FORMULATION AND EVALUATION OF GASTRO-RETENTIVE FLOATING MICROSPHERES OF LOSARTAN POTASSIUM AND HYDROCHLORTHIAZIDE

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Abstract

The present investigation sought to elaborate upon the conceptualization and evaluation of buoyant microspheres through the emulsion solvent diffusion method, employing Eudragit RS 100 and Eudragit RL 100. A groundbreaking solid dispersion of Hydrochlorothiazide-Losartan potassium was recently unearthed to amplify the aqueous solubility of Hydrochlorothiazide, an inherently insoluble pharmacotherapeutic agent, consequently ameliorating its pharmacodynamic manifestations. Prior endeavors to address the solubility quagmire of Hydrochlorothiazide have traversed an array of methodologies, and this inquiry directed its focus towards the formulation and meticulous assessment of floating microspheres. The fabricated microspheres underwent an exhaustive array of analyses, encompassing the dimensions of particle size, percentage entrapment efficiency, drug encapsulation efficiency (DEE), Fourier-transform infrared (FTIR) spectroscopy, in vitro release kinetics, and stability evaluations. The particle size distribution values of 112±0.02 and 160±0.04 µm, presenting themselves as alabaster-hued, unencumbered, and approaching near-spherical geometry. FTIR examination showed an absence of discernible interaction between the therapeutic agent and the polymeric matrix.

The developed Floating Microspheres with Losartan Potassium and Hydrochlorothiazide, specifically the F5 formulation, exhibited remarkably propitious and protracted drug release profiles, persisting up to the 24th temporal hour. This sustained therapeutic efflux is prognosticated to engender heightened patient adherence and augment bioavailability, proffering a more efficacious modality for the management of hypertensive pathophysiology. Moreover, the anticipated angiotensin receptor antagonism imparted by Losartan is poised to attenuate the proclivity for enduring complications associated with hypertensive maladies, thereby mitigating the hazards of cardiac insufficiency, congestive heart failure (CHF), myocardial infarction, and vasculopathic detriment to blood vessels and renal parenchyma.

Keywords: Losartan Potassium, Hydrochlorothiazide, Floating Microspheres, Emulsion-Solvent Diffusion Method, In-vitro drug release.

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Introduction

Floating microspheres, delineated as multipartite pharmaceutical formulations exhibiting a spherical void ensconced by an unyielding polymer envelope, have been innovatively engineered to manifest superlative levity within the gastric milieu. This dosage manifestation is meticulously contrived to hover atop the gastric fluid, endowed with a specific gravity subordinated to unity. Forged via the emulsion solvent diffusion paradigm, these levitating microspheres are laden with therapeutic moieties nestled within their outer polymeric integuments, employing a diverse repertoire of polymers amalgamated within a dichloromethane-ethanol nexus. [1] The genesis of lacunae within these microspheres is ascribed to the volatilization of dichloromethane. These buoyant microspheres, wherein the therapeutic agents are either dispersed or solubilized throughout the particulate structure, evince proclivity for modulated drug elution, sustaining their levitation across acidic dissolution environments for in excess of a dozen temporal hours in vitro. The distinctive attribute of buoyancy amidst gastric constituents facilitates gradual drug emancipation at a stipulated pace, engendering prolonged gastroduodenal retention and unwavering plasmatic drug concentrations. The encapsulated substance is disseminated within the microsphere, comprised of biodegradable synthetic polymers, ceraceous constituents, or other preservative substrates such as amylaceous materials, proteins, viscid compounds, adipose substances, and unctuous matter.[2]

The amalgamation of Losartan potassium and Hydrochlorothiazide has been demonstrated to elicit a synergistic hemodynamic effect, transcending the efficacies attributable to each individual constituent. This inquiry aspired to scrutinize the ramifications of the preparation modality on the physiognomies and pharmaceutical discharge kinetics of Losartan potassium microspheres, with the objective of fabricating sustained-release Losartan microspheres via solvent desiccation. The augmentation of the oral bioavailability of poorly hydrosoluble pharmaceutical agents posits formidable challenges in pharmaceutical product development. While methodologies such as salt formation, solubilization, and diminution of particle magnitude are conventionally employed to ameliorate dissolution velocities and bioavailability, these approaches are not bereft of associated limitations.[3-5]

Eudragit RL and RS, denominated as ammoniomethacrylate copolymers, demonstrate pH-agnostic transmissibility by virtue of the presence of quaternary ammonium functionalities. These hydrophobic polymers, ubiquitously deployed in oral capsules and tablet preparations, are judiciously selected predicated upon their dissolution propensities. Polymethacrylates, pervasive in sundry pharmaceutical applications, function as film-coating agents, cohesive adjuncts, and substrates forming matrices. In the instantiation of microballoons, ethanol and dichloromethane are harnessed for the solubilization of the internal organic phase. The interdiffusion of ethanol and dichloromethane within the polymeraceous solution, culminating in the concomitant precipitation of the polymer, engenders the genesis of vacuous structures within the microspheres. The central lacuna, progressively imbued with aqueous content during the desiccation process, precipitates the inception of floating microspheres endowed with diminished density, facilitating their efficacious buoyancy. [5-7]

Materials and Methods

Materials

Aristo Pharma Pvt. Ltd. provided a gift sample of Losartan potassium, while Cipla Ltd. Mumbai, provided a gift sample of Hydrochlorthiazide.Evonik Degussa India Pvt. Ltd. (Saki Naka, Mumbai, India) provided the polymers EUDRAGIT RS 100 and EUDRAGIT RL 100.Polyvinyl alcohol and dichloromethane were purchased from S.D. Fine Chemical Ltd.All the synthetic substances and reagents utilized were of analytical grade.

Methods

Preparation of Floating Microsphere by Emulsion-Solvent diffusion Method

The emulsion-solvent diffusion method was used to create floating microspheres using different concentrations of Eudragit RS100 and Eudragit RL100 polymers. At room temperature, the polymers were dissolved in a solution of ethanol and dichloromethane in various experimental ratios. This organic phase solution was added to an aqueous solution of polyvinyl alcohol (0.75 w/v%, 200 ml) at 40°C to create an oil-in-water (o/w) type emulsion.

The final result was an emulsion that was stirred using a propeller-type agitator for three hours at

500 rpm. The finely dispersed droplets of the polymer solution of drug were solidified in the aqueous phase via diffusion of the solvent. An aspirator was used to extract the dichloromethane from the solidified droplet, leaving the cavity of the microsphere filled with water. The resulting polymeric particle systems were sieved between 500 and 1000 mm, agitated for an hour, then dried overnight at 40°C to create floating microspheres. The formulation details are summarized in Table 1.

Table 1: Different batches of microspheres which floating are generated.

S. No.	Ingredients	Formulation Code											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1.	Losartan Potassium + Hydrochlorothiazide (mg)	50mg + 12.5mg	50mg + 12.5mg	50mg + 12.5mg	50mg + 12.5mg	50mg + 12.5mg	50mg + 12.5mg	50mg + 12.5mg	50mg + 12.5mg	50mg + 12.5mg	50mg + 12.5mg	50mg + 12.5mg	50mg + 12.5mg
2.	Glycerol Monostarate (mg)	250 mg	250 mg	375 mg	375mg	250mg	250mg	250 mg	250 mg	250 mg	250 mg	375mg	350 mg
3.	Eudragit RL 100(mg)	-	-	-	-	-	-	250mg	500mg	750mg	1000mg	500mg	750mg
4.	Eudragit RS 100 (mg)	250mg	500mg	250mg	500mg	750mg	1000mg	-	-	-	-	-	-
5.	Ethanol (ml)	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml
6.	Dichloromethane(ml)	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml
7.	Polyvinyl alcohol (0.75 w/v%, 200 ml)	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml	200 ml

Micrometric Characteristics

Angle of Repose

The present investigation employed a technique for the evaluation of the flow characteristics inherent in microspheres. A method predicated upon the stationary deployment of a consistent funnel was meticulously orchestrated to gauge the angle of repose across a spectrum of diverse formulations

Table 2: Angle of Repose and Flow Characteristics

Angle of repose	Flow Properties
<25	Higher
25-30	Excellent
30-40	Bad
>40	Very Bad

Bulk Density and Tapping Density

We determined the bulk and tapped sample densities using a graduated 10 ml cylinder. Bulk density of a compound various substantially with the method of crystallization, milling or formulation. The tap volume and bulk density of the sample were assessed through one hundred mechanical taps.

Bulk density= Weight /Bulk volume

Tapped density= Weight/Tapped volume

Carr's Index

It can be measured of potential strength that powder could build up in its arc in hopper and also the case with an arch could be broken. The micro particles Carr's index (CI) or compressibility index (CI) was computed using a specific equation.

$$\text{Carr's index (\%)} = \frac{\text{Bulk density} - \text{Tapped density}}{\text{Tapped density}} \times 100$$

Haussner's Ratio

It is an indirect index of case of measuring the powder flow. It is the ratio of tapped density and bulk density and was calculated by using the following equation

Haussner's Ratio = Tapped density/Bulk density

Table 3: Compressibility and Flowability's Relationship Haussner's Ratio Ratio

Compressibility Ratio (%)	Flowability Ratio
5-15	Excellent
12-16	Good
18-21	Fair-passable
23-35	Poor
33-38	Very poor
>40	Very very poor

Drug -Polymer interaction (FTIR) Study

Fourier transform infrared (FTIR) spectroscopic analyses were meticulously executed employing a Fourier transform infrared spectrophotometer. The pulverized substances underwent a compression regimen at a pressure magnitude of 20 for a duration of 10 minutes, facilitating the creation of pellets comprising both the pharmaceutical compounds and potassium bromide. Subsequent to this compression procedure, spectra were meticulously scanned within the wave number range of 4000-400 cm^{-1}. The paramount focus of the FTIR inquiry pertained to the nuanced scrutiny of Losartan Potassium, unraveling its intrinsic nature both in isolation and within its intricate amalgamation with the polymeric matrix [8,9].

Evaluation of Floating Microspheres

Determination of Drug Loading (%) And Entrapment Efficiency (%)

For evaluation, 100 mg of the floating microspheres was utilized. The estimation of the entrapped drug involved crushing and extracting with multiple aliquots of 0.1N HCl. After filtration, the absorbance was measured spectrophotometrically (UV 1700, Shimadzu, Japan) at 266 nm against a suitable blank following appropriate dilution. The drug loading (%) and entrapment efficiency (%) were determined using the following relationships.

Drug loading (%) = Actual drug content/ Weight of powdered microspheresX100

Efficiency of drug entrapment (%) = Actual drug content / Theoretical drug content X100

In vitro Buoyancy

The in vitro buoyancy of floating microspheres was determined using the USP dissolution apparatus type II. The dissolution basket was filled with 900 ml of a 1.2 pH buffer containing 1% w/v tween 80. Subsequently, 100 mg of the microspheres were evenly dispersed on the surface of simulated gastric fluid (0.1N HCl of pH 1.2). The mixture was agitated at 100 rpm for 12 hours at 37± 0.5ºC. After the 12-hour period, the layer of floating microspheres was pipetted and filtered to collect the sample. Similarly, particles that sank were separated by filtration to collect the sunk sample, which was then dried in a desiccator and weighed.

Buoyancy(%)=Weight of floating microspheres after time (t)/Initial weight of floating microspheres

Analysis of Particle Morphology and Size

The optical microscopy method was employed to determine the particle size of microspheres, involving the counting of approximately 100 microspheres using a calibrated optical microscope. These microspheres were evenly dispersed on a slide, and their particle size was measured along both the longest and shortest axes (cross-shaped measurement). The mean diameter of the particles was derived from the average of these two readings. The diameter calculation was performed for a minimum of 100 microspheres in each batch [10].

Swelling Index

For the determination of swelling indices, a phosphate buffer of pH 7.4 and a pH 1.2 solution were utilized at a temperature of 37°C ± 0.5°F over an 8-hour period. Test tubes containing microcapsules with the medication were collected, filtered, and weighed hourly throughout the experiment.

$$\text{Swelling index} = \frac{W_s - W_d}{W_d}$$

Where,

The weights of the settled and floating microspheres are represented by Ws and Wf respectively.

Determination of Percentage Yield

The weight of all the non-volatile ingredients used to make the floating microspheres was divided by the total weight of the collected floating microspheres.

Yield (%) = Weight of microspheres/ Total expected weight of drug and polymer X100

In-vitro dissolution of Hydrochlorothiazide and Losartan potassium

The dissolution media employed for drug release assessment consisted of a 1.2 pH buffer. Initially, 900 ml of buffer was placed in the dissolution apparatus baskets. Floating microspheres equivalent to 50 mg were introduced into the dissolution medium at 37ºC, with agitation at 100 rpm. Subsequently, 1 ml of the sample was withdrawn at specific intervals up to 24 hours. The absorbance of these aliquots was determined using an ultraviolet-visible spectrophotometer at the respective λmax after appropriate dilution, compared to the corresponding blank. The withdrawn volume was replaced with an equal volume of fresh 1.2 pH buffer, maintaining a constant volume of the dissolution medium [9].

Drug Release Kinetics

To better understand the complexities of the mechanism and kinetics governing drug release, the results derived from the in vitro drug release investigation were carefully examined using a variety of kinetic models. These models included the Higuchi model, which showed the relationship between the percentage release and the square root of time, the zero-order model, which explained the relationship between the percentage release and time, and the first-order model, which explained the logarithmic relationship between the percentage unreleased and time. In order to determine the best model for the formulation, a more detailed analysis of the drug release data was conducted using the Peppas equation, which is expressed as $Mt/M\infty = ktn$. The variables Mt indicate the amount of drug released at time t, M∞ the amount released at an infinite temporal horizon, Mt/M∞ the fraction of drug released at time t, k the kinetic constant, and n the diffusion exponent of the main mechanism controlling drug release in this equation. Regression coefficient (r2) values, a quantitative indicator of the fidelity of these models, were calculated using the linear curves that resulted from applying regression analysis to these plots[11,12].

Stability Studies

The stability assessment of the refined formulation rigorously adhered to the guidelines stipulated by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). The formulation underwent exposure to controlled environmental conditions, precisely a temperature maintained at 40 ± 2 °C and relative humidity (RH) sustained at 75 ± 5%, spanning a duration of 3 months. The Thermo lab stability chamber served as the apparatus of choice for the orchestration of this meticulous testing protocol. The evaluative focus encompassed a continuous surveillance regimen encompassing key parameters, namely the drug content, floating characteristics, and in vitro drug release profiles, meticulously scrutinized over the stipulated temporal trajectory.

Result & Discussion

Micromeretic Properties

The microspheres were subjected to a comprehensive evaluation delineating various derived properties, incorporating the Angle of Repose, Tapped Density, Bulk Density, Carr's Index, and Hausner's Ratio. The intricate and nuanced results of these discerning assessments are meticulously delineated and expounded upon in the tabulated presentation encapsulated within Table 4.

Table 4: Flow Properties of Losartan Potassium and Hydrochlorothiazide Floating Microspheres

Formulation Code	Angle of Repose (Avg. ±S.D.)	Bulk Density (Avg. ±S.D.)	Tapped Density (Avg. ±S.D.)	Car's Index (Avg. ±S.D.)	Haussener's Ratio (Avg. ±S.D.)
F1	21.170 ± 0.14	0.415± 0.04	0.321± 0.01	3.120± 0.03	1.023± 0.02
F 2	23.110 ± 0.12	0.210± 0.01	0.319± 0.03	4.100± 0.01	1.031± 0.03
F 3	19.170 ± 0.13	0.410± 0.02	0.306± 0.02	3.344± 0.04	1.042± 0.01
F 4	21.130 ± 0.16	0.321± 0.03	0.307± 0.05	3.423± 0.02	1.035± 0.05
F5	22.280 ± 0.15	0.437± 0.03	0.425± 0.01	3.125± 0.02	1.043± 0.02
F 6	23.120 ± 0.16	0.306± 0.02	0.345± 0.06	3.543± 0.03	1.036± 0.04
F 7	22.260 ± 0.13	0.430± 0.05	0.412± 0.04	4.234± 0.05	1.064± 0.02
F 8	24.230 ± 0.17	0.403± 0.02	0.421± 0.03	4.121± 0.06	1.012± 0.04
F 9	21.280 ± 0.15	0.427± 0.03	0.415± 0.01	3.115± 0.02	1.023± 0.02
F 10	20.260 ± 0.13	0.330± 0.05	0.312± 0.04	3.234± 0.05	1.034± 0.02
F 11	22.230 ± 0.17	0.303± 0.02	0.321± 0.03	2.121± 0.06	1.012± 0.04
F 12	25.280 ± 0.15	0.227± 0.03	0.315± 0.01	4.115± 0.02	1.013± 0.02

***All data are expressed as mean ± standard deviation; *n* = 3.**

Drug-Polymer Interaction (FTIR) Study

Figures 1 and 2 conspicuously portray the spectra corresponding to Losartan and Hydrochlorothiazide, elucidating the discernible manifestation of all distinctive peaks inherent to each respective compound. Figure 3, in turn, elucidates the amalgamated spectrum encapsulating both the pharmaceutical agent and the polymeric matrix, thereby demonstratively affirming the compatibility of these constituents.

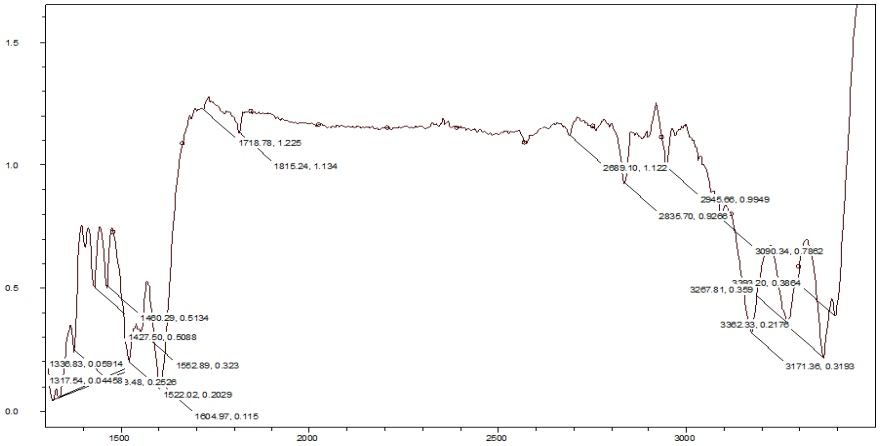

Figure 1: FTIR spectra of Pure Hydrochlorothiazide

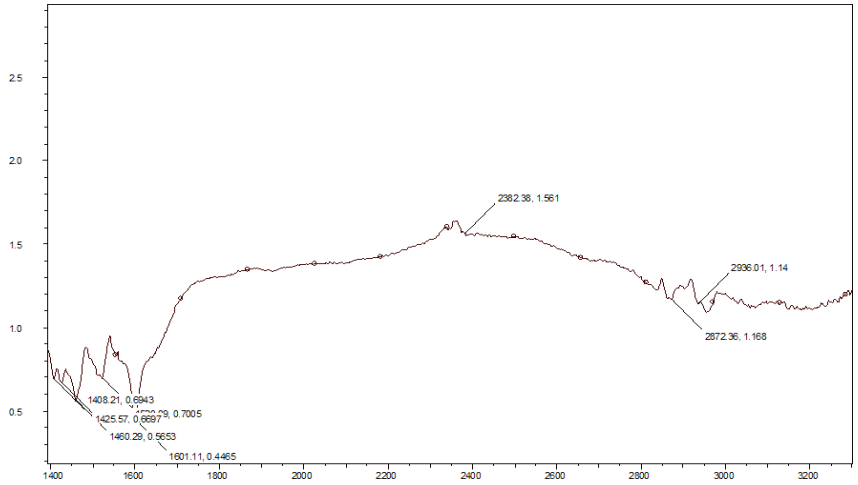

Figure 2: FTIR spectra of Pure Losartan potassium

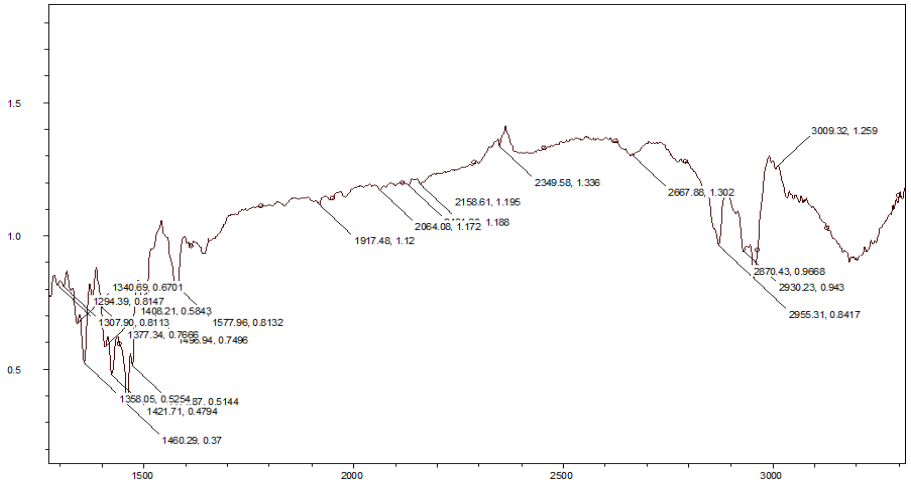

Figure 3: FTIR Spectra of Hydrochlorothiazide -Losartan Potassium and Polymer Interaction

Scanning Electron Microscopy

The Scanning Electron Microscopy (SEM) was employed to analyze the shape and surface characteristics of the microspheres. The surface morphology of the F5 formulation was scrutinized at different magnifications, specifically at 100X and 500X. These images highlighted the smooth surface of the floating microspheres and revealed the presence of small hollow cavities, contributing to their buoyant properties. SEM also exposed pores on the microsphere surface and within the hollow interior. The examination of surface morphology and internal structure through SEM, as illustrated in Figure3, suggested the development of numerous pores associated with drug release. Notably, these pores exhibited variations in size, potentially influenced by the drug's impact, resulting in the formation of both small and large pores.

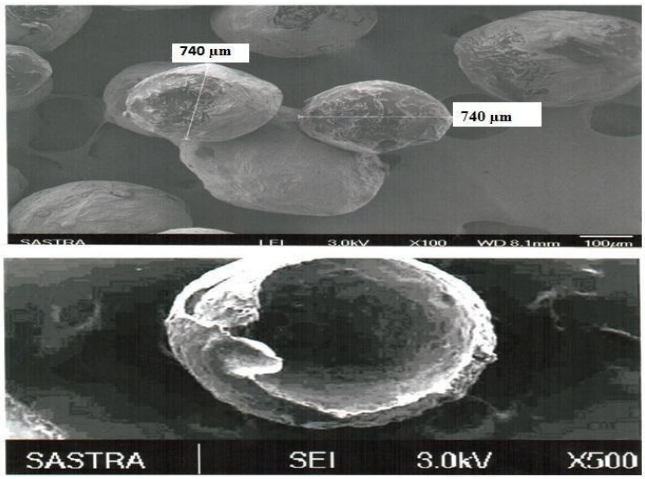

Figure 3: Scanning Electronic Microscopy of Hydrochlorthiazide and Losartan Potassium Floatng Microspheres

Buoyancy Percentage

To simulate the stomach. fluid, floating microsphers (100 mg) were distributed in JP XIII No.1 solution, which is 300 ml of HCl and NaCl (pH 1.2, 37 8C) with 0.02 w/v% Tween 20. A paddle was used for stirring the mixture at 100 rpm. The layer of buoyant particles was pipetted after 12 hours, and the floating particles were filtered off. By using filtration, the particles in the sinking particulate layer were separated. Overnight, both types of particles were dried at 40^0C. The weight ratio of the floating particles to the total of the sinking and floating particles was used to calculate buoyancy and each weight was measured.The result of the bouncy percentage of the microspheres were given in Table 5.

S. No.	Formulation Code	Percentage Buoyancy
1	**F1**	61.23±0.45
2	**F 2**	65.50±0.25
3	**F 3**	72.41±0.34
4	**F 4**	82.05±0.61
5	**F5**	92.13±0.22
6	**F 6**	70.44±0.34
7	**F 7**	75.36±0.33
8	**F 8**	78.53±0.55
9	**F 9**	81.25±0.43
10	**F 10**	83.30±0.56
11	**F 11**	78.13±0.32
12	**F 12**	68.03±0.15

*** All data are expressed as mean ± standard deviation; *n* = 3.**

Particle Size

The intricacies of the physicochemical attributes intrinsic to the SS microspheres are meticulously explicated in the comprehensive exegesis presented within Table 6. The particle size of the medicated microspheres manifested variability

spanning the confines of 112±0.02 to 160±0.04 µm. A salient observation of particular note is the discernible augmentation in the particle size of the microspheres in tandem with escalating concentrations of Glycerolmonostearate. This discerned trend is plausible elucidated by the heightened viscosity imparted by Glycerolmonostearate, engendering amplification in droplet size, thereby consequentially contributing to the observed escalation in particle dimensions.

Swelling Index

The discernment gleaned from the observation distinctly elucidated that microspheres characterized by elevated concentrations in milligrams demonstrated a more pronounced proclivity towards swelling when juxtaposed with their counterparts comprising Eudragit RS 100, as meticulously illustrated in the tabulated presentation encapsulated within Table 6.

Table 6: Characteristics of Hydrochlorthiazide and Losartan Potassium Floating Microspheres

Formulation Code	Entrapment Efficiency (%)	Particle Size (µm) Mean ± SD	Swelling index
F1	68.23±0.02	112±0.02	0.912±0.001
F 2	70.31±0.01	116±0.06	0.914±0.003
F 3	75.16±0.03	120±0.03	0.916±0.004
F 4	78.54±0.01	132±0.06	0.918±0.002
F5	95.12±0.04	160±0.04	0.929±0.006
F 6	83.32±0.02	147±0.07	0.924±0.002
F 7	89.34±0.03	150±0.02	0.926±0.006
F 8	94.45±0.01	140±0.04	0.928±0.001
F 9	71.21±0.01	114±0.06	0.908±0.003
F 10	74.16±0.03	121±0.03	0.910±0.004
F 11	76.54±0.01	133±0.06	0.912±0.002
F 12	74.31±0.01	112±0.06	0.911±0.003

*** All data are expressed as mean ± standard deviation; *n* = 3.**

In-vitro Dissolution Studies

The drug release kinetics exhibited a discernible decrement concomitant with diminishing concentrations of Glycomonostearate, thereby signifying a controlled dispensation of the drug with a concomitant augmentation in the concentration of Eudragit RS 100. This observed phenomenon is plausible elucidated by the concurrent escalation in viscosity, precipitating an amplification in particle dimensions coupled with a commensurate reduction in surface area. The heightened viscosity further engenders an elongated diffusional path length, thereby substantively contributing to the observed diminution in drug release dynamics, as meticulously delineated in the comprehensive presentation captured within Table 7 and Figure 5.

Table 7: In-vitro release profile of Hydrochlorothiazide and Losartan Potassium loaded Floating Microspheres

Time in (hrs)	% Drug Release at time (hrs)											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1	50.23	48.21	43.23	46.23	39.23	45.23	46.23	44.23	43.23	44.25	45.34	49.54
2	55.10	53.54	50.12	52.28	45.45	50.28	53.28	49.28	48.28	49.21	50.45	54.13
4	60.23	62.23	55.23	56.89	50.21	54.89	54.89	53.89	54.89	54.89	56.89	60.23
6	68.34	67.87	60.12	61.23	53.78	61.23	60.23	57.23	59.23	62.23	61.23	68.34
8	73.54	73.65	65.32	67.23	57.13	66.23	66.23	62.23	64.23	65.34	67.23	73.54
10	80.35	79.23	70.65	71.45	60.23	70.45	70.45	67.45	70.45	70.45	70.23	80.35
12	88.23	83.67	78.23	75.34	65.32	74.34	74.34	70.34	75.34	74.34	75.34	88.23
14	90.23	87.65	82.56	81.34	70.12	84.34	80.34	75.34	79.34	84.34	81.34	90.23
16	98.12	94.87	85.23	85.23	74.25	87.23	83.23	80.23	82.23	87.23	85.23	98.76
18	-	98.06	91.34	91.56	80.76	94.23	93.23	90.23	90.23	94.23	91.56	-
20	-	-	97.34	97.83	85.11	97.67	96.34	96.21	95.67	98.45	98.23	-
24	-	-	-	-	97.08	-	-	-	-	-	-	-

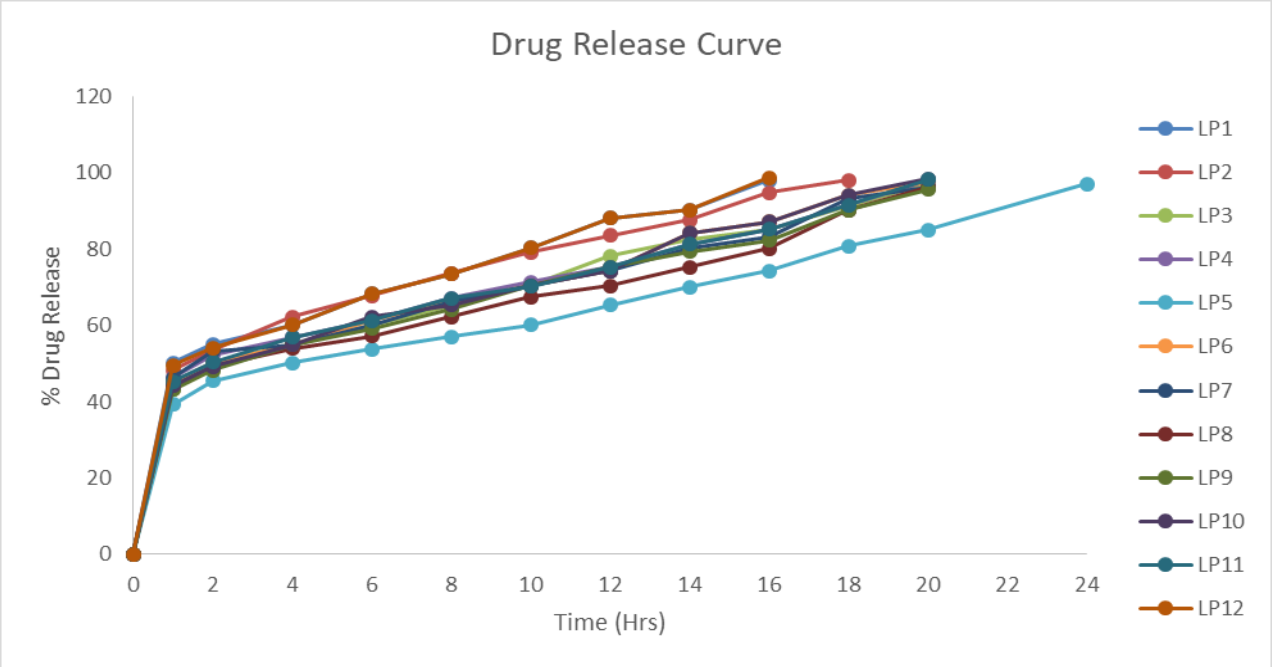

Figure 5: Percentage drug release plot

Drug Release Kinetics

The in-vitro drug release data derived from formulations incorporating Eudragit RS100 and RL100 undergone extensive fitting evaluations using various kinetic models, including the Higuchi, Peppas, zero order, and first order models, carefully presented in Table 7. The zenith of regression values was attained conspicuously for the zero-order model. Particularly noteworthy is the revelation that the release exponent value (n) across all formulations surpassed the threshold of 1, indicative of non-Fickian diffusion or a preponderance of super case-II transport as the dominant release mechanism (refer to Table 8). This underscores a discernible controlled release pattern attributed to the drug's gradual liberation via the intricate interplay of diffusion processes, intricately intertwined with the relaxation dynamics inherent to the polymer matrix. The sequential manifestation involves an initial phase of deliberate diffusion and dissolution, succeeded by a sustained and controlled release pattern.

Table 8: Kinetic of dissolution profile of floating microspheres for the mechanism of (values of r^2, k and n) drug release.

Formulation Code	Zero Order R^2	First order R^2	Higuchi R^2	Korsmeyer-Peppas		
				R^2	N	K
F1	0.9801	0.9821	0.9721	0.9561	0.7711	14.061
F 2	0.9701	0.9711	0.9623	0.9567	0.7621	15.063
F 3	0.9601	0.9451	0.9612	0.9345	0.7821	16.064
F 4	0.9501	0.9521	0.9534	0.9576	0.6411	13.065
F5	0.9951	0.9931	0.9945	0.9936	0.7711	26.066
F 6	0.9401	0.9411	0.9412	0.9465	0.7814	20.064
F 7	0.9101	0.9111	0.9345	0.9643	0.4713	24.067
F 8	0.9611	0.9621	0.9612	0.9345	0.5717	21.068
F 9	0.9451	0.9461	0.9421	0.9613	0.3715	20.063
F 10	0.9671	0.9821	0.9643	0.9547	0.5312	25.062
F 11	0.9871	0.9641	0.9810	0.9854	0.6318	17.061
F 12	0.9451	0.9321	0.9512	0.9472	0.4718	18.066

Stability Studies

A meticulous stability investigation was systematically conducted on the meticulously optimized floating bilayer tablet formulation,

spanning a duration of three months under climatic conditions of 40 ± 10°C and 75% relative humidity (RH). The evaluative parameters encompassed Drug Entrapment Efficacy, Floating Time, Particle Size, and Swelling Index. The discerned outcomes, thoughtfully presented in Table 9, unequivocally indicated a conspicuous absence of any statistically significant variations in the aforementioned parameters throughout the entire duration of the investigative study.

Table 9: Stability study of optimized formulation (F5)

S. No.	Parameters	Before	After
1	Drug Entrapment Efficacy	95.12±0.04%	95.35±0.24%
2	Floating Time	>12hrs	>12hrs
3	Particle Size	160±0.04µm	159±0.14 µm
4	Swelling Index	0.929±0.006	0.930±0.060

Conclusion

The present investigation markedly ameliorated the dissolution and pharmacokinetic profiles of Hydrochlorothiazide through the formulation of a groundbreaking Hydrochlorothiazide-Losartan Potassium solid dispersion. This innovative dispersion exhibited significantly enhanced dissolution and pharmacokinetic attributes when juxtaposed with both the physical mixture and the commercially available product. The unique composition of this solid dispersion, devoid of physiologically inert carriers, renders it resilient to humidity, thereby presenting a cost-effective and efficacious methodology devoid of the necessity for supplementary carriers. Subsequent human studies are imperative to validate the therapeutic advantages proffered by this distinctive solid dispersion.

All constituents, including the drug and excipients, attained requisite standards, affirming their compliance with defined specifications. Infrared analyses conclusively established the compatibility of the drug with the excipients, manifesting an absence of discernible interactions. The meticulously synthesized microspheres underwent a battery of assessments spanning encapsulation efficiency, drug content, drug release kinetics, Fourier-transform infrared spectroscopy (FTIR), and particle size distribution analyses. Fabricated with precision using the solvent evaporation technique and employing an innovative combination of polymers, the Losartan Potassium and Hydrochlorothiazide microspheres demonstrated commendable enhancements in in vitro release profiles, particularly with an augmentation in Eudragit RS 100 concentration.

The formulation designated as F5 among the Hydrochlorothiazide and Losartan Potassium Floating Microspheres exhibited highly advantageous drug release profiles. These profiles showcased superior and sustained drug release characteristics persisting throughout the 24-hour temporal span, thereby augmenting patient adherence and elevating bioavailability. The refined therapeutic strategy for hypertensive conditions is underpinned by the angiotensin receptor blocking attributes of Losartan.

The sustained release attributes characterizing F5 significantly contribute to its efficacy in mitigating the protracted complications associated with hypertension. By alleviating the risks of heart failure, congestive heart failure (CHF), myocardial infarction, and vascular damage to blood vessels and kidneys, F5 emerges as a promising intervention in the management of hypertension, promising a reduction in deleterious consequences associated with this prevalent medical condition.

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