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Formulation and *in-vitro* Evaluation of Carvedilol Gastroretentive Capsule as (Superporous Hydrogel)

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Abstract

The carvedilol uses in cardiovascular disease has a major problem which is low solubility (Class II).
The purpose of this study was to formulate and evaluate gastroretentive superporous hydrogel of carvedilol to improve its solubility and increase gastric residence time via utilization of various kinds and concentrations of hydrophilic polymers then incorporation of best prepared formula into capsules.

Sixteenth formulae of SPH hybrid were prepared by gas blowing technique from the following materials; monomers (Poly vinyl alcohol, and acrylamide), cross-linkers (Methylene bisacrylamide, and glutaraldehyde), hybrid agent (Chitosan), foaming agent ($NaHCO_3$) and foam stabilizer (Tween 80). Different amounts or concentrations of these materials were utilized to investigate their effect on SPH properties (density, porosity, floating, drug content, drug release, swelling time, and swelling ratio). The soaking procedure was utilized for loading of carvedilol into SPH hybrid (6.25 mg/ 2.5 g SPH).

The choice of the best formula relied on the correlation of the resulted SPH concerning to release profile of reference (Carvedilol 6.25 mg tablet/ Roche). The release of carvedilol was carried out by utilizing the dissolution apparatus (USP type II). After analysis the results and application of similarity factor (*f* 2) equation, F8 was selected as the best formula then incorporated into capsule.

The drug release data were applied to different mathematical kinetics and the results were shown to be fitted to Higuchi model and the release mechanism was (Fickian) diffusion.

The overall results suggested that the prepared SPH capsules for carvedilol are specific delivery to the stomach due to the increase in residence time and enhancement in solubility.

Key words: Superporous hydrogel (SPH), Monomer, Hybrid agent, Cross-linker, and foaming agent.

تصييغ وتقييم خارج الجسم للكارفيديلول كبسول المحتجز في المعدة (كهلام مائي فائق المسامية)

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الخلاصة

ان اكثر مشكلة تواجه استخدام الكارفيديلول لعلاج امراض القلب هي قلة ذوبانيته (يعتبر من الفئة الثانية من حيث التقسيم الصيدلاني).
الغرض من هذه الدراسة هو صياغة وتقييم خارج الجسم للهلام المائي فائق المسامية المحتجز في المعدة للكارفيديلول لتحسين قابلية الذوبان وزيادة وقت البقاء في المعدة باستخدام انواع وتراكيز مختلفة من البوليمرات المحبة للماء ثم تحضير افضل صيغة على شكل كبسول .
تم تحضير ستة عشر صيغة للهلام المائي فائق المسامية الهجين بتقنية الانتفاخ الغازي من المواد التالية؛ المونومرات (بولي فاينيل الكحول وأكريل أمايد) ، المادة الرابطة (مثيلين بسأكريل أمايد و كلوتارالديهايد) ، العامل الهجين (كيتوسان) ، العامل المولد للرغوة (بيكاربونات الصوديوم) ومثبت الرغوة (توين ٨٠) . وقد تم دراسة تأثير كمية أو تركيز هذه المواد على خصائص الهلام المائي فائق المسامية (الكثافة، المسامية، الطوفان، كمية الدواء، تحرر الدواء، وقت الانتفاخ ونسبة الانتفاخ). لقد استخدمت طريقة التنقيع لتحميل الكافيدولول في الهلام المائي فائق المسامية الهجين
بعد تحليل نتائج هذه الدراسة احصائيا وتطبيق معادلة العامل المشابه (f_2) وجد ان الصيغة F8 هي افضل صيغة يمكن اختيارها وقد تم دمجها بشكل كبسول. كما ان بيانات تجربة تحرر الدواء تم تطبيقها على اكثر من صيغة رياضية وكانت النتيجة ان اقرب صيغة رياضية للبيانات هي صيغة هيكوشي بالإضافة الى ان تحرر الدواء عن طريق الانتشار (فيكين).
ومما تقدم تظهر لنا النتيجة النهائية هي امكانية استخدام الهلام المائي فائق المسامية الهجين لزيادة ذوبانية الكارفيديلول ولابقاء الدواء بشكل خاص في المعدة ليتم امتصاصه هناك .

الكلمات المفتاحية :هلام مائي فائق المسامية ، مونومر ، العامل الهجين ، مادة رابطة ، عامل مولد للرغوة .

Introduction

The gastroretentive system can stay in the gastric region for many hours thereby prolonging the drug gastric residence time to get; better bioavailability, lower drug loss and enrich solubility for less soluble drugs in an environment with elevated pH [(1)].

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Several approaches to the gastroretentive drug delivery are being developed which involve: the floating system, the high-density sinking system, the muco-adhesive system, the magnetic system, the swellable, expandable, or unfoldable system, and superporous hydrogel [2].

The SPH is a system with 3- dimensions of non-soluble hydrophilic polymers that take up great amounts of water in a brief time due to the existence of interrelated microscopic holes. The used polymers are either natural like chitosan, alginate, gelatin, and carboxymethyl cellulose or synthetic like polyacrylamide, poly (acrylic acid), polyvinyl pyrrolidone (PVP), and polyvinyl alcohol (PVA) [3]. The hydrogel with hundreds of micrometers of pore size is considered as superporous hydrogel that varies from other forms of porous hydrogels like mesoporous and macroporous. The SPH also has hundreds of time more surface area and smaller diffusion gap than traditional hydrogels due to its porous structure; these properties cause dried SPH to swell very rapidly on contact with water to very large sizes [4].

When SPH is administered, the enlarged hydrogel can stay on in the stomach for an extended time and release the loaded drug as its volume are very large to be transferred across the pylorus sphincter. For use as the gastroretentive tool, SPH not only has rapid swelling but also exhibits features such as biocompatibility, biodegradability, flexibility, high mechanical potency, great swelling potential, and acidic stability in the stomach [5]. As example, SPH hybrids of loratidine hydrochloride was formulated and characterized by Dhingra et al [6].

Carvedilol is a weak base with a pKa (7.8) and classified as class II in the biopharmaceutical classification system (BCS). It favors solubilization in the stomach at low pH. However, it exhibits pH-dependent solubility therefore it undergoes formulation as gastroretentive superporous hydrogel [7, 8].

Carvedilol is 1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl] amino]-2-propanol with the chemical formula ($C_{24}H_{26}N_2O_4$) and has a chemical structure shown in figure (1).

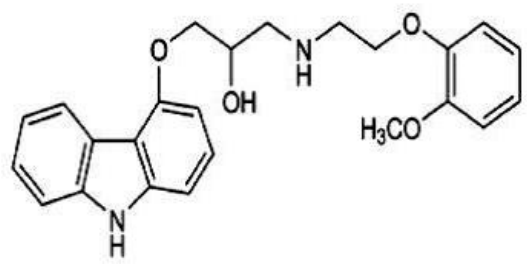

Figure 1. Chemical structure of carvedilol [9]

It is a powder with white to off white color with melting point (m.p.) 114-115 ℃. It is practically insoluble in water, soluble in methylene chloride and methanol, sparingly soluble in ethanol and isopropyl alcohol, Log P equal 4.19.

This research is attempted to formulate and evaluate gastroretentive SPH of carvedilol to improve its solubility and increase its residence time in the stomach via utilization of various kinds and concentrations of hydrophilic polymers and then incorporate the best-prepared formula into capsules.

Experimental Work

Materials

Carvedilol (Hangzhou-China), acrylamide (High Media-India), methylene-bisacrylamide (High Media-India), chitosan (Alpha chemika-India), tween 80 (Alpha chemical-India), polyvinyl alcohol (ME scientific-UK), sodium bicarbonate (Riedel-Germany), tetramethylethylenediamine, ammonium persulphate and glutaraldehyde (Central drug house-India)

Preparation of Super Porous Hydrogel hybrid of Carvedilol

The SPH formation was performed by solution polymerization of monomers utilizing a gas blowing technique. The following constituents were applied sequentially to 10 ml beaker; acrylamide AM 40% (1200 µl) as a monomer, polyvinyl alcohol PVA (150 mg) as a monomer and hybrid agent, methyl bisacrylamide Bis (450 µl) as a cross-linker, chitosan (400 µl) as a hybrid agent, tween 80 (0.2 ml) as a foam stabilizer, ammonium persulfate APS 20% (45 µl) and tetramethylehtylenediamine TEMED 20% (45 µl) as an initiator system. The admixture was shaken after adding each element. Finally, $NaHCO_3$ (100 mg) powder was added as a foaming agent. The polymerization was occurred after $NaHCO_3$ addition and finished in a few minutes (Table 1). The SPH was removed from the beaker and washed with a blend of ethanol and water at a ratio of 3:1. Then after, SPH was dried for 72 hours at room temperature [10].

The soaking procedure was utilized for loading of carvedilol. The amount of 0.1N HCl required for ideal swelling of SPH was first determined thereafter, a solution of the drug (6.25 carvedilol/ 5 ml 0.1N HCl) was prepared. The SPH was soaked in the prepared solution and left 20 minutes in the drug solution and let to dry overnight at room temperature [11].

The effect of cross-linker concentration and type on the physical properties of SPH hybrid (density, swelling, porosity, floating, drug content, and release) was studied as represented by F1-F7. Each of F1-F5 was prepared with 450 µl of N, N-Methylene-bisacrylamide (Bis) as a cross- linker at 1, 1.5, 2, 2.5, and 3% w/v, respectively. While, each of F6 and F7 were prepared with 50 and 100 µl of glutaraldehyde (GA), respectively (Table 1)。

In addition, to estimate the effect of chitosan (as a hybrid) concentration on SPH features, F1, F8, F9, and F10 were prepared with different concentration

of chitosan; 1, 2, 3 and 4% w/v, respectively with keeping all other materials, and their amounts constant as demonstrated in the table (1).

To investigate the effect of PVA (as a monomer and hybrid agent) amount on the SPH properties, formulas F1, F11, F12, and F13 were prepared with 150, 200, 250, and 300 mg PVA, respectively (Table 1).

Effect of foaming agent amount ($NaHCO_3$) on properties of SPH was also studied by F1, F14, F15, and F16 which were prepared with 100, 150, 200, and 250 mg of $NaHCO_3$ with keeping other constituents constant as shown in table (1)

Characterization of the prepared SPH

Drug content determination

Dry SPH (about 2.5 g) containing 6.25 mg carvedilol was placed in a 100 ml volumetric flask and filled up to the mark with HCl buffer (pH 1.2). The resulting solution was filtered through Whatman filter paper. Then after, the absorbance was measured by utilizing UV spectrophotometer at the appropriate lambda max (λ_{max} = 285) the amount of carvedilol in the tested formula was calculated [9, 12].

Density measurement

For determination of density, solvent displacement process was used in which a dry SPH was taken and weighed then immersed in a predetermined hexane volume in a graduated cylinder, SPH volume was measured by increases in the volume of hexane. The density calculated by the following equation [13].

$$\text{Density} = W_{SPH} / V_{SPH} \quad \ldots\ldots (1)$$

Where, W_{SPH} = Weight of dried SPH, V_{SPH} = Volume of SPH.

Swelling time determination

This is an important feature of SPH. The time of swelling of SPH was determined by placing the hydrogel in a swelling media (water or 0.1N HCl) and the time for equilibrium swelling (constant weight) was recorded [14].

Swelling ratio measurement

The completely dried SPH was placed in excess of the swelling medium then removed from the media at a set time and weighed; the swelling ratio was measured by the following equation [14].

$$Q_s = [(W_s - W_d) / W_d] * 100 \ldots\ldots (2)$$

Where, Q_s = Swelling ratio, W_s = Weight of swollen SPH, W_d = Weight of dried SPH

Porosity measurement

The dry hydrogel was immersed in the absolute ethanol overnight and weighed after excess ethanol on the surface was blotted; the porosity was calculated by following equation [15].

$$\text{Porosity} = (M_2 - M_1) / PV \ldots\ldots (3)$$

Where, M_2 and M_1 = Weight of hydrogel after and before immersion in ethanol, respectively. P = Absolute ethanol density, V = Initial hydrogel volume.

Floating study

The hydrogel was placed in a beaker containing 100 ml of 0.1N HCl, the time needed for rising of SPH to the surface and floating was known as a floating lag time while, the total period time during which SPH remained buoyant was known as a total floating time [16].

***In-vitro* drug release**

The *in-vitro* carvedilol (6.25 mg) release test for SPH hybrid (2.5 g) was performed by utilizing the dissolution apparatus (USP type II) in 900 ml 0.1N HCl at 100 rpm speed of the paddle for 12 h at 37±0.5 ℃. A sample of dissolution medium (5 ml) was withdrawn at specified time intervals then; an equal volume of fresh medium solution was substituted. The absorbance of each sample was measured via UV- spectrophotometer at the appropriate λ_{max} of carvedilol. Then after, the percent release of carvedilol was calculated [6].

Scanning Electron Microscopy (SEM)

Analysis of SEM was done to declare the morphology of dried SPH. It was carried out to assure the porous structure produced during SPH combination using the Hummer sputter coater.

Samples were plated with gold carried with a JSM-840 scanning electron microscope and collected the image using a digital capture card and digital scan generator [17].

Table 1. Formulas of SPH.

Formula Component	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
AM 40% (µl)	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200
PVA (mg)	150	150	150	150	150	150	150	150	150	150	200	250	300	150	150	150
Bis (µl) of 1%	450							450	450	450	450	450	450	450	450	450
1.5%		450														
2%			450													
2.5%				450												
3%					450											
GA (µl)						50	100									
Chitosan (µl) of 1%	400	400	400	400	400	400	400				400	400	400	400	400	400
2%								400								
3%									400							
4%										400						
Tween 80 (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
APS 20% (µl)	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45
TEMED 20% (µl)	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45
$NaHCO_3$ (mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	150	200	250
Total (g)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

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Statistical analysis

Results were expressed as mean ± SD for each. Analysis of variance (ANOVA) test was used to analyze the difference among many groups. While students' t-test was used to analyze the difference between the two groups by utilizing SPSS20 software window. A probability value ($p < 0.05$) was considered the minimum level of statistical significance.

Best formula selection

The choice of the best formula relied on the correlation of the resulted SPH concerning to release profile of reference (Carvedilol 6.25 mg tablet/ Roche).

The similarity factor (*f* 2) introduced by Moore & Flanner was utilized as a standard for determination of the best formula according to the following equation

$$f_2 = 50 \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}\omega_t\left(R_t - T_t\right)^2\right]^{-0.5} \times 100\right\} \quad (4)$$

Where, n number of dissolution time points, R and T are the reference and test dissolution values at time t [(10)].

Fourier Transform Infrared (FTIR) analysis

The SPH was desiccated and converted to a powdered form for FTIR analysis to study the compatibility of the drug with polymers. The powdered specimen (2-3mg) was combined with KBr. The FTIR spectrum was measured in the range 4000-600 cm^{-1} utilizing FTIR spectrometer [(18)].

Capsule pre-formulation tests

Angle of repose measurement

The angle of repose was measured by funnel method in which a funnel was held in a stand vertically at a specified height over a piece of paper put on the horizontal region, the bottom of the funnel was closed and sample powder was filled in the funnel, then the funnel was opened to release the powder to create a conical shape. Conical diameter was measured in different directions and the conical height was measured by utilizing a scale. The angle of repose value was determined by the following equation:

$\tan \theta = h / r$…… (5)

Where θ = angle of repose, h = conical height, r = conical radius

The angle of repose values may be used as a powder flow guide as shown in table (2) [(19)].

Table 2. Relationship between Angle of Repose and Powder Flow [(20)]

Angle of repose	Powder flow
< 25	Excellent
25-30	Very good
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
> 56	Very poor

Carr's index measurement

Carr's index provides a view about powder flow properties and can be calculated by measuring bulk and tapped densities. The bulk and tapped densities were calculated via simple filled cylinder tapping method. In this method, a graduated cylinder was filled with drug sample powder and the resulted volume (bulk volume) was measured. Then after, the cylinder was tapped on a flat surface and the resulted volume changed to (tapped volume). Both densities have been calculated by utilizing the following equations [(21)].

$D_{bulk} = M/V_b$ …. (6)

$D_{tapped} = M/V_p$ …. (7)

Where, M = mass powder, V_b = bulk volume, D_{bulk} = bulk density, V_p= tapped volume, D_{tapped} = tapped density

$$\%\ \text{Carr's Index} = [(D_{tapped} - D_{bulk})/D_{tapped}\ ] * 100 \quad \ldots.(8)$$

The correlation between index values and flow type is shown in table (3)

Table 3. Relationship between Carr's Index and Powder Flow [(20)]

Carr's Index (%)	Flow description
< 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-39	Very poor
> 40	Very poor

Evaluation of capsules

Weight variation test

Twenty capsules were taken randomly and weighed to calculate the average weight. Then after, every capsule was weighed individually and weight of the empty capsule shell was subtracted from the gross weight. If the individual capsule weight in the range of (90-110%) of average weight, it passed the weight variation test [22].

Disintegration test

This test was done by the disintegration apparatus; the water bath was filled to the mark with tap water and the temperature was adjusted to 37±0.5 ℃. The used beaker was filled with distilled water (600 ml) and suspended in the main bath, one capsule was placed in each of the six glass tubes and the disc may be used if the dosage form floats. The apparatus rotation was set at 28-32 cycles/minute and worked till all capsules were disintegrated or leaving the only small remnant of gelatin shell (soft mass with no firm core) on the mesh [23].

Drug content uniformity

The content of five capsules was weighed accurately and the content of every capsule was poured in 100 ml volumetric flask and dissolved in 0.1N HCl (volume made up to the mark of flask). This solution was filtered through Whatman filter paper, and then solution absorbance was measured at 285 nm by UV spectrophotometer to calculate drug content by using the equation of calibration curve [24].

Dissolution test

The capsule rate of release was determined using the dissolution apparatus (basket type), in the beginning, the hard gelatin capsules were put in the basket, the apparatus was operated at 37±0.5C˚ and 100 rpm then the apparatus jar was filled with 900 ml of 0.1N HCl for each capsule. Sample of 5 ml was withdrawn at 30 min interval for 4 h duration and replace with fresh buffer. The sample absorbance was measured using UV spectrophotometer at 285 nm after filtration via Whatman filter paper to calculate the percent drug release using the equation of standard curve [25].

Mathematical models of drug release

Various mathematical models were employed to describe drug release kinetics from the SPH loaded with active drug. However, the kinetics of carvedilol release from SPH was concluded by finding the best fit of release data to Zero order, First order, Higuchi and Korsmeyer-Peppas plots [26].

Stability study (effect of temperature)

The temperature effect on the selected formula (F8) of carvedilol was examined. This study was achieved by placing the capsules in ovens at various temperatures (40 and 60 C˚) for 7 weeks and samples were taken at certain intervals of time to calculate drug percent remaining [27].

Results and Discussion

Carvedilol superporous hydrogel hybrid (SPH)

The mechanism for preparation of SPH was polymerization of monomers in the presence of gas bubbles.

The blowing technique utilized for the preparation of SPH based on two processes polymerization and foaming, in the polymerization step the mixture of APS/TEMED redox pair will trigger radical polymerization then the monomers bond covalently to each other and form prolonged chain by cross-linking by bismethylacrylamide. While in the foaming process, the reaction of $NaHCO_3$ with acidic content will generate carbon dioxide gas bubbles that stabilized by tween 80. The foam size was concluded by the amount of gas bubbles released that in turn was determined by the acid and $NaHCO_3$ amount [10].

Effect of cross-linker concentration and type

The effect of concentration and type of the cross-linker (bisacrylamide and glutaraldehyd) on the physical properties SPH hybrid was represented by F1-F7 as shown in table (4).

Table 4. Effect of Cross-linker Concentration and Type on Physical Properties of Carvidelol SPH

Formula no.	Density g/^{3}cm	Swelling Time (min)	Swelling Ratio	Porosity	Floating lag time (min)	Floating Time (min)	Drug Content (%)	Drug Release (%)
F1	1.2± 0.02	75	0.36	0.33± 0.025	70	61	99%	89%
F2	1.23± 0.01	55	0.32	0.31± 0.015	70	75	106%	89%
F3	1.24± 0.005	50	0.29	0.29± 0.05	75	72	93%	86%
F4	1.27± 0.01	35	0.26	0.26± 0.01	80	70	108%	86%
F5	1.28± 0.05	30	0.24	0.23± 0.025	_	0	89%	80%
F6	0.83± 0.05	75	0.46	0.15± 0.025	90	140	102%	96%
F7	0.93± 0.05	55	0.41	0.1± 0.025	75	210	98%	95%

Results showed that the increase in cross-linker concentration (both types) led to density increase because of diminishing of network space and less water entered the hydrogel. While, porosity decreased due to formation of strong bonds among the polymers tend to reduce interconnecting pores size. Swelling ratio and time decreased due to the hydrogel took water molecules up by capillary force much faster than diffusion. However, there was drug release reduction because of reducing the porosity. Since the polymers were compatible with carvedilol, the drug content was within the acceptable range. The floating property for bismethylacrylamide containing formulas was due presence of swellable polymer (Chitosan) and effervescent agent ($NaHCO_3$) except, (F5) because it exhibited the least swelling capacity. While formulas contain glutaraldehyde (F6 & F7) showed low densities (<1 g/cm^3) although the presence of swellable polymer and effervescent agent [17, 28].

Statistically the cross-linker effect was significant ($P < 0.05$) on the density, swelling ratio, and drug release [29].

Effect of chitosan concentration

The effect of chitosan concentration on the SPH hybrid properties was represented by F1 (1%), F8 (2%), F9 (3%) and F10 (4%) as shown in table (5).

Table 5.Effect of Chitosan Concentration on SPH Hybrid Properties

Formula No.	Density $g/^3cm$	Swelling Time (min)	Swelling Ratio	Porosity	Floating Lag time (min)	Floating Time (min)	Drug Content (%)	Drug Release (%)
F1	1.2± 0.02	75	0.36	0.33± 0.025	70	61	99%	89%
F8	1.21± 0.02	60	0.29	0.19± 0.02	84	160	86%	79%
F9	1.24± 0.001	55	0.27	0.16± 0.001	55	80	102%	76%
F10	1.28± 0.03	50	0.23	0.13± 0.02	55	80	87%	75%

The results showed that increase in chitosan concentration resulted in porosity reduction and density increase (significant effect, $P < 0.05$) due to prevent the bubbles from escaping from the solution mixture (increased viscosity) and accumulation at the periphery of the pore. As well as, there was a decrease swelling time and ratio since, the formed hydrogen bond between chitosan and other polymers decrease the ability to form hydrogen bond with water molecules thus limiting water absorption. There was a significant effect ($P < 0.05$) on floating properties (A decrease in floating lag time and increase in floating time) because of increasing concentration of swelling polymer. The decrease in the drug release (significant effect, $P < 0.05$) was due to decrease in the porosity. The drug content was in the acceptable range due to compatibility of chitosan with the active ingredient [28, 30].

Effect of PVA amount

The effect of PVA amount on the SPH hybrid properties was represented by F1, F11, F12 and F13 which were prepared with 150, 200, 250, and 300 mg PVA, respectively. The results were shown in table (6).

Table 6. Effect of PVA Amount on SPH Properties.

Formula No.	Density $g/^3cm$	Swelling Time (min)	Swelling Ratio	Porosity	Floating Lag time (min)	Floating Time (min)	Drug Content (%)	Drug Release (%)
F1	1.2± 0.02	75	0.36	0.33± 0.025	70	61	99%	89%
F11	1.25± 0.04	70	0.35	0.2± 0.03	65	90	93%	80%
F12	1.3± 0.01	65	0.32	015± 0.07	73	100	103%	77%
F13	1.35± 0.03	55	0.3	0.12± 0.02	75	110	109%	75%

The results showed that, the increase in PVA amount led to; density increase due to cellulosic fibers presence in the structure of polymer, decrease in the porosity and swelling properties owing to the increase of solution viscosity during gelation, drug release reduction because of decreasing the porosity, a significant increase ($P < 0.05$) in floating time due to the increased viscosity prevents the bubbles from escaping and because of compatibility of PVA with

carvedilol, the drug content was within acceptable result [31, 32] .

Effect of foaming agent amount

Formulas; F1, F14-F16 were prepared with different amounts of foaming agent ($NaHCO_3$) and evaluated to show the foaming agent amount effect on SPH properties as demonstrated in table (7) .

Table 7. Effect of Foaming Agent Amount on SPH Properties.

Formula No.	Density g/^{3}cm	Swelling Time (min)	Swelling Ratio	Porosity	Floating Lag time (min)	Floating Time (min)	Drug Content (%)	Drug Release (%)
F1	1.2± 0.02	75	0.36	0.33± 0.025	70	61	99%	89%
F14	1.18± 0.03	75	0.32	0.18± 0.02	70	110	85%	84%
F15	1.15± 0.01	80	0.3	0.16± 0.04	60	130	98%	82%
F16	1.1± 0.03	85	0.25	0.12± 0.02	55	150	95%	78%

The results showed that increase in the foaming agent amount led to; decrease in porosity and density due to accumulation of generated carbon dioxide, slow swelling owing to the reduced porosity, since the foaming agent led to carbon dioxide generation which resulted to floating of SPH. The reduced porosity led to decrease drug release while, drug content within acceptable range due to no interaction between carvedilol and $NaHCO_3$ [33, 34].

Scanning Electron Microscopy (SEM) of SPH

The scanning electron microscopic photographs of the selected formula (F8) at various magnification powers were shown in the figure (2).

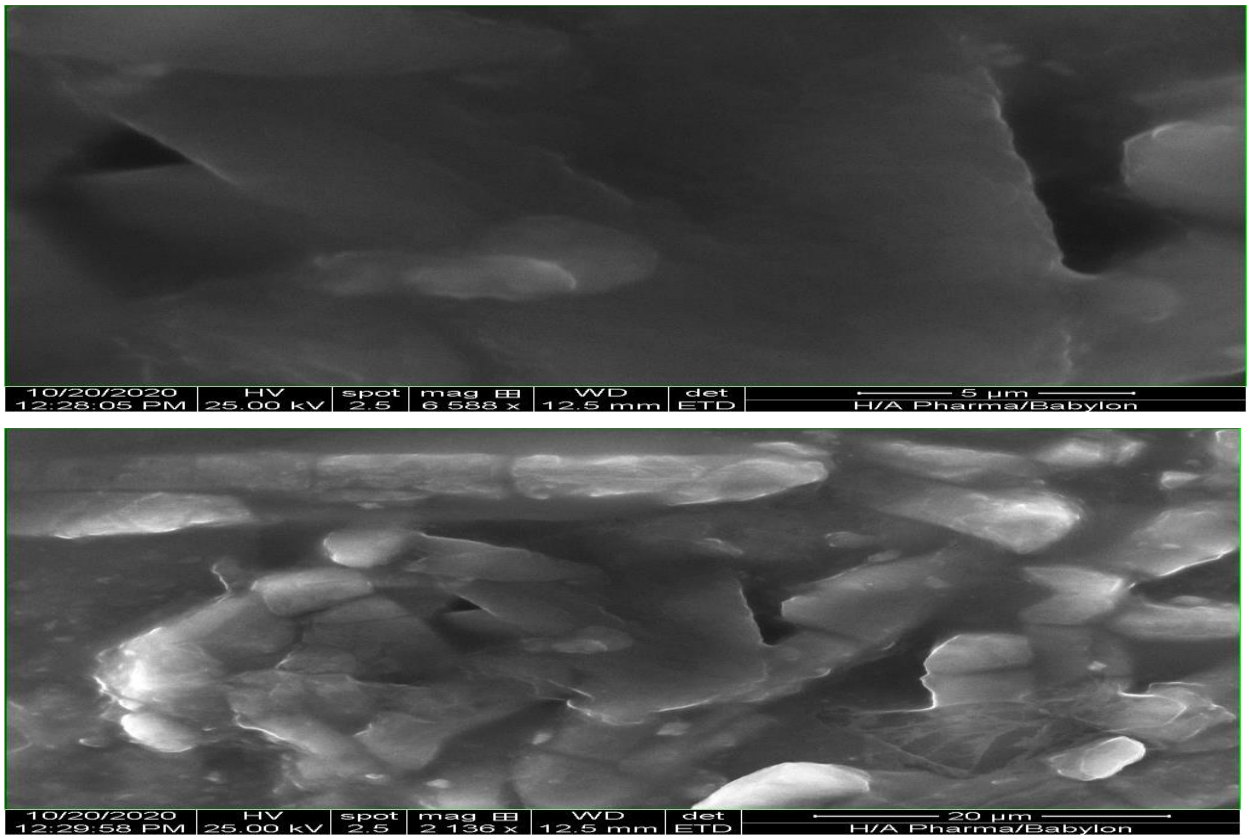

Figure 2. Scanning electron microscopic photographs of SPH

The best formula

By comparing the dissolution profile of formulas which exhibited significant differences in many properties (F2, F4, F5, F6 and F8) with that of reference (Carvedilol 6.25 mg tablet/Roche) to select best formula by similarity factor *(f2)* equation, F8 showed the higher value as shown in table (8) while, figure (3) showed the drug release comparison between selected formula (F8) and carvediol reference tablet.

Table 8. Similarity Factor Values for Selection of Best Formula

Formula No.	*f2* value
F2	29
F4	31
F5	32
F6	42
F8	56

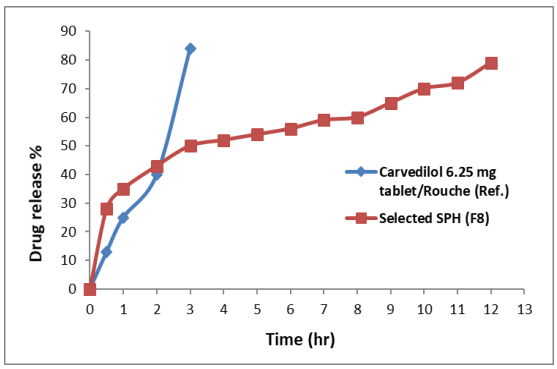

Figure 3. Dissolution profile of carvidelol tablet/Roche and selected SPH (F8)

Fourier Transform Infrared (FTIR)-Compatibility study

To examine the compatibility of drug with polymers of SPH, two samples were tested by FTIR (pure carvedilol and dried SPH) as shown in figures (4 and 5) and some variations were listed in table (9).

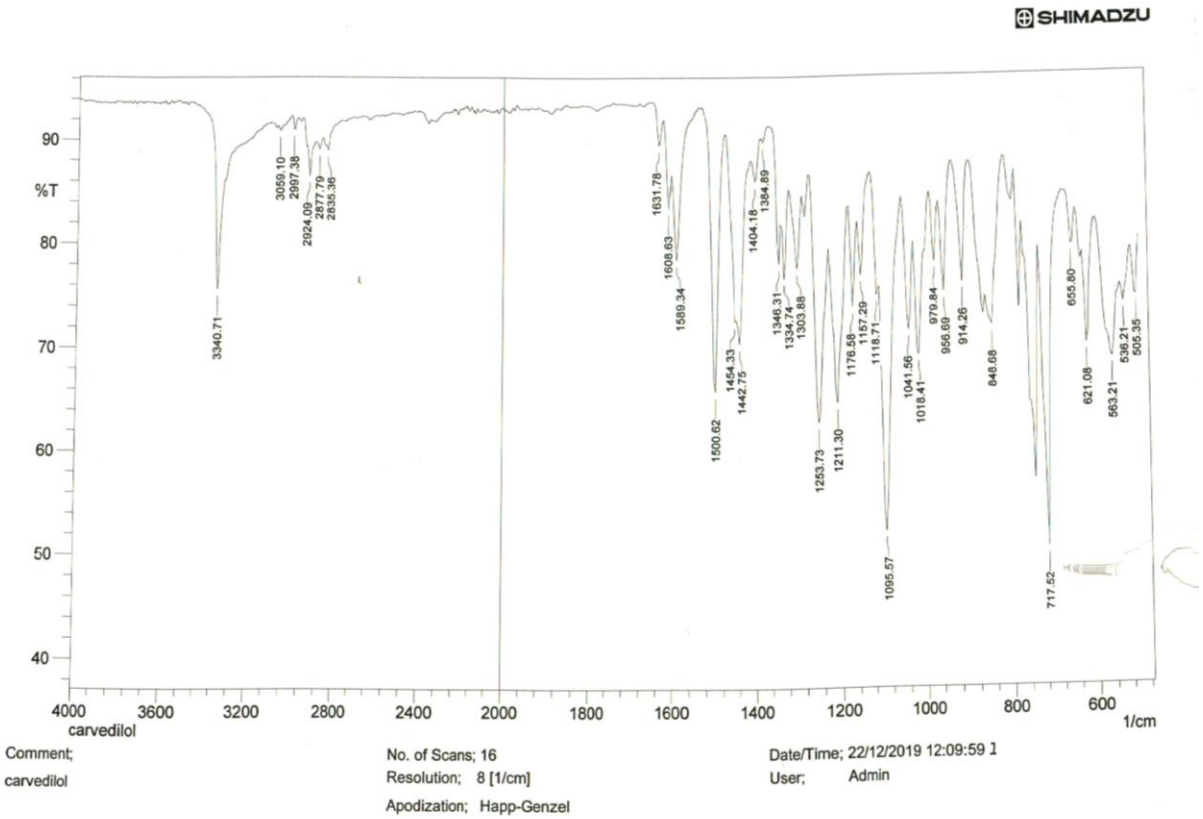

Figure 4. Pure carvedilol FTIR spectrum

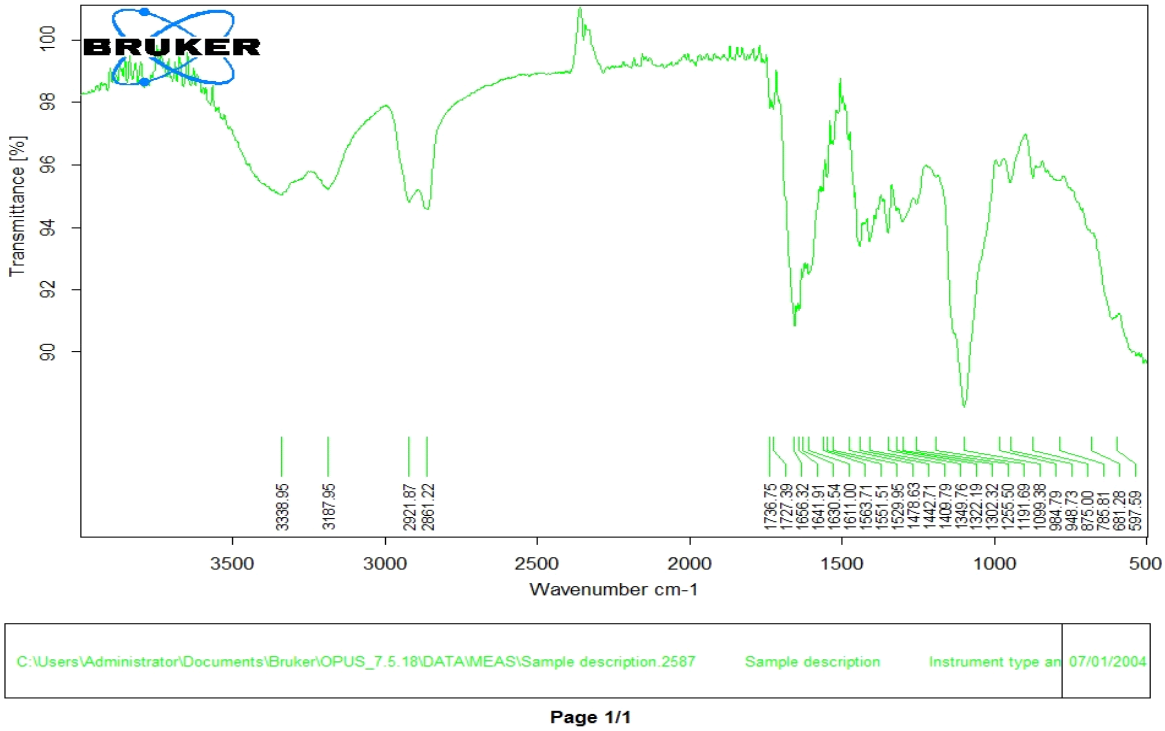

Figure 5. Dried SPH hybrid FTIR spectru

Table 9 Variation in FTIR Analysis of Carvedilol and SPH Hybrid (F8)

No.	Assignment groups	Theoretical Values	Carvedilol	Dried SPH hybrid
1	Aliphatic secondary NH stretch	3360-3310	3340.71	3338.95
2	Secondary NH bond	1650-1550	1631.78	1630.54
4	Aromatic secondary CN stretch	1350-1280	1346.31	1349.76
5	OH in plane bend	1350-1260	1303..88	1302.32
6	OH out of plane bend	720-590	621.08	597.59
7	Aromatic CH in plane bend	1325-950	1211.3	1191.69
8	C-N stretch	1350-1000	1095.57	1322.19
9	C-O stretch	1150-1050	1118.71	1099.38

The results (Figure 4 and 5) showed that, the major peaks of pure carvedilol and F8 were not affected and predominantly observed in the theoretical range, which indicated no interaction between the drug and the polymers. The change in figure (5) was in the near and mid IR region due to presence of (OH) group in the carvedilol and formula polymers [35, 36].

Results of Capsule Pre-Formulation

Angle of repose and Carr's index

The result values of angle of repose were in the range of excellent flow properties (Θ = 15.6-22.3) of the pre-formulation mixture. As well as, all the resulted values of Carr's index were in the range of excellent, good, and fair flow properties (9%-16%) [37].

Capsule evaluation

No variation in weight of capsules since, results of weight variation were within acceptable limits [38]. In addition, results of disintegration time were in the range 14-17 min. These results were passed the criteria of disintegration of capsules in the British Pharmacopoeia [9]. Drug content uniformity results were within the range of 85-115% which indicated the uniform distribution and proper dose of active ingredient in the selected formula (capsule) [38].

Dissolution of carvedilol SPH as capsule

Dissolution test was done for the selected formula (F8) after encapsulation and compared with that of reference tablet (Carvedilol 6.25 mg tablet/Roche). Capsules of F8 gave the highest drug release within 4 hr. as shown in the figure (6).

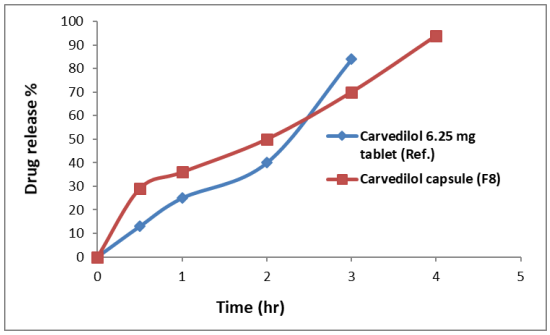

Figure 6. Drug release profile of carvedilol SPH as capsule (F8) in comparison with carvedilol 6.25 mg tablet/Roche

Mathematical model of drug release

For determining the release mechanism of carvedilol capsule, table (10) showed the correlation coefficient for each model by using MS-Excel software.

Table 10. Mathematical Models Correlation Coefficient Values

No.	Mathematical model	Correlation coefficient R2
1.	Zero order	0.9612
2.	First order	0.5643
3.	Higuchi	0.9623
4.	Korsmeyer-Peppas	0.9488

The results indicated that, dissolution release data were best fitted to the Higuchi model due to the highest R^2 value and the release mechanism was (Fickian) diffusion.

Stability of carvedilol SPH hybrid capsule

The shelf life of carvedilol (F8) capsule was calculated by constructing the Arrhenius plot as shown in figure (7). The rate constant of degradation K_{25} at 25˚C was found to be $1.58*10^{-3}$ $week^{-1}$ and the shelf life was 66.5 weeks since, carvedilol degradation followed first order kinetic [39].

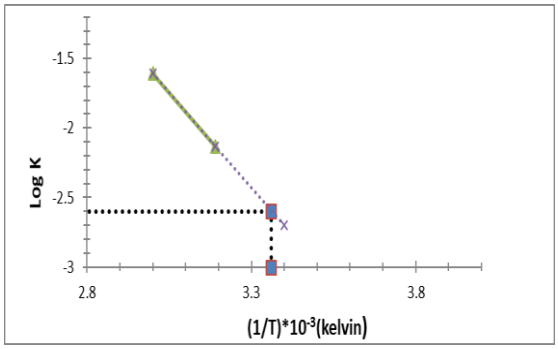

Figure 7. Arrhenius plot of carvedilol (F8) capsules

Conclusions

Based on the results gained, one can conclude the following: Carvedilol SPH is a good tool to improve the solubility (from the floating time, increase gastric residence time). The best formula of carvedilol SPH was (F8) which composed of chitosan (2%), Bis (1%), PVA (150 mg) and NaHCO3 (100 mg). The release of carvedilol was best fitted to Higuchi model with mechanism of fickian diffusion, and the estimated shelf- life of carvedilol SPH capsules was 66.5 weeks.

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