Original Article

Floating microspheres encapsulating carvedilol for the effective management of hypertension

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ABSTRACT

Carvedilol (CVD) is an antihypertensive agent with a short half-life, pH-dependent solubility, and narrow absorption window. The purpose of this research was to prepare a floating-drug delivery-system of carvedilol to increase its half-life. The present study investigates the preparation of carvedilol-floating microspheres, evaluates the floating-drug delivery-system (FDDS) (by scanning electron microscope), it's *in vitro* stability, and *in vivo* profile. Floating microspheres were prepared by solvent-evaporation (oil-in-water emulsion) technique using hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) as the rate controlling polymers. The surface morphology of the prepared microspheres was characterized by scanning electron microscopy. In this study, the particle size analysis, drug entrapment efficiency, surface morphology, buoyancy percentage, and release studies were performed. The microspheres were found to be spherical and porous. The results showed that the mean/mean (SD) values of tapped density, Carr's compressibility index, angle of repose, percentage yield, *in vitro* buoyancy, %entrapment efficiency of CVD-loaded floating microspheres were 0.42 (0.012), 12.5 (1.895), 23.5 (1.856), 80.2 %, 79.0 %, and 85.81(1.40), respectively. The developed floating-microsphere of CVD released the drug for 24 h and based on *in vivo* studies, the drug-loaded floating microspheres help in maintaining the mean (SD) systolic blood pressure within the range of 120 (0.32) to 120 (1.02) mmHg and diastolic pressure within 91 (0.71) to 92 (0.79) mmHg. Thus, floating microsphere of CVD offers a suitable and practical approach for prolonged release of the drug over an extended period, and thus improves the oral bioavailability and efficacy of the drug as well as the patient's compliance.

Introduction

Many drug delivery systems on the market are oral delivery type (1). These systems have evolved from immediate release to site-specific delivery. Now, researchers focus mainly on orally-administrated and controlled drug-delivery systems because of their ease of preparation and administration. The controlled release refers to the delivery of drug over an extended period. It also implies delayed pharmacological action and sustained therapeutic effect (2). It means not only the prolonged duration of drug delivery and extended release but also predictability and reproducibility of drug release kinetics.

Considerable efforts have been made to design orally-controlled drug-delivery systems that produce more predictable and higher drug bioavailability. However, the progress is precluded by several physiological difficulties, like inability to retain and localize the drug delivery system within the desired regions of the gastrointestinal (GI) tract and highly variable nature of the gastric emptying process. An important factor, which may adversely affect the performance of an orally-controlled drug-delivery system, is GI transit time. The time for absorption in the GI transit in humans is approximately 8-10 h from mouth to colon. This time is relatively short, with considerable fluctuation (3, 4).

GI transit time varies widely between individuals and depends on the physical properties of the ingested material and the physiological condition of the gut. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels. One of the essential determinants of GI transit is the residence time in the stomach (5).

Controlled-release or extended-release dosage forms with prolonged residence time in the stomach are highly sought for drugs that are insoluble in water; targeted at upper GI tract; bioavailable through active transport mechanism; irritating the mucosa; unbalancing, irritating or unsafe in the lower GI region; more effective when plasma levels are constant; locally active in the stomach, with absorption window in the stomach or the upper small intestine; unstable in the intestinal or colonic environments; and with low solubility at high pH values (6-9). Floating-drug-delivery systems (FDDS) have a bulk density less than gastric fluids so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in increased gastric residence time and better

control of the fluctuations in plasma drug concentration (10-12). Recently, gastroretentive floating microspheres are gaining much more favor among various other dosage forms. Numerous potential benefits of these multiparticulate systems are as follows:

- Improving the patient's comfort and compliance by decreasing dose frequency,
- Enhancing the bioavailability and therapeutic efficacy of drugs with a narrow absorption window in the upper part of the GI tract,
- Increasing gastric retention time because of buoyancy principle and releasing drug in a controlled manner for a prolonged period,
- Delivering at a specific site and releasing drug uniformly with no risk of dose dumping,
- Avoiding gastric irritation and reducing inter- and intra-subject variability,
- Minimizing the counter activity of the body leading to higher drug efficiency and minimizing fluctuations in drug concentration (13-20).

Hypertension is a public health problem and a term used to describe high blood pressure. It is a condition that occurs as a result of repeatedly elevated blood pressure (a systolic pressure above 140 with a diastolic pressure above 90). However, normal blood pressure is below 120/80. The readings between 120/80 and 139/89 are called pre-hypertension. Systolic blood pressure is the pressure in the arteries as the heart contracts and pumps blood forward into the arteries, whereas diastolic pressure represents the pressure as a result of relaxation of the arteries after contraction. "Hypertension is the blood pressure that is too high. As a pump, your heart creates pressure to force blood to all parts of your body (21)." Damaged, narrowed arteries cause blood to be pumped with excessive force against the walls of the arteries, overworking the heart and arteries. Carvedilol, sold under the brand name of Coreg among others, is a beta blocker used for treating mild to severe congestive heart failure and left ventricular dysfunction following a heart attack in otherwise stable people, and for treating high blood pressure. Carvedilol also blocks alpha receptors, which are found on blood vessels, and relaxes the blood vessels, dilating them, which lowers blood pressure and vascular resistance. It is a nonselective beta blocker/alpha-1 blocker and belongs to the third generation of beta blockers (21, 22). With these considerations, the objective is to develop a unique orally-controlled release-dosage form, which stays in the stomach and releases the drug from there, in a controlled and prolonged manner, so that the drug can be supplied continuously to its absorption sites in the upper gastrointestinal tract.

Materials and methods

Carvedilol (AR grade) was kindly provided as a gift sample by Jai Radhe Sales, Ahmedabad, India. Dichloromethane (DCM), dimethylformamide (DMF), hydroxypropyl methyl cellulose (HPMC), ethyl cellulose (EC), and Tween 80 were obtained from Sigma Co. (USA). All other chemicals/reagents were of analytical grade, available commercially and used as such without further processing.

Preparation of microspheres

Microspheres were prepared by solvent evaporation (oil-in-water emulsion) technique. Carvedilol, HPMC, and EC (1:1) were dissolved in a mixture of DMF and DCM (1:1) at room temperature. The mixture was poured into 250 mL water containing 0.02% Tween 80 maintained at a temperature of 30 °C-40 °C and subsequently stirred at ranging agitation speed for 20 min to allow the volatile solvent to evaporate. The microsphere formed were filtered, washed with water and dried in vacuum.

Characterizations of floating microspheres

The floating microspheres of the prepared carvedilol were characterized for the following parameters.

Particle size and surface morphology

The particle size of the floating microspheres was evaluated using an optical microscope fitted with a calibrated eyepiece micrometer. It randomly measures the particle diameters of about 100 microspheres, and the average particle size was determined using the Edmondson's equation:

$D_{mean} = \Sigma nd / \Sigma n$,

where "n" stands for the number of counted microspheres, and "d" for the mean size range.

Scanning electron microscopy (SEM) was performed to characterize the surface of formed floating microspheres using (HITACHI SU 1500, Japan). Samples for SEM were prepared by lightly sprinkling the powder on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with the gold film under reduced pressure. The film acts as a conducting medium on which a stream of the electrons was allowed to flow, and then the photograph was taken with a scanning electron microscope (23).

Percentage of buoyancy/floating behavior

Floating microspheres (50 mg) were dispersed in simulated gastric fluid (pH=1.2, 100 mL, 37⁰C) containing Tween 20 (0.02% w/v). Tween was used to impart the wetting effect of natural surfactants such as phospholipids in the GI tract. The mixture was stirred at 100 rpm in magnetic stirrer. After 12 h, the layer of the buoyant particle was pipetted, and the floating particles were separated by filtration; the particles in the sinking particulate layer were separated by filtration. Both particle types were dried at 40⁰C overnight. Each part was weighted, and buoyancy was determined by the weight ratio of the floating and sinking particles (24).

% buoyancy = $\dfrac{W1}{Wf + Ws} \times 100$,

where Wf and Ws are the weights of the floating and settled floating microspheres, respectively.

Drug entrapment efficiency
Dried micro balloons (50 mg) containing drug were taken, crushed by triturating, and suspended in a minimal amount of DCM (10 mL) for dissolving the coat shell of the microspheres. The suspension was suitably diluted with 0.1 N HCl and filtered to separate the shell fragments. Drug entrapment efficiency was analyzed after suitable dilution by spectrophotometric technique (with a UV-detector, Shimadzu, UV-1800) at 241 nm. The drug entrapment efficiency was calculated as follows:

$$\text{Drug entrapment efficiency} = \frac{Calculated\ drug\ concentrration}{theoretical\ drug\ content} \times 100$$

Micromeritics properties
Floating microspheres are characterized for their micromeritic properties, such as particle size, tapped density, compressibility index, and flow properties. The size was measured using an optical microscope and mean particle size was calculated by measuring 200-300 particles with the help of calibrated ocular micrometer.

$$\text{Tapped density} = \frac{mass\ of\ micro\ balloons}{volume\ of\ microballoons\ after\ tapping} \times 100$$

$$\text{\%compressibility index} = [1\text{-}V/V_0] \times 100,$$

where V and V_0 are the samples after and before the standard tapping, respectively.
The angle of repose θ of the floating microspheres, which measures the resistance to particle flow is determined by a fixed funnel method and calculated as follows:

$$\tan\theta = 2H/D,$$

where 2H/D is the surface area of the free-standing height of the floating microspheres heap that is formed on a graph paper after making the floating microspheres flow from the glass funnel. The $\tan^{-1}$ of the height of the pile and radius of its base gave the angle of repose.

In vitro drug release
A USP XXIII basket type dissolution apparatus has been used to study in vitro drug release from micro balloons. A weighed amount of floating microspheres equivalent to 50 mg drug was filled into a gelatin capsule (No. 0) and placed in the basket of dissolution rate apparatus. An amount of 900 mL simulated gastric fluid with pH 1.2 containing 0.02% w/v Tween 20 was used as dissolution fluid. The dissolution medium was maintained at 37 ± 0.5 ℃ at a rotation speed of 100 rpm. Perfect sink condition prevailed during the drug release study. Five milliliter sample was withdrawn at each 30 min interval and analyzed by spectrophotometric technique at a wavelength of 241 nm (Shimadzu, UV-1800). The volume replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition (25).

Stability studies
The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time and a variety of environmental factors such as temperature, humidity, and light. The next objective is to establish a re-test period for the drug substances or shelf life for the drug product and recommend storage conditions. Improper storage of pharmaceutical products can lead to their physical deterioration and chemical degradation resulting in reduced activity and occasionally the formulation of a toxic degradation product. Stability of pharmaceutical product is essential for three main reasons; the safety of the patient, legal requirements concerned with the identity, strength, purity, and quality of the drug; and prevention of economic repercussions of marketing as an unsuitable product. Degradation may particularly occur under tropical conditions of high ambient temperature and humidity. The most important factor that influences the rate and extent of degradation are:

- Environmental factors such as heat, moisture, light, and any other form of physical stress like freezing, thawing, vibrations, etc.
- Product-related factors such as physiochemical properties of the drug substance and the excipients used in dosage form and its composition, manufacturing process, and packaging and storage conditions.

Stability of drug-loaded gastroretentive floating microspheres during storage is undoubtedly another important prerequisite for its successful clinical application. Hence the prepared floating microspheres were tested for durability on storage at 15 ± 2 ℃, 27 ± 2 ℃, and 50 ± 2 ℃. Effect of storage condition on the particle size of floating microspheres and the impact of storage condition on drug entrapment efficiency of floating microspheres were carried out for the evaluation of the stability of floating microspheres.

Effect of storage condition on the particle size of floating microspheres
Carvedilol loaded floating microspheres were kept at 15 ± 2 ℃, 27 ± 2 ℃, and 50 ± 2 ℃ and observed after 30 days for any change in particle size.

Effect of storage condition on drug entrapment efficiency of the floating microspheres
Carvedilol-loaded floating microspheres were kept at 15 ± 2 ℃, 27 ± 2 ℃ and 50 ± 2 ℃, and then they were evaluated after 30 days for a change in drug entrapment efficiency.

In vivo studies
The therapeutic effectiveness of the developed delivery system was evaluated by in vivo experiments. *In vivo*

studies are important to evaluate the physiological availability of the drug in a designed dosage form. Institutional Animal Ethics Committee granted permission to perform the in vivo study with number SIPS/EC/2014/53. All the experiments were carried out following the protocols approved by the committee. The administered dose to rats was calculated (according to body surface area ratio of rats to humans) by extrapolating the therapeutic dose to rat dose based on body surface area ratio (conversion factor 0.18 for rats)(26) as following:

Dose (mg/200 g of rat) = Human dose (mg) × conversion factor

Animals were divided into 4 groups, each containing 4 rats. Cardiovascular parameters were measured by the tail-cuff method. DOCA-induced hypertension is salt dependent, because neither administration of DOCA, nor partial removal of the renal mass is effective in increasing BP when applied without salt administration (27). To induce hypertension, rats weighing about 100 g were kept on a diet high in sodium chloride, and drinking water was replaced by 2% sodium chloride solution ad libitum. After they attain a weight of about 250 g, they were given DOCA dissolved in sesame seed oil at a dose of 10 mg/kg, twice weekly for 43 days (28).

Group I was kept as control, group II was treated with DOCA salt, while group III and group IV were treated with DOCA salt + formulation and DOCA salt + pure drug, respectively. On the 31st day of DOCA salt treatment, when animals became hypertensive, group III and group IV were treated orally with 1.8 mg/kg equivalent formulation in the suspension form and pure drug as a solution in pH 7.0 phosphate buffer, respectively. Their arterial blood pressure was measured at 0, 1, 2, 6, 12, and 24 h with the tail-cuff method. Tail-cuff is a common and convenient method to measure systolic pressure in rats. Tail-cuff is inflated and then deflated. Pulsations disappear when the cuff is inflated. When the cuff is deflated, the pulsations start appearing, and the recorded pressure in the cuff equals systolic pressure. The cuff is attached to a tail cuff sphygmomanometer or more commonly to pressure transducer and BP is recorded on a chart. Training the animal and warming the tail are required for this method (29, 30, 31). The computerized tail-cuff instrument can also be used (29).

Statistical analysis

The in vivo study was analyzed by one-way analysis of variance followed by Tukey's multiple comparison test at the significant level of $P < 0.05$ and $P < 0.001$, respectively in SPSS (USA).

Results

The drug-loaded floating microspheres were characterized by various parameters. The particle size of the formulation was determined, and the mean particle size of the microspheres was found to be 161.57±4.93 μm. The determination of shape and surface morphology was done by scanning electron

microscope (SEM) (HITACHI SU 1500, Japan). SEM analysis of the formulation revealed that all prepared plain and carvedilol-loaded floating microspheres were smooth and almost spherical. The shape and surface morphology of the microspheres were studied, and the images showed microspheres with a cavity at the center, smooth surface, and spherical shape. The microspheres had a porous internal surface and a smooth and dense outer surface. The microsphere shell also showed some porous structure. It may be caused by the evaporation of solvent entrapped within the shell of the microspheres (Fig. 1 and 2).
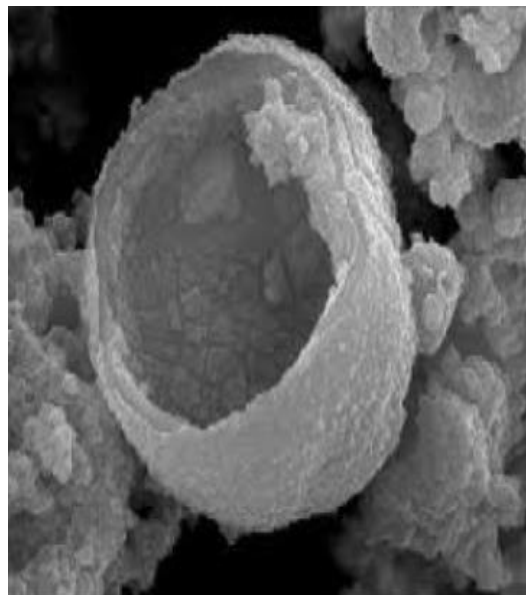

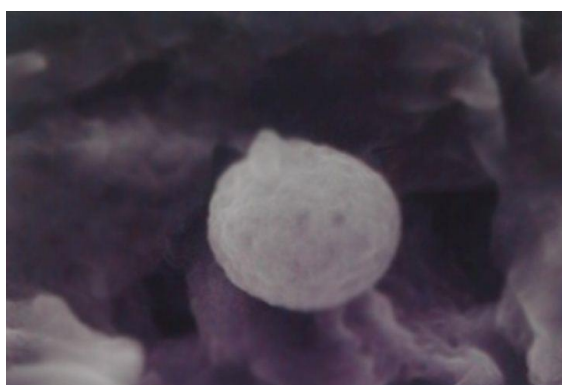**Figure1** Scanning electron microscope of plain microspheres

Figure 2 Scanning electron microscope image of carvedilol-loaded floating microspheres

In vitro buoyancy study for carvedilol-loaded floating microspheres was found to be 79.0%. The prepared carvedilol-loaded floating microspheres showed the maximum buoyancy due to the size and polymer concentration of prepared floating microspheres. The %entrapment efficiency of carvedilol-loaded floating

microspheres were found to be 85.81±1.40. According to various micromeritic properties, the tapped density for carvedilol-loaded floating microspheres was found to be 0.42±0.012 followed by Carr's compressibility index for carvedilol-loaded floating microspheres which was found to be 12.5±1.895. It was within the range of 5-15, which shows excellent flowability. The angle of repose for carvedilol-loaded floating microspheres were found to 23.5±1.856 degrees. The angle of repose was under 25°, which indicate the excellent flow of the formulations. The percentage yield of carvedilol-loaded floating microspheres was calculated and found to be 80.2% (Table 1).

The developed gastroretentive microspheres of carvedilol released the drug in the controlled fashion for 24 hours (Fig. 3).

Table 1 Various micromeritic parameters of formulation (mean ± SD, n = 3)

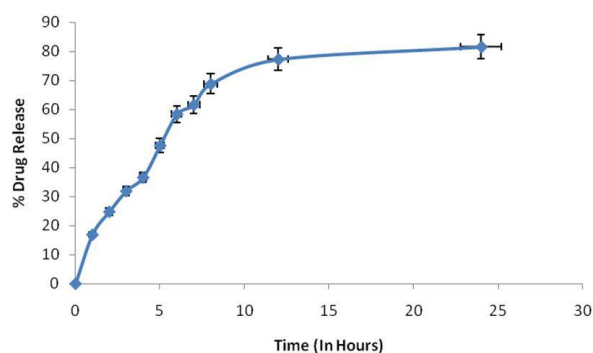| Micromeritic parameters	Carvedilol-loaded floating microspheres
Tapped density (g/cm^3)	0.42±0.012
The angle of repose, degree	23.5±1.143
Carr's index	12.5±2.042
Percentage yield	80.2%
In vitro buoyancy	79.0%
%entrapment efficiency	85.81±1.40

Figure 3 %*In vitro* drug release from carvedilol loaded floating microspheres

According to ICH guidelines Stability studies, drugs were carried and stored for 30 days at 15 ± 2 °C,   27 ± 2 °C, and 50 ± 2 °C. The particle size of the formulation was determined by optical microscopy using a calibrated ocular micrometer. The particle size of the floating microspheres was found to increase slightly at 50 ± 2 °C, which may be attributed to the aggregation of particles at a higher temperature. The formulation was

stored at 15 ± 2 °C, 27 ± 2 °C, and 50 ± 2 °C, and the %residual drug content of the formulation was measured after 30 days. The results indicate negligible changes in residual drug content after storage for 30 days at 15 ± 2 °C and 27 ± 2 °C, which shows that drugs are stable at these temperatures. The remaining drugs content was found to decrease at 50±2 °C. The results from particle size and drug content suggest that the formulation are stable at 27±2 °C as there is no aggregation found due to which the floating microsphere will remain stable (32) (Table 2).

Hypertension was induced using DOCA, and tail-cuff is a common and convenient method to measure blood pressure in rats. Carvedilol-loaded floating microspheres resulted in mean (SD) effective maintenance of systolic blood pressure as 120 (0.32), 119 (0.72), 121 (0.60), 120 (0.89), 122 (1.05), 120 (1.02) mm Hg and diastolic pressure as 91 (0.71), 92 (1.23), 90 (1.05), 91 (0.37), 91 (1.20), and 92 (0.79) mm Hg (Table 3).

Discussion

Carvedilol often shows poor bioavailability or absorption due to its limited solubility and extensive first-pass metabolism because it belongs to BCS class II drugs (poorly water-soluble drugs) (33,34). The currently commercially available carvedilol product is a conventional, tablet form drug prescribed BID. In the present research work, we planned to develop a gastroretentive controlled/sustained release drug delivery system, which can remain in the stomach for several hours. This long time would significantly improve bioavailability, reduce drug waste, and enhance the solubility of drugs. Prolongation of gastric residence time (GRT) of oral drugs by using floating microspheres reduces the inter-subject variability and the so-called "peak and valley" effect and leads to predictability and bioavailability of the dosage form, especially for molecules with a narrow absorption window (35). The particle size was examined by optical microscopy, which was found to be small, indicating the enhanced solubility of the drug. Morphology of microspheres was examined by SEM. The view of the microspheres showed a hollow spherical structure with a smooth surface. Some of the microspheres showed a dented surface structure, but they showed good floating ability on the surface of the medium, indicating an intact surface. The internal surface was porous that may be caused by the evaporation of solvent entrapped within the shell of microspheres after forming a smooth and dense layer.

The prepared formulation was characterized by various micromeritic properties. Tapped density for carvedilol-loaded floating microspheres was found to be 0.42 ± 0.012 followed by Carr's compressibility index of 12.5 ± 1.895. It was within the range of 5-15, which shows excellent flowability. Also, the angle of repose for carvedilol loaded floating microspheres were found to

Table 2 Effect of storage condition on the particle size of the floating microspheres (mean ± SD, n =3) and drug entrapment efficiency of various floating microspheres (mean ± SD, n =3)

Formulation	Particle size (after 30 days)			
	Initial	15±2 °C	27±2 °C	50±2 °C
Carvedilol-loaded floating microspheres	161.57±4.93	160.28±3.52	161.32±4.91	188.23±1.26
% Residual drug content on storage				
Carvedilol-loaded floating microspheres	100	99.54	99.82	98.64

Table 3 *In vivo* studies for anti-hypertensive studies

Animal groups

Time, h	Control (group I)		DOCA salt (group II)		DOCA salt + formulation (group III)		DOCA salt + pure drug (group IV)	
	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP
0	130 ± 0.32	89 ± 0.71	162 ± 1.36*	119 ± 1.08*	120 ±0.32	91 ± 0.71	153 ± 0.71##	100 ± 0.42##
1	125 ± 0.72	94 ± 1.23	164 ± 0.71*	120 ± 0.58*	119 ±0.72	92 ± 1.23	142 ± 1.08##	98 ±1.07##
2	127 ± 0.60	91 ± 1.05	162 ± 1.13*	121 ± 0.71*	121 ±0.60	90 ± 1.05	131 ± 1.59##	97 ±0.41##
6	128 ±0.89	92 ± 0.37	163 ± 2.32*	120 ± 1.47*	120 ±0.89	91 ± 0.37	132 ± 1.68##	101 ± 0.71##
12	126 ± 1.05	90 ± 1.20	162 ± 0.51*	119 ± 1.68*	122 ±1.05	91 ± 1.20	137 ± 1.0##	103 ± 1.04##
24	128 ± 1.02	95 ± 0.79	163 ± 1.01*	119 ± 1.15*	120 ±1.02	92 ± 0.79	139 ± 0.87##	109 ± 0.85##

Abbreviations: BP; Blood pressure, DOCA; Deoxycorticosterone acetate.
Data are expressed as mean ± SEM (n = 4).
Statistical analysis was done by 1-way analysis of variance followed by Tukey's multiple comparison test.
*P < 0.001, when compared with the control group.
#P<0.05, when compared with DOCA-treated group.
##P<0.001, when compared with DOCA-treated group.

23.5 ± 1.856 degrees. The angle of repose was below 25°, indicating that the microspheres are free-flowing or cohesive in nature and non-aggregated. Therefore, they had excellent flow property, resulting in the formation of spherical microspheres. The percentage yield of carvedilol-loaded floating microspheres was 80.2%, indicating that the solvent evaporation method is suitable for the creation of floating microspheres. In vitro buoyancy study for the carvedilol-loaded floating microspheres was found to be 79.0%. The prepared microspheres showed the maximum buoyancy due to the size and polymer concentration of prepared floating microspheres, so the system would remain buoyant for longer duration and release drug to its site for a longer period. The % entrapment efficiency of floating microspheres was found to be 85.81 ± 1.4, which indicated maximum entrapment of the drug and would result in releasing the medicine in a sustained manner for a longer time.

Nila *et al.* developed floating microspheres of carvedilol as gastroretentive drug delivery system of 3^2 full factorial design and in vitro evaluation showed the drug release time of up to 12 h (36). While the in vitro drug release of the formulated microspheres of carvedilol lasted 24 h providing a more prolonged release to its target site because of the drug's entrapment in the floating microspheres. The extended-release will result in enhancing its bioavailability and the effective treating of hypertension. It also will provide sustained drug action at a predetermined rate by maintaining a relatively constant, adequate drug level in the body with simultaneous minimization of undesirable side effects. Stability studies of floating microspheres formulation were determined for 30 days' period at 15 ± 2 °C, 27 ± 2 °C, and 50 ± 2 °C, in terms of their change in particle size and % residual drug content in comparison to freshly prepared floating microspheres. The results indicate that floating microspheres are

more stable at 15 °C to 27 °C. Increase in temperature adversely affects floating microspheres formulation.

In vivo effect of formulation and the pure drug was determined by using the tail-cuff method to measure arterial blood pressure. The results revealed that group III with the drug-loaded microspheres maintained the reduced systolic and diastolic arterial pressure up to 24 h, while an increase in the pressure after 6 h was seen in group IV with pure drug. When compared to other studies, it is proven that the main aim of our study, i.e., to increase the half-life of the drug has been accomplished (36). For drugs with a relatively short half-life, the sustained release of the drug into the gastrointestinal tract maintain an adequate concentration of medicine in the systemic circulation for a long time and result in flip-flop pharmacokinetics. So, formulating floating microspheres for short half-life drugs shows sound therapeutic effects (16). Our results prove that the proposed system has confirmed the primary objective of the study.

Conclusion
Floating microspheres of carvedilol were successfully formulated by employing a solvent evaporation technique. The formulated floating microspheres showed the highest encapsulation efficiency, loading efficiency, and drug release. These benefits result in the sustained release of the drug. Further *in vivo* studies showed a significant increase in drug effectiveness and permeability, leading to increased bioavailability. Besides, *in vivo* studies proved that the drug-loaded floating microspheres had a better option for the effective maintenance of blood pressure. In sum, the overall investigations present an alternative drug delivery system for increasing the carvedilol bioavailability through the floating microspheres.

Future Prospects
Our studies confirmed that floating microspheres could be used as a possible alternative to a conventional oral formulation. Our results further concluded that floating microspheres could be explored as a potential drug carrier for dissolution enhancement of other insoluble drugs.

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Conflict of interest
The authors declared no conflicts of interest.

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