm	1gm	1gm
Calcium chloride	2%	2%	2%	2%	2%	2%	2%	2%

Determination of absorption maxima

A drug solution with a concentration of 10 µg/ml in 0.1N HCl was prepared. To detect the UV spectrum of the drug, a dual-beam UV/Vis spectrophotometer was utilized. Verapamil hydrochloride's absorption maxima were identified by scanning the drug solution over a range of wavelengths from 200 to 400 nm.

Construction of Standard graph of Verapamil hydrochloride in HCl (0.1N)

A stock solution I of Verapamil hydrochloride with a definite concentration of 1000 µg/ml was prepared in a volumetric flask by dissolving 100 mg of the drug in 10 ml of ethanol and then making up the volume to 100 ml with 0.1 N HCl (stock I solution). From this stock I solution, 10 ml was taken and made up to 100 ml with 0.1 N HCl to obtain stock II solution with a concentration of 100 µg/ml. To create a series of dilutions, aliquots of the stock II solution were taken and further diluted to obtain drug concentrations of 10, 20, 30, 40, 50, 60, and 70 µg/ml. The absorbance values of these concentrations were measured using UV-visible spectroscopy at 278 nm. Subsequently, the measured absorbance values were plotted against the corresponding drug concentrations [7].

Drug Excipient Compatibility Study

FTIR Spectroscopy

FTIR (Fourier Transform Infrared Spectroscopy) studies were conducted using a Shimadzu instrument to assess drug-polymer compatibility utilizing the KBr pellet method. Both an optimized formulation and pure drug samples were analyzed via FTIR.

The compatibility studies aimed to investigate potential interactions between the excipients in the formulations and Verapamil hydrochloride. The IR spectra of pure Verapamil hydrochloride, excipients, and the optimized preparation were observed in the range of 4000 to 400 cm^{-1}.

DSC

DSC (Differential Scanning Calorimetry) study was employed to examine the physicochemical compatibility between the drug and excipients. Thermograms of both the pure drug and the optimized formulation were obtained using a DSC instrument (Perkin-Elmer, 4000). Calibration of the device was performed using an Indium standard. The samples (2-4 mg) were heated in sealed

aluminum containers at a temperature range of 20°C to 300°C, using nitrogen-purged gas, with a constant scanning speed rate of 10°C per minute [8].

Evaluation of Verapamil hydrochloride loaded hollow microspheres

Micromeritic properties

The micromeritic properties, such as bulk density, tapped density, Hausner's ratio, and Carr's compressibility index, were assessed for the hollow microspheres that were prepared [9]

The tapped density was determined using the tapping method. A graduated measuring cylinder was utilized to measure both the bulk density and tapped density of the materials. The sample was initially placed into the cylinder, and the bulk volume was recorded. Subsequently, the cylinder was subjected to 100 taps to obtain the final tapped volume.

Tapped density = "V_b – Vt / $V_b \times 100$"

Here, V_b and V_t are bulk & tapped volume resp.

Hausner's ratio and Carr's compressibility index for the microspheres were calculated using the following formulas [10]

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

$$Carr's\ Index = \frac{\text{Tapped denisty } - \text{Bulk density}}{\text{Tapped density}}\ x100$$

Angle of repose (AOR)

The angle of repose for the hollow microspheres was determined using the fixed funnel method. The angle of repose is defined as the highest angle that can be formed between a pile of freely floating microspheres and the horizontal plane.

To measure the angle of repose, the peak of the conical pile of hollow microspheres was allowed to freely fall through the funnel until it contacted the tip of the funnel. The funnel was attached with its end to graph paper and placed at a fixed height on a horizontal flat surface. The angle of repose can be calculated using the following formula [11].

$$Tan\theta = \frac{\text{h}}{r}$$

Where r = Cone base radius, h = Height of cone

Measurement of Particle Size

The particle size of the manufactured hollow microspheres was determined using an optical microscope. This involved computing the size of a hundred particles with an ocular micrometer, from which the mean size of the particles was derived [12].

Scanning Electron Microscope (SEM) analysis

The surface morphology of the optimised formulation examined using SEM. Hollow microspheres were scanned and analyzed using an electron microscope and a fine coat, Ion sputter. After being placed into a "Copper sample holder", the sample was spatter coated with gold and Carbon[13].

Percentage Yield

To determine the percentage yield, divide the weight of the dried hollow microspheres by the total quantity of the drug in the formulation, as well as the weight of all non-volatile excipients, then multiply by 100[14].

The following formula is used to calculate it:

$$\text{Percentage Yield} = \frac{\text{Weight of dried hollow microspheres}}{\text{Total amount of the drug+ non volatile substances}} X\ 100$$

Entrapment Efficiency (EE)

Based on overall drug content as well as the amount of unentrapped drug in the floating Hollow microspheres, the quantity of drug that has been trapped in the Hollow microspheres was computed. By using one dose equal of floating Hollow microspheres and washing them using 0.1N Hydrochloric acid to eliminate free drug on the surface and the unentrapped drug has been identified. By dispersing 120mg of the formulation (which was weighed precisely) in 10mlof 0.1M Hydrochloric acid and then stirred for about 12 hrs using a "magnetic stirrer" to mix the polymer and obtain the drug, the drug content of hollow microspheres was defined. A Whatman filter was used to filter both the whole and unentrapped drug solutions. The drug concentration was then measured at 278 nm spectrophotometrically after the required dilution with 0.1N HCl (15).

EE (%) was evaluated by the methodology below.

$$\text{EE (\%)} = \text{"}\frac{\text{Total drug content - unentrapped drug x100}}{\text{Total drug content}}\text{"}$$

***In vitro* Buoyancy studies**

To determine In-vitro buoyancy studies for floating microspheres USP type II dissolution apparatus was used. 120mg of microspheres were placed on top of 900ml of 0.IN HCI pH 1.2 and stirred at 50 rpm for a period of 12 h. Filtration was used to separate the layer of buoyant microspheres from the settling microspheres. The particles were dried completely and weighed separately [16].

The following formula was used to compute the buoyancy of microsphere

$$\text{Buoyancy (\%)} = Q_F/(Q_F+Q_S) \times 100$$

Here, Q_S and Q_F = weight of settled and floating Hollow microspheres respectively.

Drug Content

UV Spectrophotometry was used to determine the amount of drug in respectively formulation equivalent to a unit dose (120 mg). Each formulation was removed and pulverised to a fine powder in a glass mortar before being dissolved for 6 hours in a 0.1N HCl solution. After filtering the solution, the absorbance at 278 nm was measured [17].

***In vitro* Drug Release studies**

Verapamil hydrochloride release from the hollow microspheres was assessed using a USP Type 2 dissolution tester. The dissolution tests were conducted in 900 mL of 0.1 N HCl as the dissolution medium, with a rotation speed of 50 rpm and a temperature maintained at 37 ± 0.5 °C. Sample solutions of 5 mL were withdrawn at predetermined 12-hour intervals to analyze the release profile. To maintain sink conditions, an equal volume of dissolution media was replenished after each

withdrawal. The samples were then analyzed using a UV spectrophotometer at a wavelength of 278 nm. All experiments were conducted in triplicate [18].

Drug release Kinetic Studies

The release data was analyzed by fitting it to various kinetic equations, such as zero order, first order, Korsmeyer-Peppas, and Higuchi models. R^2 profile values were calculated for each model, enabling the determination of the release mechanism.

Statistical Analysis

The results of cumulative drug release for all formulations, corresponding to different ratio polymers were compared using one-way analysis of variance (ANOVA). This analysis was conducted using the Minitab 21.4.2 statistical package [19].

RESULTS

Absorption maxima wavelength of Verapamil Hydrochloride

Absorption maximum of Verapamil hydrochloride pure sample was found to be at 278nm using UV-Visible spectrophotometer

Standard graph of Verapamil hydrochloride in Acidic Buffer P^H 1.2

Verapamil hydrochloride standard graph data showed significant linearity over a concentration range of 0- 70µg/ml, with an R^2 value of 0.999, as shown in Table 2 and Fig 1. The equation was y= 0.0127x - 0.0062

Table 2: UV Spectrophotometric data of Verapamil hydrochloride in acidic buffer.

S. No	Concentration(µg/ml)	Absorbance
1	0	0
2	10	0.121
3	20	0.253
4	30	0.369
5	40	0.487
6	50	0.633
7	60	0.746
8	70	0.898

All the values are represented as Mean ± SD (n=3)

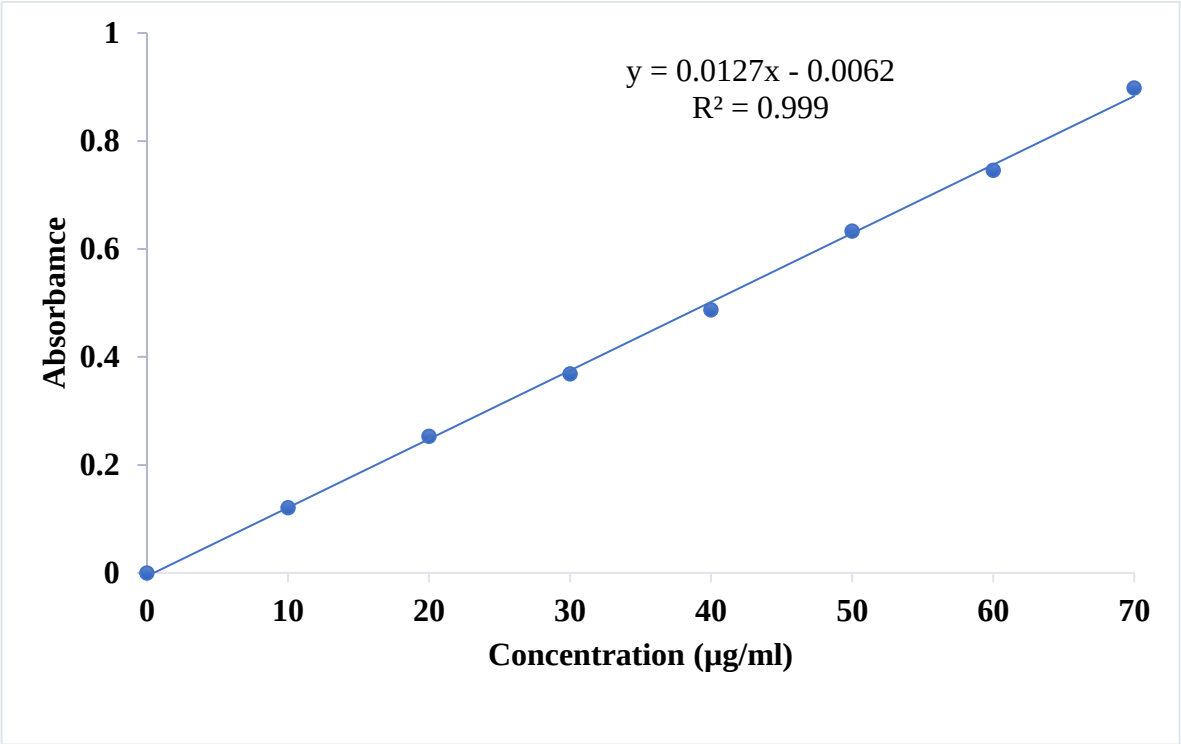

Fig 1: Standard curve of Verapamil hydrochloride in acidic buffer pH1.2.

Drug Excipient Compatibility Study

FTIR Spectroscopy

The drug-excipient compatibility study was carried out using Fourier transforms infrared spectroscopy. FTIR spectra indicated peaks at 3466, 2971,2868, 1443, 1259,1373,1052 and 515 cm-1, attributable to stretching of the C-H, N-H, N-O, -OH, C-O, C-N and meta substituted benzene respectively. Peaks of 3357, 1608, 1523, 1451, 1235,1023 and 702 cm-1 were visible in the FTIR spectrum of polymer. In Fig 2 and 3 the FTIR spectrum of the optimized formulation revealed both peaks associated with the drug and the polymer, showing no interaction with the drug polymer.

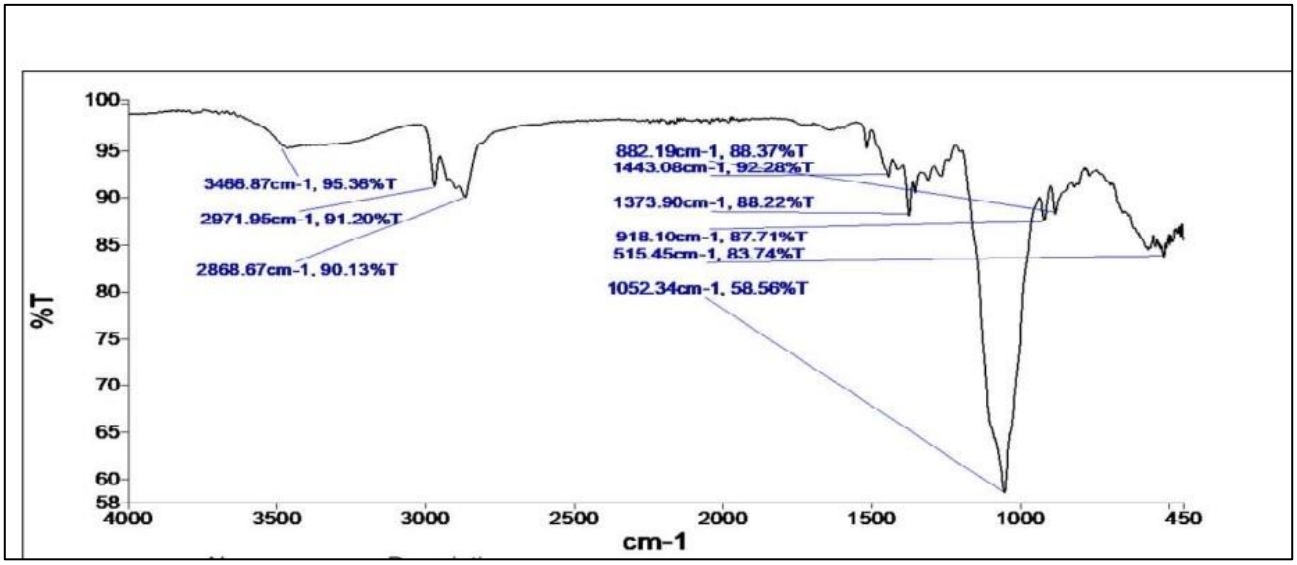

Fig 2: FTIR spectrum of Verapamil Hydrochloride pure drug.

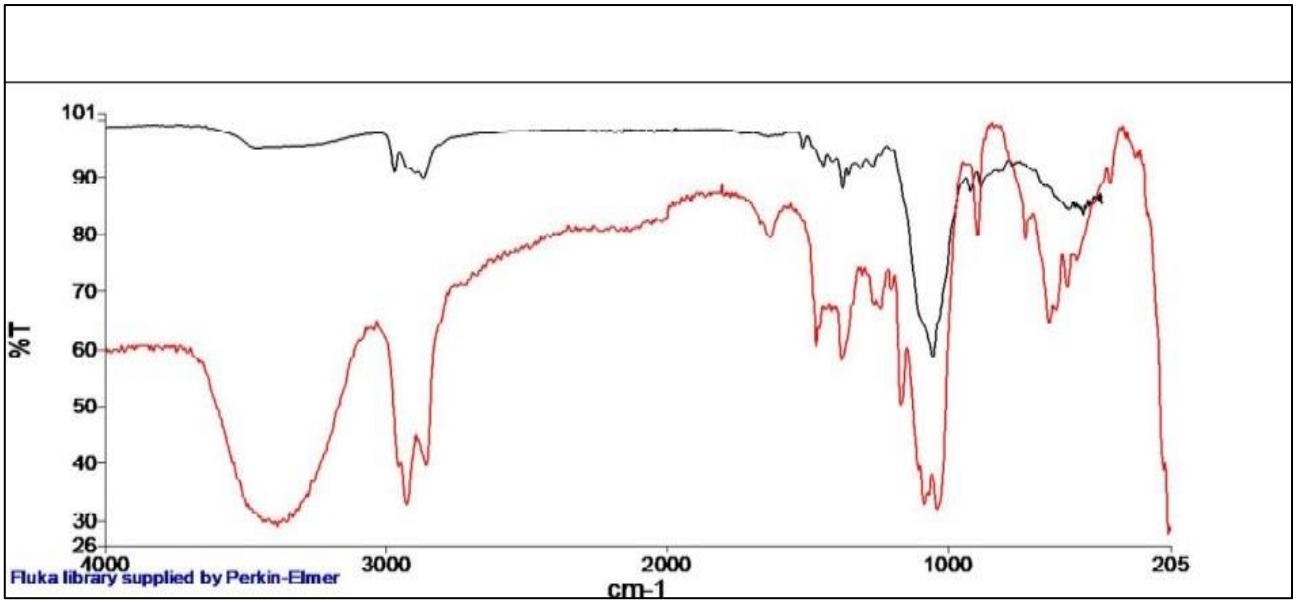

Fig 3: FTIR spectrum of optimized formulation.

SEM

SEM analysis revealed that floating microspheres (F7) were found to be smooth, slightly spherical, and slightly sharp edges shown in Fig 4

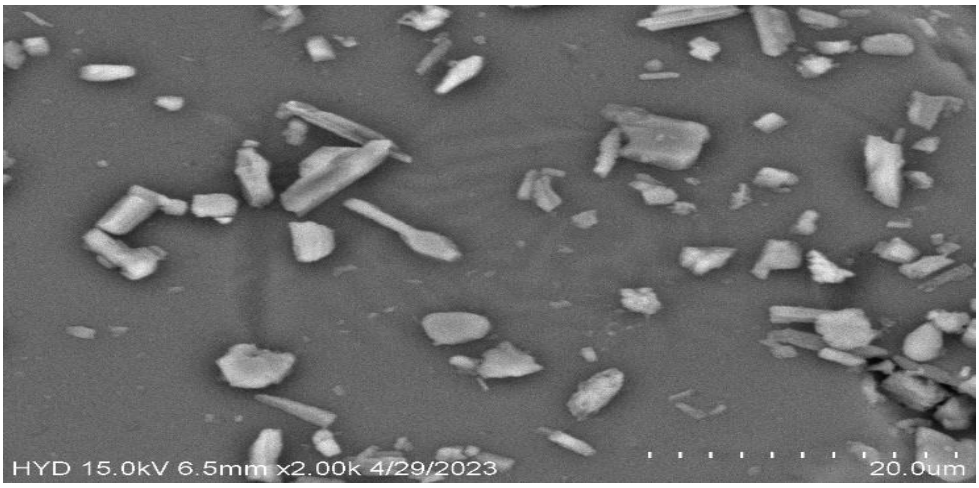

Fig 4: SEM image of optimized formulation F7.

Micromeritic Properties

The measured Hausner's ratio, Carr's index, and angle of repose were all within acceptable ranges, indicating adequate flow properties. All parameter values are shown in Table 3. Images of optimized formulation & Microscopic image of optimized formulation(F7) shown in Fig 5 a& b.

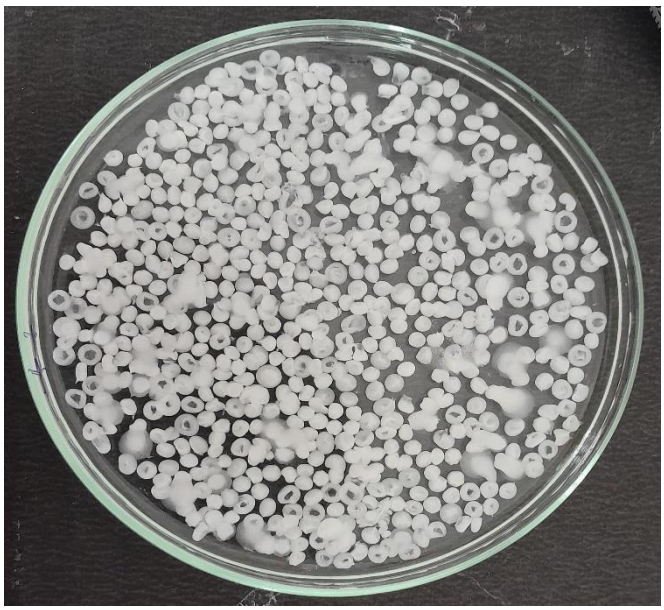

Fig 5 a: Image of Verapamil HCl loaded hollow microspheres F7

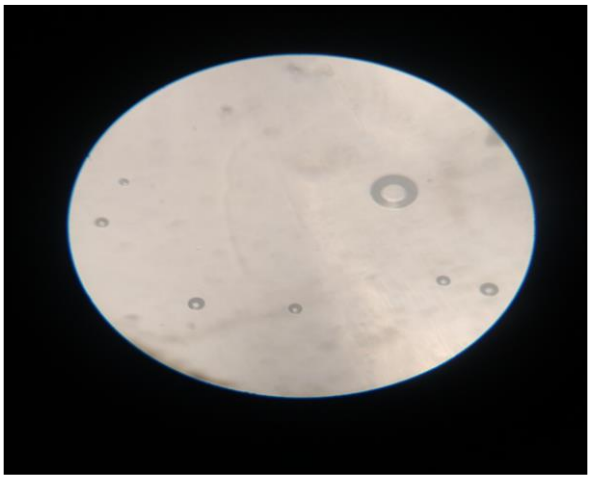

Fig 5b: Microscopic image of optimized formulation(F7).

Particle Size

The microsphere formulations (F1-F8) were observed to have a mean particle size that ranged from 126 to 186 µm

Table 3: Micromeritic Properties of all Formulations.

Parameter	F1	F2	F3	F4	F5	F6	F7	F8
Mean particle size(µm)	186.24±1.23	175.34±1.45	168.32±1.49	157.26±1.57	149.24±2.01	140.54±1.22	132.23±1.31	126.39±1.54
Bulk density	0.747±0.14	0.758±0.97	0.829±0.65	0.672±0.06	0.688±0.88	0.646±0.54	0.89±0.43	0.69±32
Tapped density	0.760±0.24	0.767±0.18	0.857±0.92	0.723±0.22	0.691±0.18	0.654±0.19	0.93±0.28	0.78±0.17
Compresibility index	4.23±0.19	8.437±0.26	6.28±0.19	6.94±0.92	7.84±0.94	8.94±0.22	7.27±0.91	8.29±0.84
Angle of repose	25.14±0.49	26.83±0.28	24.04±0.29	26.23±0.34	28.98±0.18	27.49±0.28	26.17±0.91	26. 33±0.18
Drug content	95.12±0.17	97.44±0.18	94.56±0.13	95.79±0.12	96.49±0.74	97.01±0.59	98.66±0.61	96.55±0.77

Percentage yield

The % yield of the all formulated microballoons was calculated. Table.4 shows percentage yield outcomes. For all formulations, the percentage yield ranged from 73 to 95%. Increasing the concentration of sodium alginate increases the percentage yield.

Table 4: Various Evaluation Parameters of all Formulations.

Formulation Code	%Yield	%EE	%B
F1	73.4	71.9	69.5
F2	82.3	81.5	74.3
F3	84.2	87.5	80.9
F4	85.8	90.5	85.2
F5	90.5	92.8	88.2
F6	91.3	92.1	90.7
F7	92.5	93.6	95.5
F8	95.1	90.2	98.7

All the values are presented as Mean ± SD (n=3)

Entrapment efficiency

The entrapment efficiency of floating microballoons was calculated, and the results are summarized in Table 4. The optimized formulation exhibited an entrapment efficiency of 93.6%, while the range varied from 71% to 93% for all formulations. Formulations containing low concentrations of sodium alginate tends to entrap less amount of drug due to porous nature compared to that of F7. A comparison of percentage yield, particle size, and entrapment efficiency is illustrated in Fig 6, represented by a clustered column and line chart.

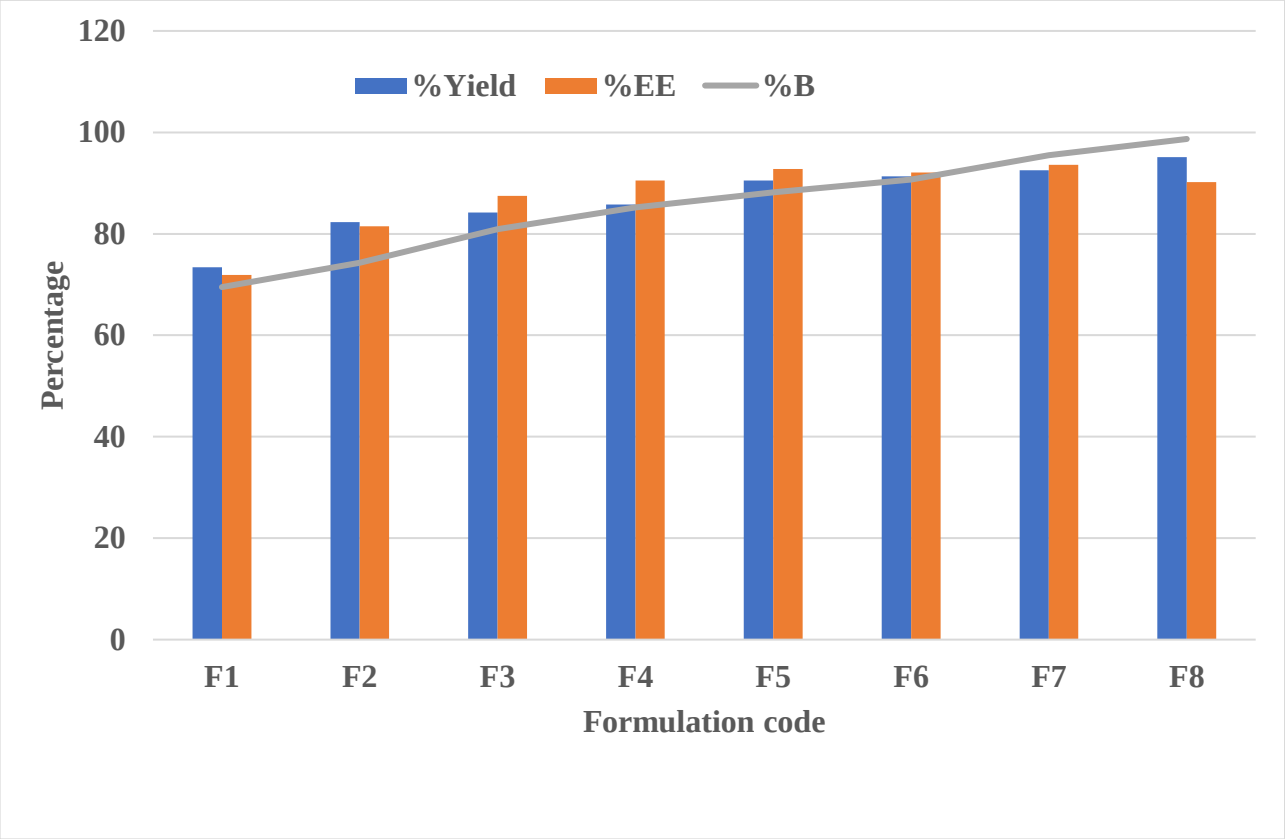

Fig 6: Comparison of %Yield, Entrapment efficiency and %Buoyancy for all formulations.

***In vitro* Buoyancy**

To examine the buoyancy of produced microspheres, an *In vitro* buoyancy test was conducted. The table below displays the floating ability for the formulations (F1 to F8). The results also indicated that a microsphere's ability to float increased with increasing the concentration of sodium alginate. All formulations exhibited buoyancy and obtained percentage buoyancy between 69 and 98%; the optimized formulation had a percentage buoyancy of 95.5 %.

Drug content

The drug content of all prepared formulations falls within the range of 95% to 98.0%. These values are within acceptable limits. The specific values obtained are represented in Table 4.

***In vitro* drug release studies**

All formulations were dissolution tested using a USP paddle type dissolution apparatus. Different formulations dissolution profiles were compared. Tables 5 show the cumulative % drug releases of F1-F8 at the end of 12 hours, while Figure 7 depict the dissolution profile. Formulations containing low concentration of sodium alginate are unable to sustain the drug release due to numerous pores

in microspheres. For formulations containing high concentration of sodium alginate retard the drug release up to 12h.

Table 5: Percentage drug release data of Verapamil hydrochloride loaded hollow microspheres F1 – F8.

Time (h)	%Drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	35.5±0.08	20.8±0.5	18.6±0.02	17.6±0.02	16.6±0.12	14.4±0.93	5.3±0.32	5.1±0.98
1	66.5±0.28	57.4±0.18	40.2±0.23	37.5±0.32	32.9±0.24	28.2±0.26	10.9±0.42	8.2±0.45
2	80.12±0.49	69.2±0.45	53.3±0.42	49.3±0.47	42.2±0.43	37.6±0.47	27.5±0.09	15.5±0.57
3	99.3±0.32	87.8±0.38	74.9±0.21	69.8±0.98	57.6±0.66	52.5±0.32	37.5±0.58	27.3±0.17
4		99.6±0.73	81.5±0.22	75.4±0.26	68.9±0.85	64.9±0.82	43.4±0.41	39.2±0.83
6			99.1±0.31	90.2±0.32	80.27±0.41	72.5±0.17	56.2±0.95	49.5±0.37
8				99.4±0.04	95.49±0.33	91.4±0.04	72.4±0.73	66.4±0.88
10					100.1±0.58	99.9±0.04	83.5±0.29	80.5.5±0.21
12							98.1±0.11	94.4±0.65

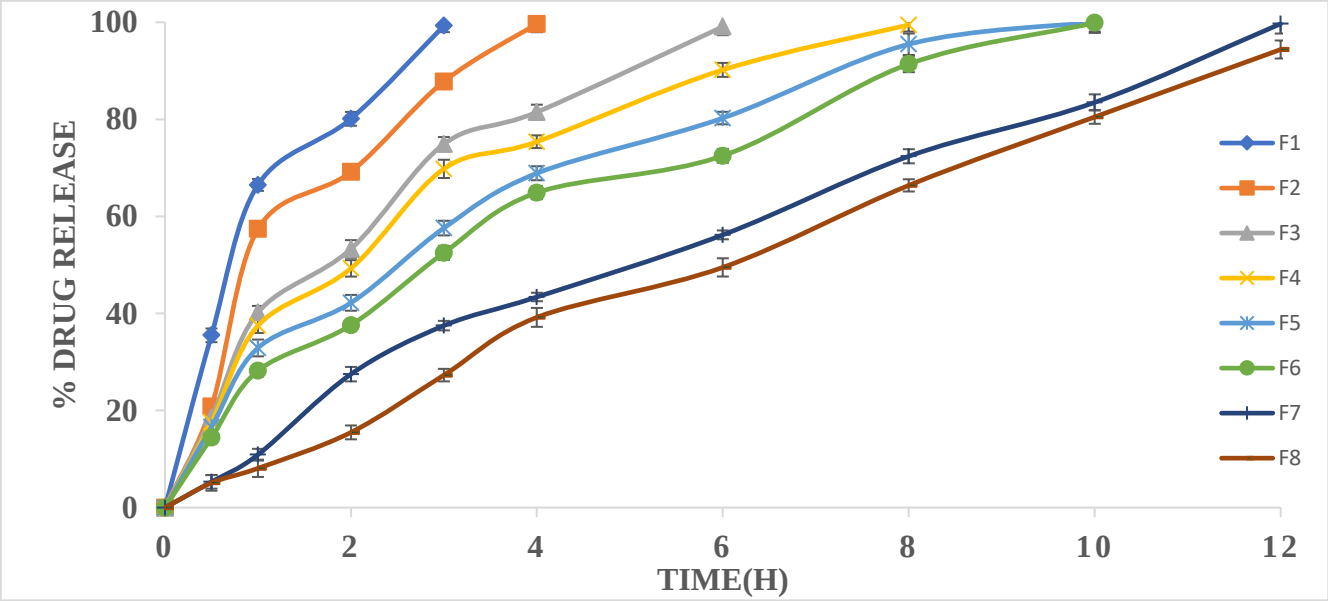

Fig 7: *In-vitro* drug release of Verapamil hydrochloride loaded hollow microspheres F1 – F8.

By comparing release data with mathematical models, the release kinetics of specific classes of controlled-release systems can be modeled to predict solute release rates and understand solute diffusion behavior through polymers. Plotting dissolution data serves the purpose of elucidating release mechanisms and quantitatively analyzing and translating them into mathematical terms.

Optimized Formulation *In vitro* drug release order kinetics

The above mentioned data show that the release of drug followed a mechanism of zero order since the value of the regression coefficient, which is 0.997 in the case of a zero-order plot, is closer to unity given in Table 6 and shown in Fig 8 . When the first-order equation is used to plot this data, it shows less linearity. Hence, it can be said that zero order kinetics is the primary drug release mechanism shown in Fig 9.

Table 6: Optimized formulation's drug release kinetics.

Formulation Code	Zero Order	1st Order	Korsmeyer-Peppas	Higuchi
	R^2	R^2	R^2	R^2
F7	0.997	0.614	0.744	0.950

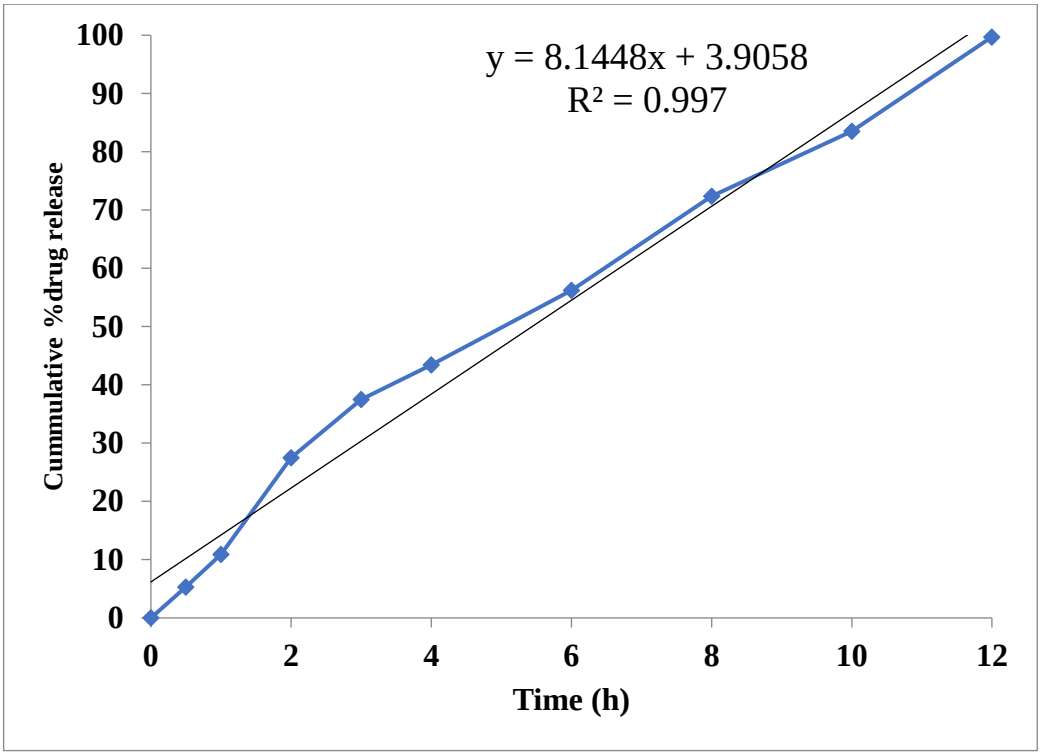

Fig 8: optimized formulation F7 zero order plots.

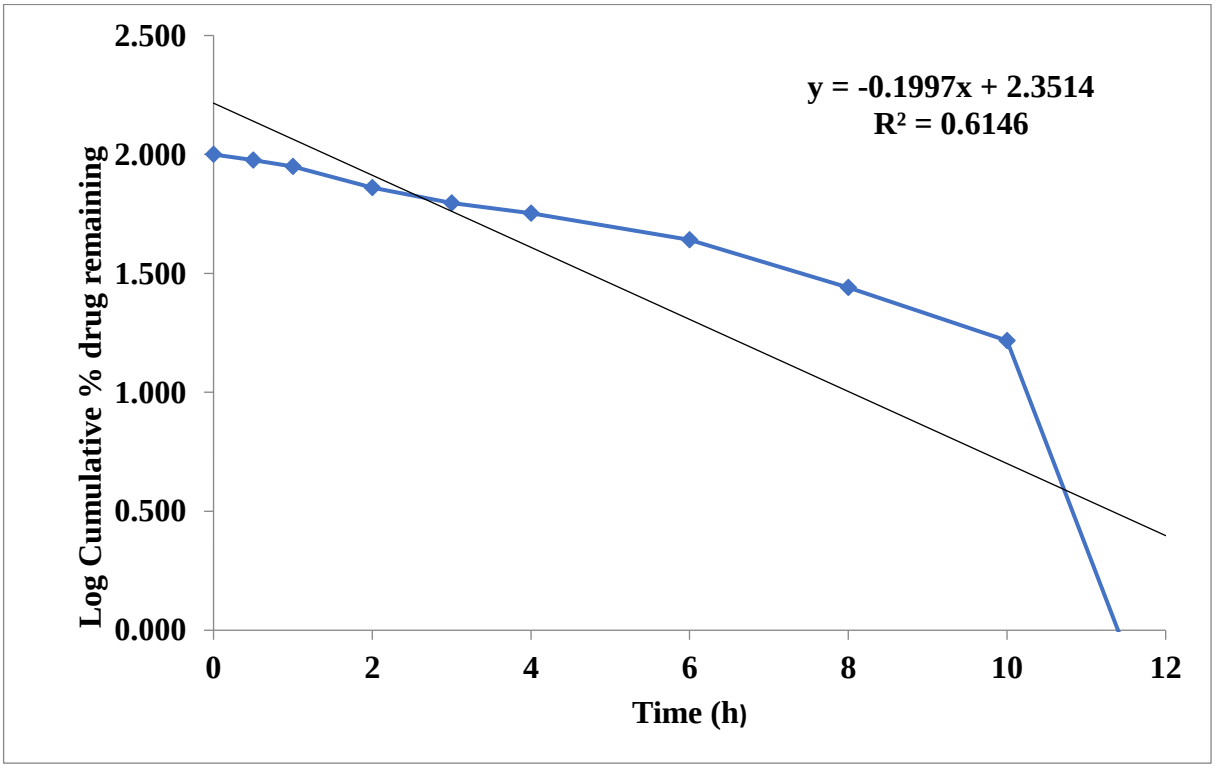

Fig 9: 1st order plots for the optimized formulation F7.

Furthermore, by putting data from the dissolving investigations into different mathematical modeling, including Korsmeyer- Peppas and Higuchi plots, it was possible to comprehend the process of drug release shown in Fig 10 and Fig 11.

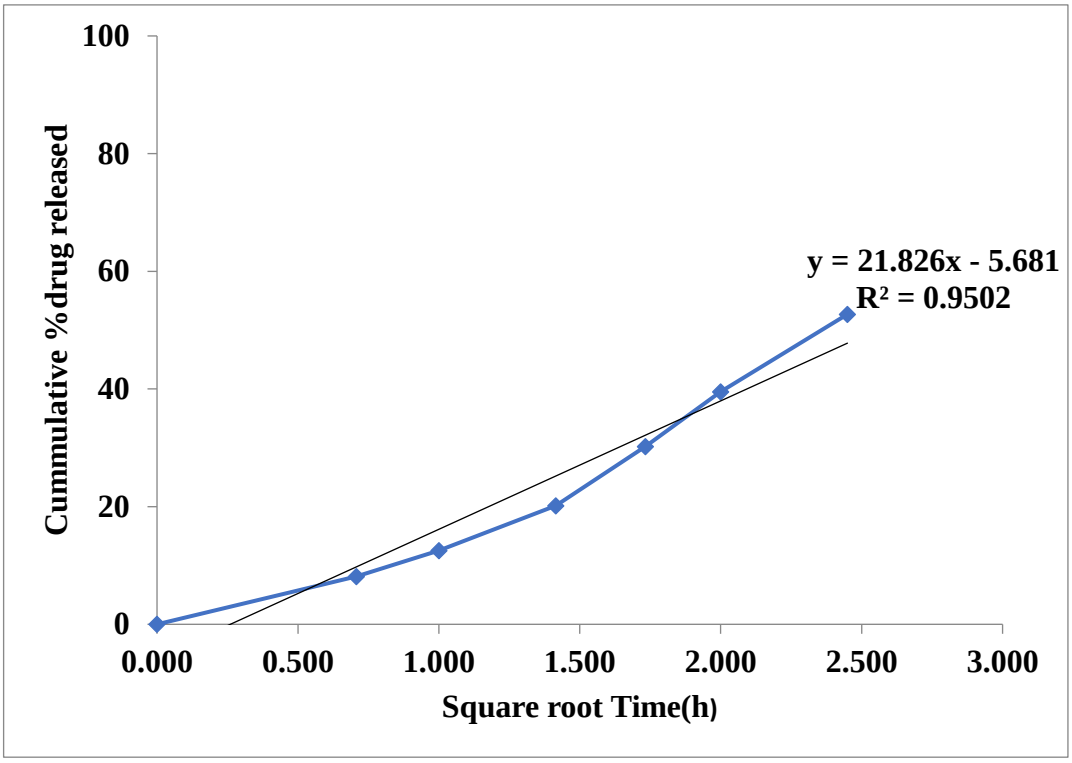

Fig 10: Optimized formulation F7 Higuchi plots.

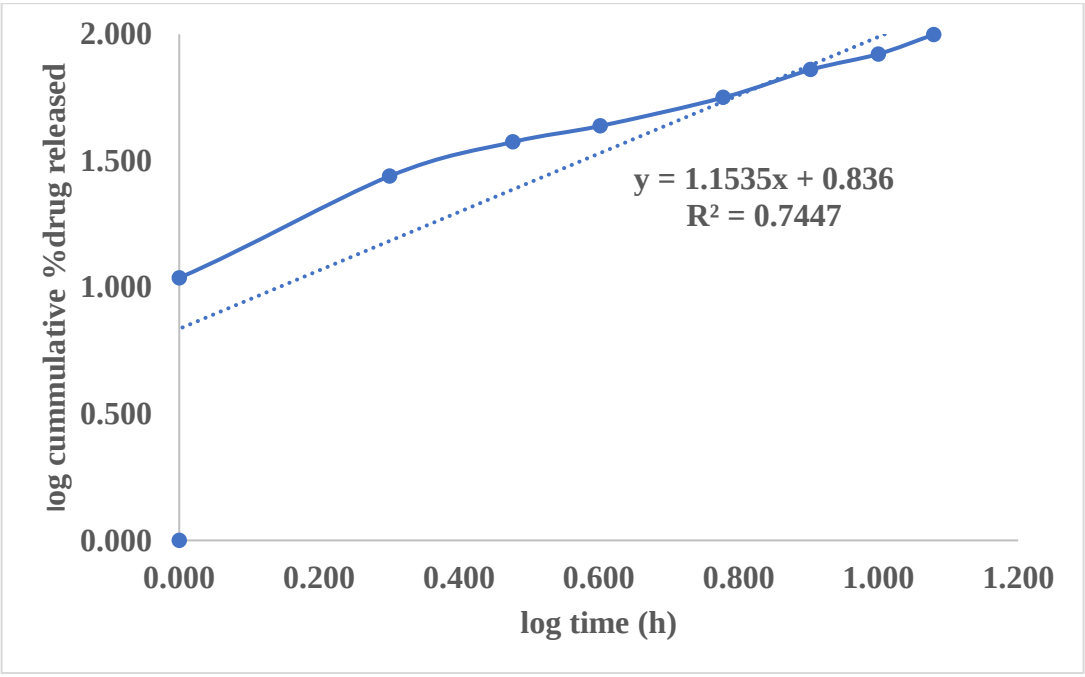

Fig 11: Optimized formulation F7 korsmeyer-peppas plots.

Statistical analysis

ANOVA was performed using Minitab version 21.4.2 software trial version (Minitab Inc., State College, PA, USA)[20] for Drug release of all formulations and the values are shown in Table 7. Based on ANOVA there is no significant differences between all formulations.

Table 7: ANOVA of %Drug release values for all the formulations.

Source	Degree of freedom	Sum square	Mean square	F value
Factor	7	2570.34	367.19	0.3
Error	56	69179.18	1235.34	
Total	63	71749.52		

CONCLUSION

In the current work sodium alginate, calcium carbonate and calcium chloride were used to formulate verapamil loaded hollow microspheres. According to the study's findings, hollow microspheres can be successfully formed with the Ionic gelation approach. The drug was determined to be compatible with all of the excipients utilized in the research after a drug-excipient compatibility analysis was performed by FTIR . Prepared Hollow microspheres were evaluated for the following in vitro evaluation tests such as micromeritic properties, tapped density, particle size measurement, percentage yield, entrapment efficiency, in vitro buoyancy, drug content, results of all the tests were within the Pharmacopoeial specifications and the Microballoons remained buoyant for more than 12 hrs in 0.1NHCl. The *in vitro* experiments showed that the largest amount of medication was released from hollow microspheres made with high concentration of sodium alginate (F7). As a result, it is regarded as the optimal formulation. The improved formulation (F7) is said to release the drug in zero order according to the *in vitro* drug release kinetics, which is based on first-order regression values for the Korsmeyer- Peppas and Higuchi models, respectively.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SEM: Scanning electron microscopy; **FTIR:** Fourier -transform Infrared spectroscopy;
EE: Entrapment efficiency : **AOR:** Angle of repose.

SUMMARY

Hollow microspheres of Verapamil hydrochloride were prepared by ionic gelation method approach to reduce the dosing frequency and to improve the bioavailability of drug by gastric retention for the treatment of hypertension. For the formulation of hollow microspheres mainly depends on the quantity and type of polymers selected. Natural polymer sodium alginate were selected for formulation of microballoons. All formulation were evaluated for preformulation studies, Invitro dissolution, Entrapment efficiency. Among them F7 formulation is considered as optimized as maximum amount of drug release with 12h, high entrapment efficiency and high buoyancy percentage. The optimized formulation claimed to release the drug at zero order.

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