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Development, Characterization, and In Vitro Assessment of Valsartan-Loaded Porous Microspheres Using Emulsion Solvent Evaporation Technique

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ABSTRACT

This study aims to develop and evaluate floating microspheres of valsartan using the emulsion solvent diffusion technique to improve drug release and bioavailability. Single-unit formulations often pose issues such as gastrointestinal obstruction and irritation, whereas multiple-unit systems like floating microspheres ensure uniform movement through the gastrointestinal tract, thereby enhancing absorption and reducing variability. Valsartan microspheres were prepared using ethanol and dichloromethane as solvents, with a 1:1 ratio of dichloromethane to ethanol found optimal for forming free-flowing microspheres. Various drug-to-polymer (ethyl cellulose) ratios (1:1, 1:2, 1:3, 1:4, 1:5) were tested. Increasing polymer concentration improved entrapment efficiency, yield, and buoyancy, while decreasing loading efficiency. Micromeritic properties indicated excellent flowability with an angle of repose less than 40 degrees. In vitro drug release studies showed that formulations with lower polymer ratios (1:1 and 1:2) had the highest drug release rates, best fitting the first-order kinetic model, while higher polymer ratios (1:4 and 1:5) were best described by the Korsmeyer-Peppas model, indicating diffusion-controlled release. Fourier-transform infrared spectroscopy confirmed no significant interaction between valsartan and excipients. Calibration curves in methanol, distilled water, and phosphate buffer (pH 6.8) were linear, with high correlation coefficients.

Keywords*:* Floating Microspheres, Emulsion Solvent Diffusion Technique, Drug Entrapment Efficiency, Drug Loading Efficiency

INTRODUCTION

Hypertension is a prevalent cardiovascular condition affecting millions globally, and its management often necessitates the use of antihypertensive drugs. Valsartan, an angiotensin II receptor blocker (ARB), is extensively employed in treating high blood pressure and heart failure due to its efficacy in reducing cardiovascular morbidity and mortality. Despite its therapeutic benefits, Valsartan's clinical application is limited by its poor water solubility and bioavailability, necessitating innovative drug delivery systems to enhance its performance (Lee et al., 2013).

Microspheres have emerged as a promising drug delivery system owing to their ability to encapsulate active pharmaceutical ingredients, thus improving solubility, stability, and controlled release properties. Porous microspheres, in particular, offer advantages such as a high surface area-to-volume ratio, tunable porosity, and efficient drug loading capacity. The emulsion solvent evaporation technique is a widely used method for preparing drug-loaded porous microspheres due to its simplicity, cost-effectiveness, and capability to produce uniform particles (Hajba-Horváth et al., 2020).

This study aims to develop and evaluate Valsartan-loaded porous microspheres using the emulsion solvent evaporation technique. The preparation involves dissolving Valsartan in a suitable solvent and emulsifying it into an aqueous phase containing a stabilizer. Subsequently, the solvent is evaporated, forming microspheres with Valsartan encapsulated within the porous matrix. Various parameters, such as the type and concentration of the stabilizer, solvent selection, and emulsion conditions, are optimized to achieve microspheres with desired characteristics (Prieto et al., 2021).

Characterization of the prepared microspheres is conducted using techniques such as scanning Fourier-transform infrared spectroscopy (FTIR) to confirm drug encapsulation and compatibility with excipients. Additionally, the encapsulation efficiency, drug loading capacity, and in vitro release profile of Valsartan from the porous microspheres are evaluated to ascertain their potential as a controlled release system (Zhao et al., 2016).

The development of Valsartan-loaded porous microspheres aims to address the challenges associated with its poor solubility and bioavailability. By enhancing these properties, the microspheres are expected to improve the therapeutic efficacy of Valsartan, offering a promising approach for better management of hypertension and related cardiovascular conditions. This research contributes to the growing field of advanced drug delivery systems, highlighting the potential of porous microspheres in enhancing the performance of poorly soluble drugs (Sadoun-Daikha et al., 2022; Šoltys et al., 2019).

MATERIALS AND METHODS

Valsartan, received as a complimentary sample from Torrent Pharmaceuticals in Ahmedabad, India, Ethyl cellulose, dichloromethane, ethanol, polyvinyl alcohol, and Tween-80 were procured from Research Lab, Mumbai, India.

Preformulation Studies:

Determination of λmax of Valsartan

The optimal absorption wavelength (λmax) of valsartan was determined using a solution comprising methanol, water, and phosphate buffer at pH 6.8.

IR Spectrum of Valsartan

The infrared (IR) spectrum of valsartan was obtained using a Fourier Transform Infrared (FTIR) spectrophotometer. After collecting the sample, it was transferred to the IR platform, and the spectral wavelength was swept between 4000 and 400 cm^{-1}.

Interaction between Valsartan and Excipients

The physical IR spectrum of the valsartan and carrier mixture was obtained using an FTIR spectrophotometer. A small sample was placed directly onto the IR apparatus, and the spectrum was scanned from a wavelength of 4000 to 400 cm^{-1}.

Calibration Curve of Valsartan

The optimal dosage (λmax) of valsartan was determined by employing a solution consisting of methanol, water, and phosphate buffer (pH 6.8) (Tatar and Sağlık, 2002).

Preparation of Microspheres

The emulsion solvent diffusion technique was employed for the formulation of microspheres. The polymer and drug were dissolved in a solvent mixture of dichloromethane and ethanol in a 1:1 ratio. This dispersion solution was then added drop by drop into a 1.5% PVA solution containing 0.3% Tween-80. The resulting emulsion was stirred at 500 rpm using a propeller-type agitator for 2 hours. Afterward, the microspheres were separated by filtration, washed with water, and dried at room temperature in a desiccator for 24 hours (O'Donnell and McGinity, 1997; Arshady, 1989).

Evaluation of Microspheres

The microspheres were characterized based on their micromeritic properties, including particle size, tapped density, compressibility index, and flow properties.

Size and Size Distribution

The particle size of the microspheres was determined using an optical microscopy method. The size was measured with an optical microscope, and the mean particle size was calculated by measuring 200–300 particles using a calibrated ocular micrometer (Chaurasia, 2016).

Bulk Density (ρb)

Density of fine particles is often determined by using a measuring cylinder.

ρb =M / Vb

Where, M = Powder mass, Vb = Powder bulk volume (ρb) = Bulk density

Tapped Density

Tapped density of the microspheres was calculated as the ratio between the mass of the microsphere sample (g) and its volume (ml) after 100 tappings (Gopinath and Naidu, 2011).

Compressibility Index

% Compressibility index= [1- V/Vo] X 100

Here V and Vo are the volumes of the sample after and

before the standard tapping, respectively (Vilegave et al., 2013).

Angle of Repose

The angle of repose, which measures the resistance to particle flow, was determined using the fixed funnel method and calculated as:

The mixture was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained.

A = tan-1 (h/r)

The radius of the heap (r) was measured & angle of repose can be calculated.

Carr's Compressibility Index

The simplest method of measurement of powder flow is compressibility and sign of the ease with which a material can be induced to flow is given by compressibility (106). The compressibility index of the granules was calculated by Carr's compressibility index which is determined by using the following formula:

C= (V0-Vt / V0) ×100 (Patel, 2020)

Hausner's Ratio

It is an indirect index of ease of powder flow (109). It is determined by the following formula:

Hausner's ratio = ρt /ρb

Where, ρt = Tapped density ρb = Bulk density

Lower Hausner's Ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Drug Entrapment Efficiency:

To assess the drug content, 20 mg of microspheres were weighed and dissolved in 0.1N HCl solution under ultrasonication. After filtration through a Whatman filter paper, the resulting solution was further diluted, and the Valsartan content was determined spectrophotometrically using a UV 1800 Shimadzu (Japan) at 296 nm. In the concentration range of 1–8 µg/ml, the absorbance of Valsartan (Y) correlated well with its concentration (X):

Y=0.1411X (r2=0.9997, n=3) (Bharate and Vishwakarma, 2013; Tong and Whitesell, 1998)

The percentage drug entrapment and yield of microspheres were calculated as follows:

% Drug Entrapment= (Theoretical Drug Content Experimental /Drug Content) ×100

% Yield= (Total Weight of Drug and Polymer Used/Total Weight of Microspheres) ×100

Drug Loading Efficiency:

Percent drug loading was calculated as follows:

% Drug Loading Efficiency = (Weight of Drug Loaded in Microspheres/Total weight of Powdered Microsphere) ×100 (Graffner et al., 1985)

In-Vitro Buoyancy Studies:

For the in-vitro buoyancy studies, 50 mg of microparticles were added to a solution containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm using a magnetic stirrer. After 8 hours, the buoyant microparticles were pipetted off and separated by filtration. The particles in the sinking particulate layer were also separated by filtration. Both types of particles were dried in a desiccator until they reached a constant weight. The buoyancy was then determined by the weight ratio of floating particles to the total weight of both floating and sinking particles.

$$\% \text{ Buoyancy} = [Wf / (Wf + Ws)] \text{ X } 100$$

Where Wf and Ws are the weights of the floating and settled Micro particles, respectively. All the determinations were made in duplicate (Nyqvist, 1986; Viseras, and Lopez-Galindo, 1999; Borhade et al., 2012).

In-Vitro Drug Release Study:

The in-vitro release study of the microspheres was conducted using the USP rotating basket method. A weighed quantity of microspheres was placed in the basket, which was then immersed in 500 ml of dissolution medium (SGF, pH 1.2, HCl) at 37 ± 0.5 °C with a paddle rotation speed of 50 rpm. At intervals of 1, 2, 3, 4, 6, 8, and 10 hours, 5 ml samples were withdrawn, filtered through a Whatman filter, and analyzed using a Shimadzu 1800 UV spectrophotometer at 296 nm to determine the concentration of Valsartan. To maintain a constant volume, 5 ml of fresh dissolution fluid was added to the medium after each sample withdrawal (Soni et al., 2010; Wan et al., 2021).

Release Kinetics:

Zero-Order Model

Description: In zero-order kinetics, the drug release rate is constant and independent of the concentration of the drug.

Application: Ideal for controlled-release formulations where a constant drug release is desired over time.

Key Feature: The amount of drug released over time is linear.

First-Order Model

Description: In first-order kinetics, the drug release rate is directly proportional to the concentration of the drug remaining.

Application: Common in systems where the drug release rate decreases exponentially over time, such as in many immediate-release formulations.

Key Feature: The amount of drug released over time follows an exponential decay.

Higuchi Model

Description: The Higuchi model describes drug release as a diffusion process based on Fick's law, typically from a matrix system.

Application: Used for formulations like ointments and transdermal patches where the drug diffuses through a porous matrix.

Key Feature: The amount of drug released is proportional to the square root of time.

Korsmeyer-Peppas Model

Description: The Korsmeyer-Peppas model is used to analyse drug release from polymeric systems when the mechanism is not well known or is complex.

Application: Suitable for a wide range of drug delivery systems, especially when the release mechanism involves both diffusion and erosion.

Kinetic Models Used

$Q_t = K_0\, t$ (zero-order equation)

$\ln Q_t = \ln Q_0 - K_1\, t$ (first-order equation)

$Q_t = K_h\, t^{1/2}$ (Higuchi equation)

Application and Results

1. **Zero-Order Kinetics**: Suitable for systems where the drug release rate is independent of its concentration.
2. **First-Order Kinetics**: Suitable for systems where the release rate is concentration-dependent.
3. **Higuchi Model**: Describes drug release as a diffusion process based on Fick's law.

RESULT AND DISCUSSION

Single-unit formulations can pose issues such as sticking together or causing obstructions in the gastrointestinal tract, potentially leading to irritation. In contrast, a floating system composed of multiple unit forms offers several advantages over single-unit preparations. Multiple-unit particulate dosage forms, such as microspheres, can move uniformly through the gastrointestinal tract. This uniform movement helps to avoid the unpredictable nature of gastric emptying and allows for adjustable release. Additionally, these forms reduce inter-subject variability in absorption and minimize the risk of local irritation (Streubel, et al, 2002; Shah and Gupta, 2023).

The floating microspheres were prepared using the emulsion solvent diffusion technique. Ethanol and dichloromethane served as the primary solvents, with a PVA solution used as the continuous phase. Using ethanol alone did not facilitate the formation of a primary emulsion of the aqueous phase in the polymer solution; instead, ethanol's water miscibility caused the polymer (ethyl cellulose) to precipitate immediately upon mixing. To address this, dichloromethane, a non-polar solvent, was combined with ethanol to decrease the polarity of

the polymer solution. The optimal ratio of dichloromethane to ethanol was found to be 1:1, which enabled emulsion formation and produced good, free-flowing microspheres.

Valsartan microspheres were prepared using varying drug-to-polymer (ethyl cellulose) ratios of 1:1, 1:2, 1;3, 1:4 and 1:5. These microspheres were analyzed for drug entrapment, drug loading, yield, and buoyancy. The floating test was conducted to evaluate the buoyancy of the prepared microspheres. It was observed that increasing the polymer concentration improved entrapment efficiency, yield, and buoyancy, but decreased loading efficiency.

The micromeritic properties of the microspheres were characterized by measuring parameters such as mean diameter, angle of repose, tapped density, bulk density, and compressibility. All formulations exhibited excellent flowability, indicated by an angle of repose of less than 40 degrees.

Further, all microspheres underwent in vitro drug release studies. The resulting data were fitted into various kinetic models to determine the release properties The microspheres with drug-to-polymer ratios of 1:1 and 1:2 showed the highest correlation for first-order drug release, while those with a 1:5 ratio showed the highest correlation for the Higuchi model. The n value from the Korsmeyer-Peppas model ranged from 0.4957 to 0.5601 for the different drug-to-polymer ratios, indicating that the drug release from the microspheres was diffusion-controlled.

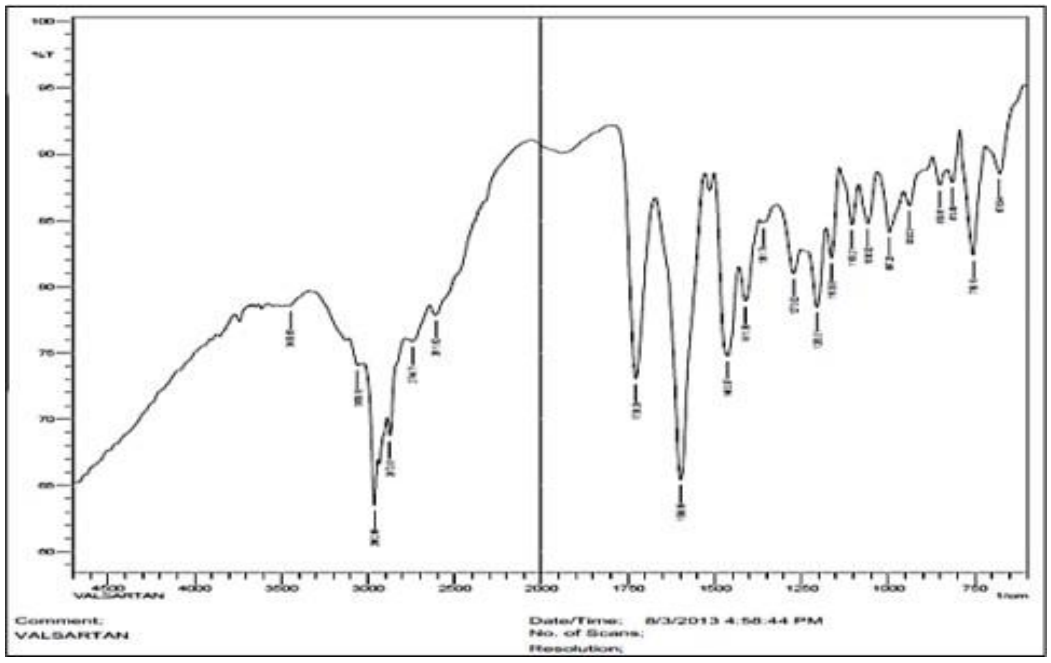

Figure 1: FTIR of Pure Valsartan

Table 1: FTIR Interpretation of Pure Valsartan

Sr. No	Type of Peak	Observed Peak (cm^{-1})
1	C-N Tertiary Amine	1205.33
2	C=O Ketone	1732.73
3	N-H Secondary Amine	1602
4	C-H Alkane	2963.76

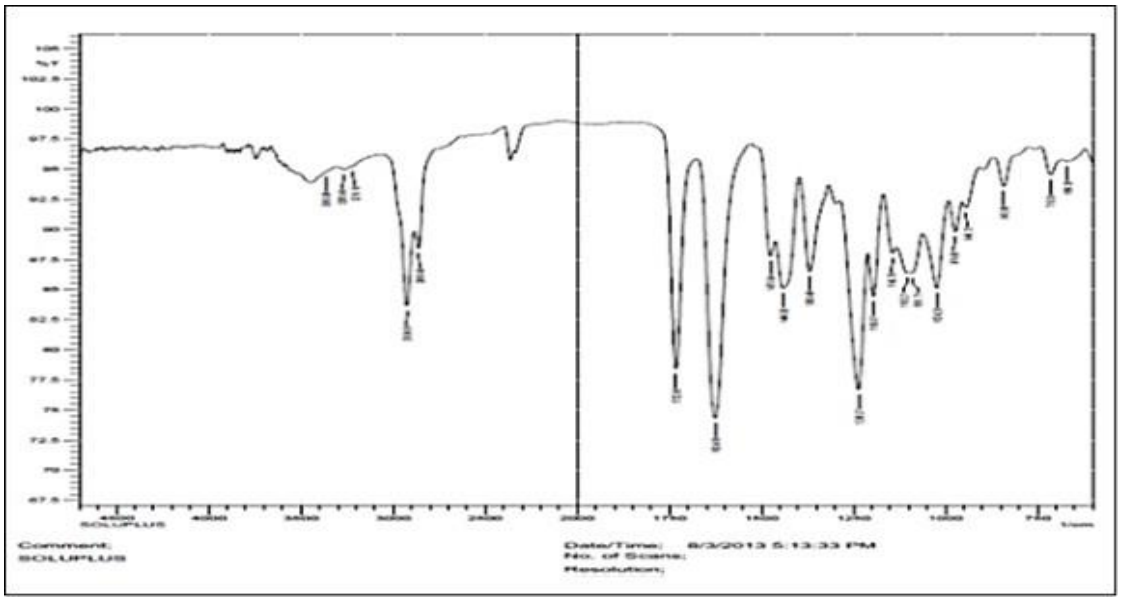

Figure 2: FTIR of Pure Valsartan and Excipients

Table 2: FTIR Interpretation of Valsartan and Excipients

Sr. No	**Type of Peak**	**Observed Peak (cm^{-1})**
1	N-H Secondary Amine	1602
2	C-H Alkane	2963.76
3	C-N Tertiary Amine	1205.33
4	C=O Ketone	1732.73

Calibration Curve of Valsartan

Table 3: Calibration Curve of Valsartan in Methanol

Concentration (µg/mL)	Absorbance
5	0.150
10	0.300
15	0.450
20	0.600
25	0.750
30	0.900

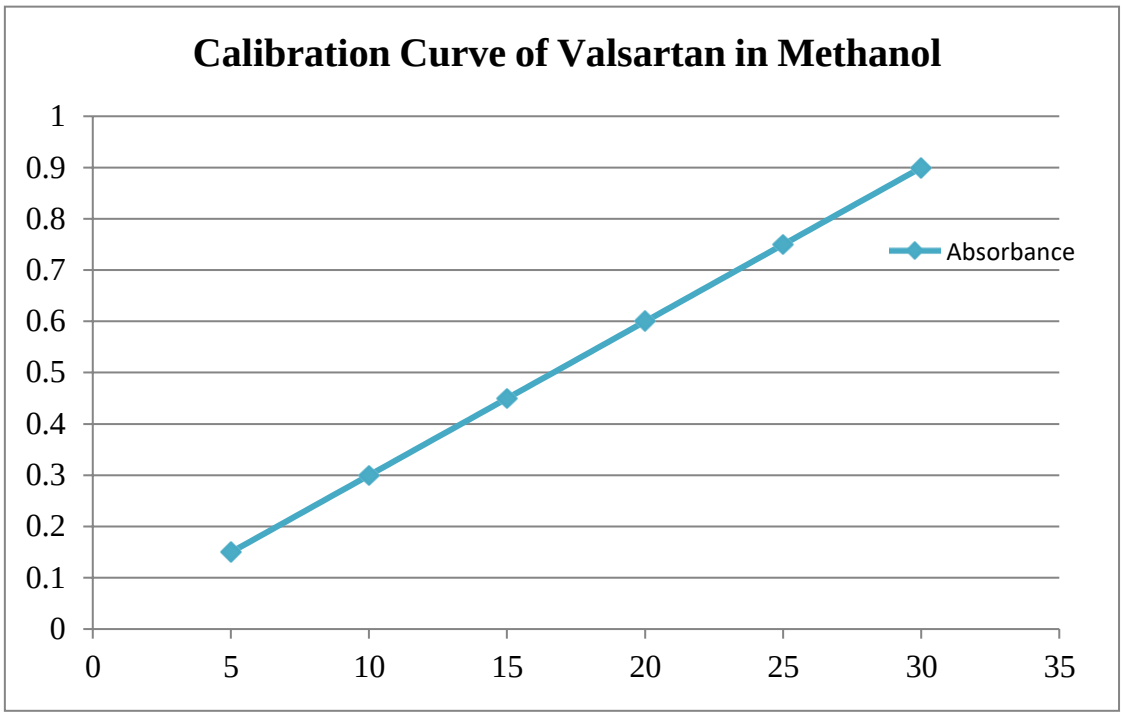

Figure 3: Calibration curve of Valsartan in Methanol

Table 4: Calibration Curve of Valsartan in Distilled Water

Concentration (µg/mL)	Absorbance
5	0.140
10	0.280
15	0.420

20	0.560
25	0.700
30	0.840

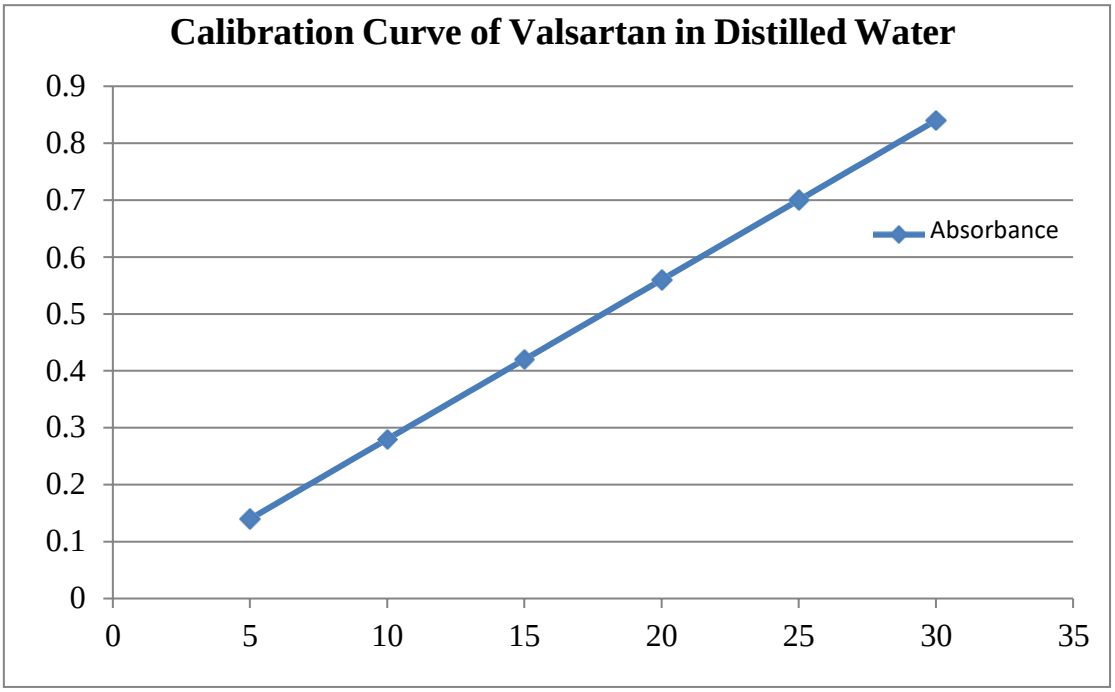

Figure 4: Calibration curve of Valsartan in Distilled Water

Table 5: Calibration Curve of Valsartan in PBS (pH 6.8)

Concentration (µg/mL)	Absorbance
5	0.160
10	0.320
15	0.480
20	0.640
25	0.800
30	0.960

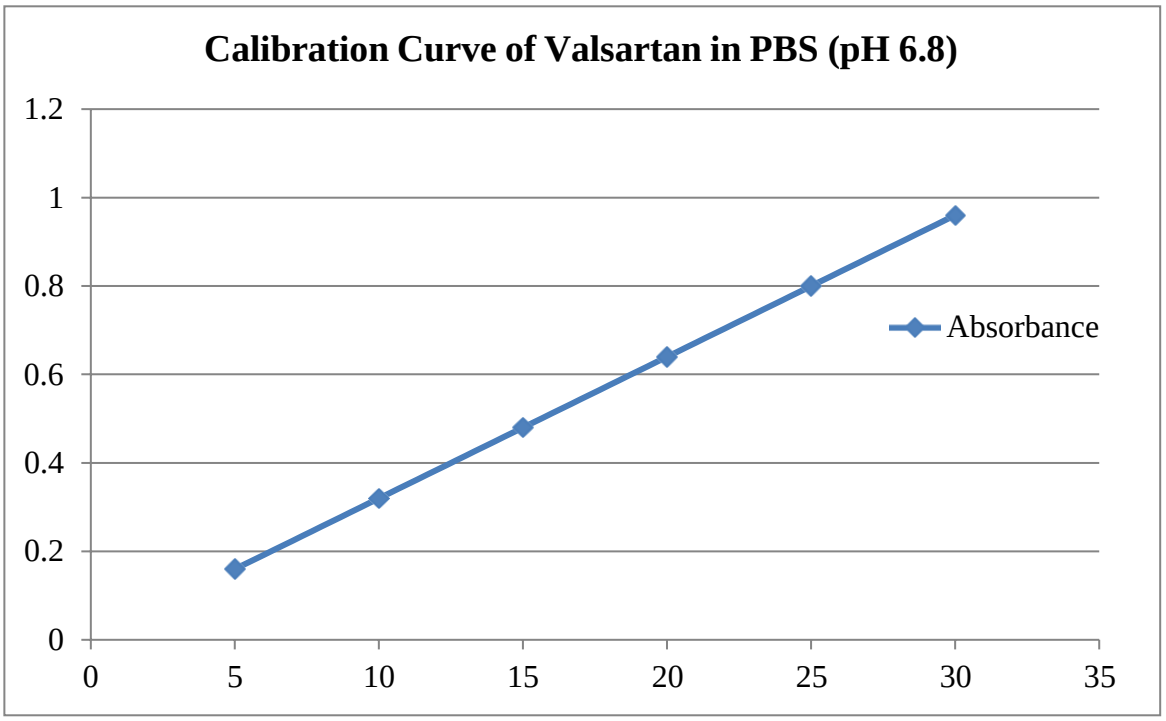

Figure 5: Calibration curve of Valsartan in PBS 6.8

Table 6: Physicochemical Properties of Valsartan floating Microsphere

Drug/Polymer Ratio	Entrapment Efficiency (%)	Theoretical Loading Efficiency (%)	Practical Loading Efficiency (%)	Yield (%)
F1 (1:1)	63.23±1.27	50.00	31.62	83.34±1.11
F2 (1:2)	74.08±1.68	33.33	24.69	87.58±1.32
F3 (1:3)	77.54±1.45	25.00	21.88	89.23±1.47
F4 (1:4)	79.32±1.52	20.00	18.54	90.12±1.58
F5 (1:5)	81.69±1.74	16.67	13.62	91.69±1.81

Table 7: Micromeritic Properties of Valsartan Floating Microsphere

Drug/Polymer Ratio	Mean Diameter (µm)	Tapped Density (gm/ml)	Bulk Density (gm/ml)	Compressibility (%)	Angle of Repose (°)
F1 (1:1)	84.73	0.375	0.273	27.27	11.48
F2 (1:2)	97.46	0.429	0.231	46.15	22.73
F3 (1:3)	88.12	0.445	0.250	43.82	19.54
F4 (1:4)	91.23	0.460	0.265	42.39	20.67
F5 (1:5)	92.81	0.500	0.200	60.00	16.99

Table 8: In vitro Drug Release of Valsartan Floating Microsphere

Time (hours)	F1	F2	F3	F4	F5
0	0.00	0.00	0.00	0.00	0.00
2	28.82±013	25.92±0.17	23.39±0.06	22.89±0.87	21.34±0.05
4	49.34±0.05	45.12±0.12	40.55±0.09	38.12±0.12	38.12±0.09
6	63.94±0.10	59.37±0.09	54.16±0.16	50.11±0.94	51.32±0.18
8	74.33±018	69.88±0.54	64.65±0.19	62.21±0.52	61.71±0.04
10	88.73±0.22	77.69±0.41	72.75±0.07	70.45±0.33	69.88±0.56

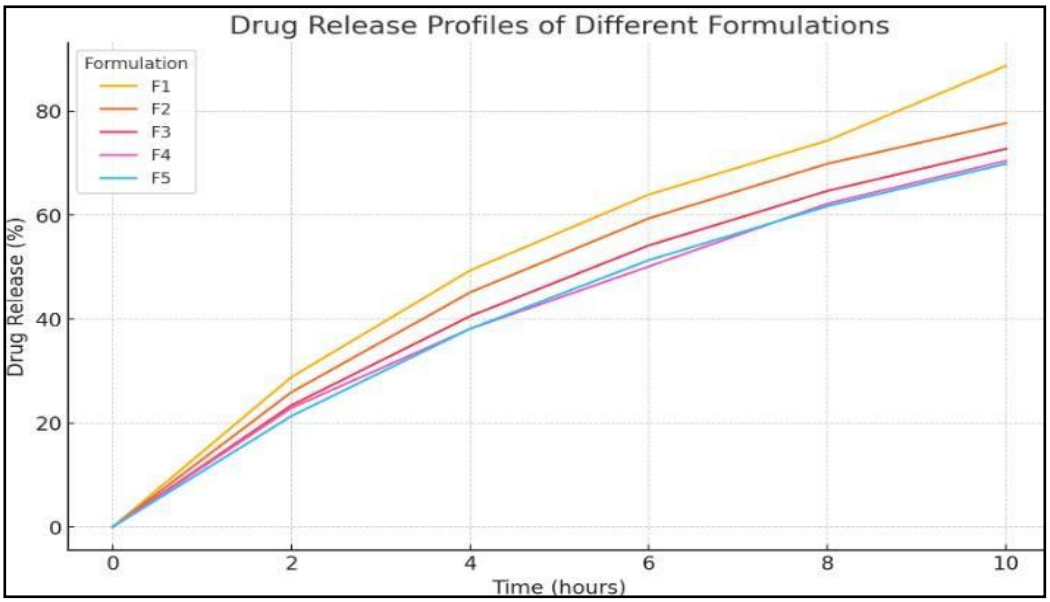

Figure 6: In-vitro Drug Release Profile of Valsartan Microsphere

F1: Shows the highest drug release percentage at each time point, reaching nearly 89% at 10 hours.

F2: Follows with a slightly lower release, reaching around 78% at 10 hours.

F3: Exhibits a more moderate release profile, achieving about 73% at 10 hours.

F4: Has a similar profile to F3 initially but shows slightly higher release at later time points, reaching about 70% at 10 hours.

F5: Shows the lowest release profile among the formulations, reaching about 70% at 10 hours.

Table 9: In vitro Drug Release Kinetic Parameter of Valsartan Floating Microsphere

Drug/ polymer ratio	Zero		First		Higuchi Model		Korsemeyer-peppas model	
	R^2	K0	R^2	K1	R^2	Kb	R^2	n
F1 (1:1)	0.987	5.42	0.993	0.17	0.992	23.76	0.995	0.4957
F2 (1:2)	0.991	4.68	0.996	0.15	0.994	21.43	0.997	0.5053
F3 (1:3)	0.988	4.21	0.992	0.14	0.991	20.56	0.996	0.5234
F4 (1:4)	0.989	3.94	0.995	0.13	0.993	19.87	0.998	0.5387
F5 (1:5)	0.992	3.58	0.997	0.12	0.995	18.94	0.999	0.5601

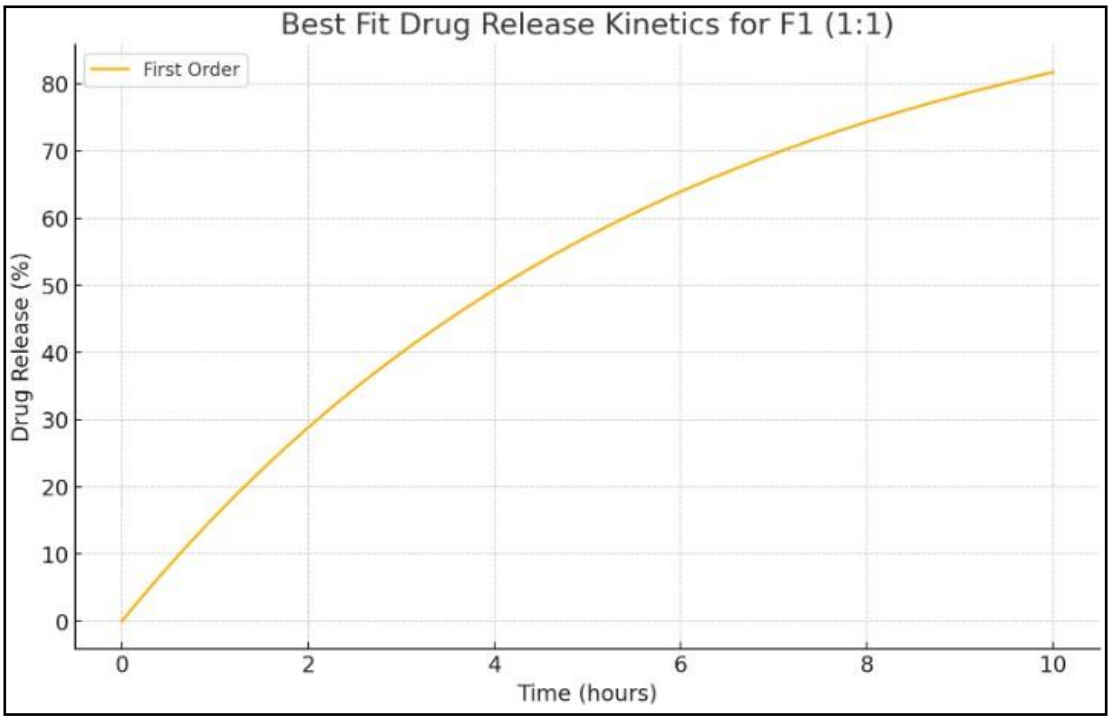

Figure 7: Best fit Drug Kinetics for F1

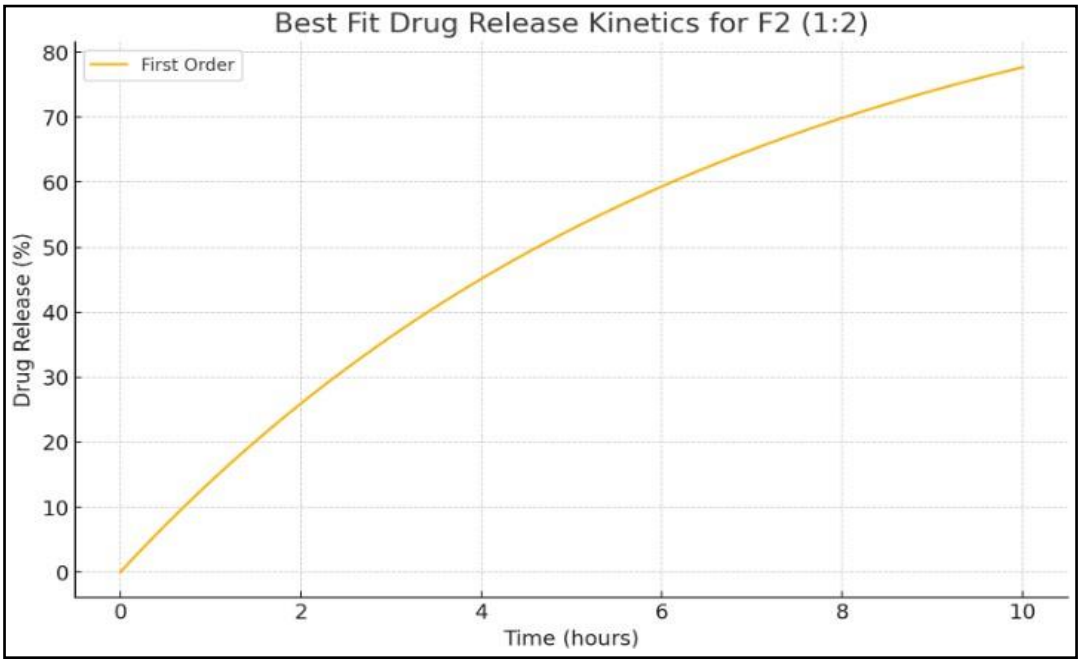

Figure 8: Best fit Drug Kinetics for F2

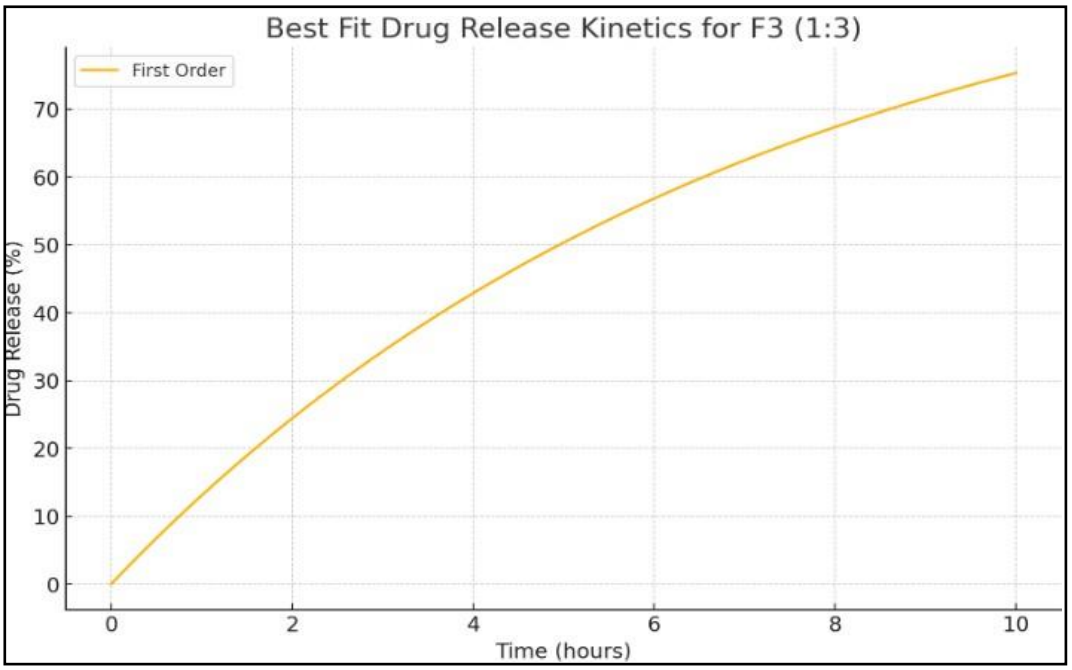

Figure 9: Best fit Drug Kinetics for F3

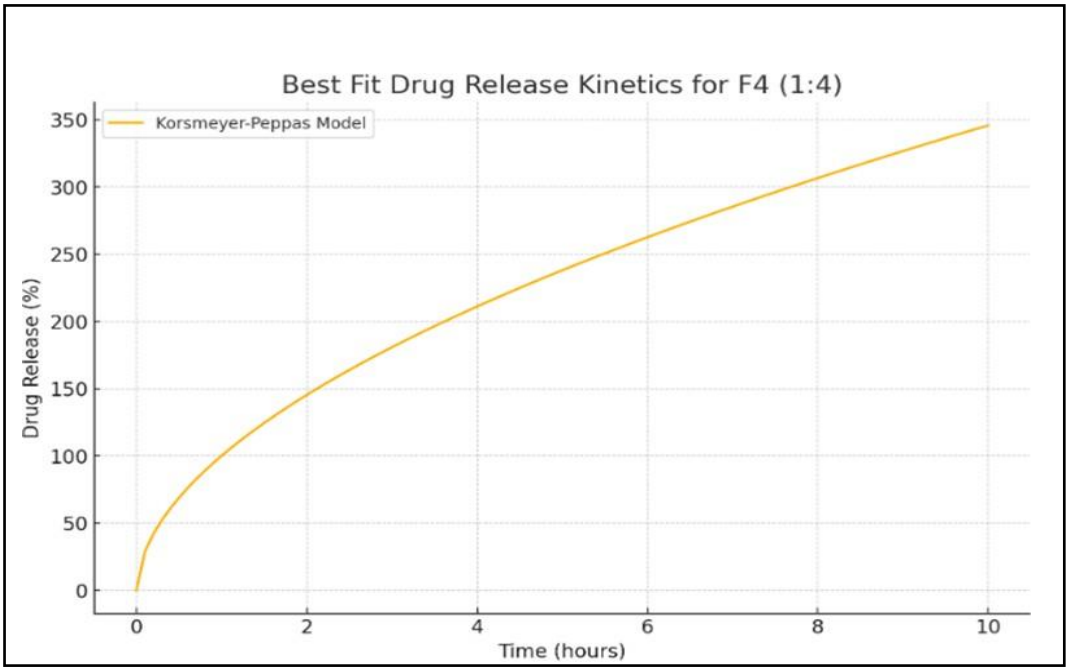

Figure 10: Best fit Drug Kinetics for F4

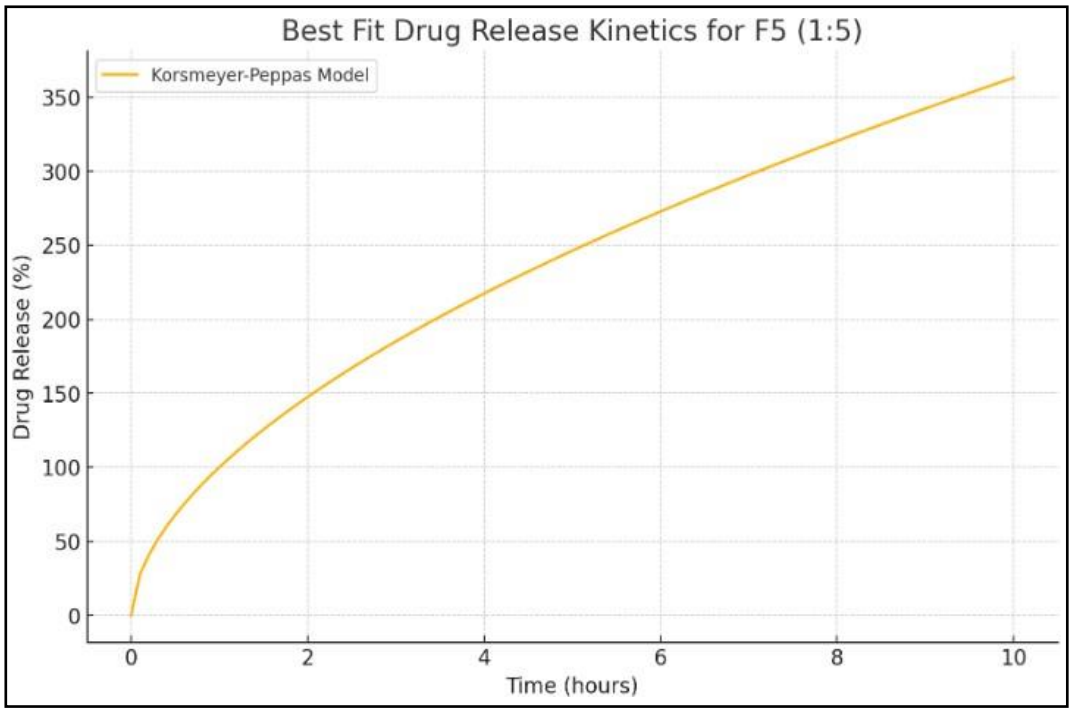

Figure 11: Best fit Drug Kinetics for F5

F1 (1:1): Best fit is the First Order model.

F2 (1:2): Best fit is the First Order model.

F3 (1:3): Best fit is the First Order model.

F4 (1:4): Best fit is the Korsmeyer-Peppas model.

F5 (1:5): Best fit is the Korsmeyer-Peppas model.

CONCLUSION

The study successfully developed floating microspheres of Valsartan aimed at enhancing bioavailability and therapeutic efficacy. Using the emulsion solvent diffusion technique with an optimal 1:1 ratio of dichloromethane to ethanol, the resulting microspheres were both free- flowing and stable. An increase in polymer concentration improved entrapment efficiency, yield, and buoyancy, although it reduced loading efficiency. The optimal drug-to-polymer ratiowas found to be 1:5, achieving an entrapment efficiency of 81.69% and a yield of 91.69%. Micromeritic analysis confirmed excellent flowability. In vitro drug release studies showed that lower polymer concentrations, such as the 1:1 ratio, resulted in the highest drug release (88.73% at 10 hours), while higher polymer concentrations,

like the 1:5 ratio, provided a more sustained release (69.88% at 10 hours). FTIR analysis confirmed no interaction between Valsartan and the excipients, ensuring the stability of the formulation. Calibration curves in different media were linear, supporting accurate and reliable drug quantification.

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