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Review Article

Liquid and Solid Self-Emulsifying Drug Delivery Systems to Improve Dissolution of Carvedilol

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ABSTRACT

Carvedilol has poor oral bioavailability, which is attributed to its limited aqueous solubility, intestinal efflux, and pre-systemic hepatic metabolism. This work aimed to increase carvedilol bioavailability via a self-emulsifying drug delivery system (SEDDS). Liquid-SEDDS were initially prepared, and the best formula with the highest drug release was converted into powder form to improve stability. A ternary phase diagram was performed using various ratios of Olive oil, Tween 80, and Propylene Glycol (as oil, surfactant, and co-solvent, respectively) to obtain 21 formulations. All formulations were characterized by visual inspection, accelerated aging, emulsification time and precipitation assessment, and in vitro drug dissolution studies. The best SEDDS formula was adsorbed onto a carrier to be transformed into solid powder, Fumed Silica, Avicel PH101, and their combinations to obtain solid-SEDDS. Drug dissolution, DSC, and ray diffraction were performed to formula showing the best flow properties. All SEDDS showed enhanced drug dissolution relative to the pure drug, with high initial drug release. Formula F14 showed a prompt drug of about 92% within 5 minutes, with a percentage dissolution efficiency of 93% after ten minutes. Formulas prepared using Avicel PH101 showed the best flow properties and were used for further investigations. Drug dissolution parameters were best from solid-SEDDS using Avicel PH101 alone. For DSC and X-ray diffraction studies, the drug characteristic peaks disappeared, indicating a reduction in drug crystallinity. Solid-SEDDS could enhance the Carvedilol dissolution rate with subsequent improved oral bioavailability by decreasing its pre-systemic metabolism.

Keywords: Carvedilol, Self-emulsifying, Olive oil, Tween 80, and propylene glycol

1. INTRODUCTION

Poor drug solubility is considered a major problem to formulate oral drugs into oral dosage forms. Many strategies were investigated to enhance the rate of dissolution and, consequently, absorption and bioavailability of weakly water-soluble drugs. Examples of these approaches were solid dispersion[1], liquisolid tablets[2], and lipid-based formulations[3]. Self-emulsifying drug delivery systems (SEDDS) are lipid systems that can serve as an effective substitute for oral emulsions since they are lipid dispersions with higher physical stability. SEDDS are isotropic mixtures of a drug, lipids, emulsifiers, and hydrophilic co-solvents[4]. SEDDS form fine oil in water emulsion spontaneously when added into the aqueous phase with slight stirring. After administration, SEDDS disseminates easily in the digestive system GIT with the help of the stomach's and intestine's

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motility, which creates the agitation required for the self-emulsification process[5, 6].

The main advantages of SEDDS are its ability to bypass the hepatic portal pathway and pass through the lymphatic pathway, thus avoiding hepatic first-pass effect and Cytochrome-P450 enzymes and/or inhibiting P-glycoprotein (P-gp) efflux[7, 8]. This is due to the nano-sized globules of the lipids and emulgents[9]. However, its limited stability and Production difficulties frequently impede its pharmaceutical utilization[10].

Solid-SEDDS (S-SEDDS) were recently considered to overcome some of the liquid SEDDS, such as stability, ease of handling, and economical benefits of their production[11]. Therefore, S-SEDDS is highly considered as it provides all the benefits of liquid and solid systems at the same time, in addition to ease of large-scale production. It is, therefore, a promising method to enhance the therapeutic properties and bioavailability of numerous medicines.

Carvedilol (CRV) is a non-selective beta blocker recommended to treat congestive heart failure, hypertension, and ischemic heart diseases[12]. It was categorized by the Biopharmaceutical Classification System as a Class II drug (i.e., poorly soluble and highly permeable). Its limited solubility has an impact on its serum concentration in addition to intestinal efflux transporter P-glycoprotein and its hepatic first-pass metabolism, causing limited oral bioavailability[13]. Therefore, it is a suitable candidate for formulation into SEDDS.

This research's goal was to increase the water solubility of CRV. The choice of SEDDS is according to the fact that CRV is a substrate to the intestinal efflux transporter P-glycoprotein, in addition to its pre-systemic metabolism by hepatic enzymes. The drug will be formulated in liquid SEDDS first. From the stability point of view, the best formula of liquid-SEDDS, concerning dissolution, will be converted into Solid-SEDDS using various carriers such as Avicel PH101, Fumed silica, and their mixture.

2. MATERIAL AND METHODS

2.1. Materials

Carvedilol (CRV) was a generous gift from Sigma Egypt co. ltd, Egypt. Oleic acid, Tween 80, and propylene glycol (PG) were obtained from Merck Pvt. Ltd., Mumbai. Soybean oil, olive oil, and sesame oil were purchased from SD Fine chemicals, Mumbai. Fumed Silica (A'sil 200) from LEHYOSS, UK Ltd. Microcrystalline cellulose (Avicel PH 101) was purchased from Memphis Co. (Cairo, Egypt). All other chemicals were of analytical grades.

2.2. Methods

2.2.1. Construction of calibration curve

To prepare standard solutions, 100 mg of a standard drug sample was dissolved in methanol to prepare 1 mg/ml solution. The working standard solutions of 5-30 µg/ml of CRV were obtained from this by making the appropriate dilutions in methanol. At 284 nm, the absorbance for CRV was determined by a UV spectrophotometer (Apel Co., Ltd., Japan). Analyses of five replications were performed. To create the calibration graph, absorbance vs. concentrations were plotted. The calibration curve had an r-value of 0.998, was linear in the measured range, and followed Beer's law.

2.2.2. Saturation solubility study

A solubility study is done to examine the drug's ability to dissolve in certain vehicles. SEDDS are then formulated with the vehicle, which achieved better solubility. The solubility of CRV in various oils (olive oil, oleic acid, soybean oil, and sesame oil) was determined (Table 1). An Excess drug was added to 5 ml of oil present in a capped tube. The mixtures were put in a thermostatic shaking water bath (LSB-030S, Daihan Lab Tech Co., LTD, Indonesia) and kept at 25°C for 48 hrs. After equilibration, the excess drug was removed by centrifugation at 4000 rpm for 10 min, then diluting the supernatant with methanol for UV analysis[14, 15].

Table 1: Saturation solubility study of carvedilol in different oils:

Oils	Solubility (mg/ ml)
Olive oil	50.8 ± 1.8
Oleic acid	42.4 ± 2.1
Soybean oil	27.6 ± 2.4
Sesame oil	38.9 ± 2.7

2.2.3. Construction of ternary phase diagram

Pre-optimization studies involved the preparation of a ternary phase diagram to assess the self-emulsifying potential of various systems. According to the results of solubility studies, olive oil was chosen as the oil phase. According to previous studies, Tween 80 and propylene glycol (PG) were chosen as surfactant and co-solvent, respectively[16, 17].

Different concentrations of oil (10, 20, and 30%) were used to prepare several formulations. Surfactant and co-solvent were mixed in various weight ratios of 1:1, 2:1, 3:1, 4:1, 1:2, 1:3, and 1:4, respectively (Table2). About twenty-one formulations were made by placing the appropriate amount of each component in a glass container and vortexing the mixture till obtaining a transparent mixture. From each system, 0.2 ml was added to 100 ml of water in a beaker at 37 ^{o}C then a magnetic stir bar was used to mix the contents gently.

Both the tendency for spontaneous emulsification and the growth of emulsion droplets were monitored. The potential to produce an emulsion was considered "excellent" when oil droplets readily dispersed in water and produced a

clear or blue solution, and it was regarded as "bad" when a poor emulsion was formed due to the immediate coalescence of oil droplets, especially when stirring was ceased[18]. A ternary-Phase diagram was created by locating the good self-emulsifying zone using Tri plot v1- 4 software.

Table 2: Compositions and visual inspection of different Liquid-SEDDS formulations:

Formula	Components (mg)			Visual observation
	Oil	Tween 80	PG	
F1	100	450	450	Good
F2	100	600	300	Good
F3	100	675	225	Good
F4	100	720	180	Good
F5	100	300	600	Good
F6	100	225	675	Good
F7	100	180	720	Good
F8	200	400	400	Bad
F9	200	533.3	266.7	Bad
F10	200	600	200	Good
F11	200	640	160	Good
F12	200	266.7	533.3	Good
F13	200	200	600	Good
F14	200	160	640	Good
F15	300	350	350	Bad
F16	300	466.7	233.3	Bad
F17	300	525	175	Bad
F18	300	560	140	Good
F19	300	233.3	466.7	Good
F20	300	175	525	Good
F21	300	140	560	Good

2.2.4. Formulation of CRV Liquid- SEDDS

12.5 mg CRV /1 g of each formulation showed good visual inspection and was dissolved in PG in a water bath adjusted at 45ºC. Oil and surfactant were added after cooling and stirred on a vortex until obtaining a transparent solution. The preparations were kept at room temperature for 48 hours to monitor phase separation or turbidity[19].

2.2.5. Characterization of Liquid-SEDDS

2.2.5.1. Freeze Thawing (Accelerated aging)

This test was performed as accelerated stability testing of the prepared formulations. The preparations were freezed and thawed 3 to 4 times; each freeze and thaw cycle was as follows: freezing at – 4°C for 24 hours, then thawing at 40°C for 24 hours. At the end of all cycles, centrifugation at 3000 rpm for 5 minutes was conducted. After that, the formulations were visually inspected. Stable formulations that didn't show phase separation were chosen for additional investigations[21].

2.2.5.2. Determination of Emulsification Time and Precipitation Assessment:

The emulsification time of the stable Liquid-SEDDS formulations was evaluated in a USP dissolution apparatus (SP6-400, G.B. CALEVA Ltd., Dorset, England). Liquid-SEDDS formulation equivalent to 12.5 mg of CRV was introduced drop by drop to 0.5 liter of distilled water kept at a temperature of 37±0.5°C with mild stirring using a paddle rotating at 50 rpm. The emulsification time was carefully noted. After 24 hours, the resulting emulsion was visually inspected to assess the precipitation. Following that, the formulations were evaluated as either clear (transparent), non-clear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours)[21].

2.2.5.3. Determination of droplet Size and Zeta Potential

The emulsion droplet size plays a critical role in the effectiveness of SEDDS as it affects drug release rate and extent and consequently drug absorption, the emulsion droplets' average size and Zeta potential were measured by Zetasizer (Malvern Instruments, Malvern, UK). The dispersed formulations were diluted with distilled water (1:1000 v/v) and then measured.

2.2.6. Preparation of Solid-SEDDS

The best liquid-SEDDS formula was transformed into solid powder by adsorption onto a suitable carrier to prepare Solid-SEDDS. The used solid carriers were Fumed silica (A'sil 200), microcrystalline cellulose (Avicel PH101), or combination of both at different percentages. Briefly, the optimized liquid-SEDDS was added drop by drop on the carrier placed in a wide porcelain dish. The mixture was mixed using a glass rod after each addition till obtaining a damp mass was sieved through sieve no. 120, then exposed to ambient temperature to dry and stored until needed[22].

2.2.7. Characterization of Solid-SEDDS

2.2.7.1. Flow properties

The bulk and tapped densities were examined by placing 5gm of each S-SEDDS in 50 ml measuring cylinder; then, after recording the initial volume and calculating bulk density (d_{bulk}), The cylinder was tapped using Powder Tapped Density Tester (Campbell electronics, India) till a constant volume, which was also recorded and tapped density was calculated (dtap). Carr's compressibility index (CI) was determined for each sample using the following equation: CI =100 (d_{tap} - d_{bulk})/ d_{tap}. Additionally, the Hausner ratio (HR) was also determined using the following equation: HR= d_{tap}/ d_{bulk} .

Powders with a CI between 5% and 18% are suitable for producing tablets, and those with an HR value less than 1.25 are considered good flowability[17].

2.2.7.2. Solid State Characterization

Differential Scanning Calorimetry (DSC) is applied to investigate any drug excipients' physicochemical interaction. DSC analysis was carried out employing a Model DT-60 DSC (Shimadzu). Samples of pure drug, Avicel PH101, and optimized S-SEDDS formula (S-F4), each weighing 3-6 mg, were put in sealed aluminum pans and heated over 30°C–300°C temperature range at a rate of 10°C/min under a nitrogen stream.

2.2.7.3. X-ray Powder Diffraction (XRPD)

XRPD of the drug, Avicel PH101, and optimized S-SEDDS formula (S-F4) were examined using an X-ray diffractometer (Mnisantis XMD-300 Powder Diffractometer) employing a scanning rate of 8°/min over a 2θ range of 0–50.

2.2.8. In-vitro Release Studies

The in-vitro release of pure CRV, Liquid- and Solid-SEDDS were done in 900 ml distilled water kept at a temperature of 37 ± 0.5oC using USP Dissolution Tester Apparatus II[23] An amount equivalent to 12.5 mg of CRV for L- SEDDS and 6.25 mg for S-SEDDS formulation (due to the bulkiness of the powder form) were filled in hard gelatin capsules and put in the dissolution vessel rotated at 50 rpm. Samples of 5 ml were withdrawn at pre-determined time intervals for 60 min, membrane filter of 0.45 µm pore size was used to filter the samples, which measured spectrophotometrically for CRV. The taken samples were compensated with fresh medium to keep constant volume.

2.2.9. Statistical Analysis

All experiments were performed in triplicates, and ANOVA was employed for Statistical analysis. Results were considered significant, where $P< 0.05$.

3. RESULTS AND DISCUSSION

3.1. Saturation solubility study

It is important to avoid drug precipitation during the preparation of self-emulsifying systems. Therefore, The system's constituents should ensure effective drug solubilization. Results of saturated solubility studies are shown in (Table 1). The results clarified that olive oil had better solubilization for CRV and was used for the preparation of SEDDS.

3.2. Ternary phase diagram

A ternary phase diagram was used to specify the self-emulsifying zone and to determine the most suitable oil, surfactant, and co-solvent concentrations required to obtain a stable system (Figure 1). The phase diagram consists of oil, surfactant, and co-solvent at each angle of the diagram representing 100% concentration of each component. In our study, the diagram was constructed with oil, surfactant, and co-surfactants. The ratio of water to liquid SEDDS was (500:1).

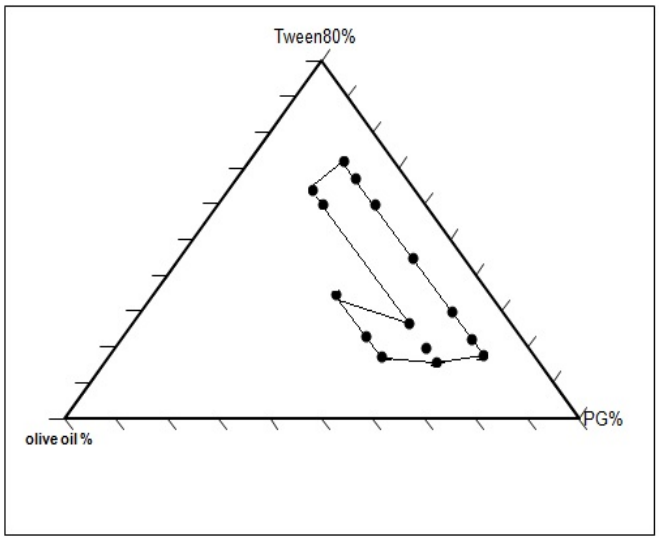


Figure 1: Ternary phase diagram of a mixture consisting of different ratios of olive oil, surfactant (Tween 80), and co-solvent (propylene glycol, PG).

The zone of self-emulsification is represented by the dotted area. All emulsions were stable at zero time; this may be explained by the larger HLB value of Tween 80 (HLB=14) and the higher PG solubilizing capacity, SEDDS produce fine o/w emulsions when added to aqueous media with only mild stirring. The introduction of larger ratios of co-solvent (1:3 and1:4 w/w surfactant: co-solvent, respectively) within the self-emulsifying zone helped the self-emulsification process to be more spontaneous. As reported, self-emulsification happens when the entropy changes that favor dispersion are higher than the energy needed to increase the dispersion's surface area[24]. Additionally, it was reported that co-surfactants fluidize the interfacial film's hydrocarbon area, lowering the film's bending stress and enabling the reduction of interfacial tension[25]. The better surfactant and co-surfactant adsorption at the oil/water interface hence increased the thermodynamic stability of the SEDDS and decreased the interfacial energy needed for preventing coalescence[26]. All formulations showed good emulsification, except formulations F8, F9, and F15-17 which were not further involved in the following studies.

3.3. Characterization of Liquid-SEDDS

3.3.1. Freeze Thawing (Accelerated aging)

Micro-emulsions are supposed to be thermodynamically stable systems with no signs of instability. Thus, the liquid formulations were put through a freeze-thaw cycle stress test. All formulations, except F21, were stable with no indication of phase separation.

3.3.2. Emulsification Time and Precipitation Assessment

For the evaluation of emulsification efficiency, the emulsification rate is a critical factor. The SEDDS should spread readily when introduced to aqueous solutions under gentle stirring. So, the emulsification time was determined, and the results are shown in (Table 3). There was a trend of decreasing self-emulsification time with decreasing Tween 80 concentration and subsequent increase in PG concentration.

It was stated that increasing the co-solvent concentration accelerated self-emulsification, whereas increasing the surfactant led to an increase in the time for efficient self-emulsification due to gel-like layer formation[27]. The presence of co-solvent augments the reduction in the interfacial tension at the O/W interface and also impacts the curvature of the interfacial film, which affects spontaneous emulsion formation[28]. Formulations that showed turbid dispersion or emulsification time of more than 2 minutes were excluded from this study[29]. As a result, formulas F1, F2, and F11 were excluded. The results of droplet size of different formulations are represented in (Table 3). It can be noted that as the oil concentration increases, the mean droplet size increases. Keeping surfactant:co-solvent ratio fixed at 1:3, the droplet size in F6 (10% w/w oil) was 420 nm while that of F20 (30% oil) was 775 nm. Increasing the amount of surfactant results in droplets with smaller mean sizes at the same oil content. As in the case of F4, with a surfactant: co-solvent ratio of 4:1 demonstrated the smallest particle size of 365 nm. This might be because the presence of a suitable surfactant concentration is required to stabilize the oil-water interface and improve the closed-pack film at the oil-water interface, which speeds up the droplet formation and subsequently reduces the droplet size[5].

Also, there is a trend to decrease the size of the droplets with increasing the co-solvent concentrations, fixing the oil concentration at 20%; the formula showed the lowest droplets size was F14 (288 nm) with surfactant: co-solvent ratio 1:4. Generally, the main effect on the particle size is expected to be that of the concentration of surfactant: co-surfactant mixture. Sometimes, increasing the surfactant-co-surfactant concentration could decrease droplet size; this might be explained by the oil droplets' stabilization by surfactant molecules that are adsorbed at the oil/water interface[30].

Table 3: Emulsification time, droplet size, zeta potential, % drug released after 5 (Q5) and 60 (Q60) minutes, and dissolution efficiency at 10 minutes (%DE10) of different self-emulsifying liquid formulations:

Formulation	Emulsification time (sec)	Mean droplet size (nm)	Zeta potential (mV)	Q5	Q60	%DE10
F3	20±1.3	440 ±9.9	-9.73 ±0.16	76±1.6	88.0±2.1	86.5
F4	17±0.5	356±2.6	-13.7 ±0.2	90±2.4	95.2±1.1	89.6
F5	20±1.1	404±5.6	-8.76 ±0.12	75±2.1	90.7±2.0	76.7
F6	20±0.9	420±4.9	-5.7 ±0.1	80±1.7	88.7±1.8	80.7
F7	29±1.3	459 ±5.5	-5.45±0.3	78±2.3	88.2±0.9	81.0
F10	34±1.7	477±1.07	-5.18 ±0.2	87±2.0	95.3±0.8	90.1
F12	17±1.5	471±3.6	-6.84±0.1	83±1.9	96.0±1.7	86.9
F13	23±0.6	380±5.6	-11.9±0.2	79±2.2	95.5±2.1	88.1
F14	27±0.8	288±11.6	-15.4±0.6	94±1.1	100±0.6	95.5
F18	32±1.3	423±4.4	-8.6 ±0.03	78±0.9	94.0±1.7	85.4
F19	75±3.2	823±3.2	-3.7±0.5	77±3.1	85.0±2.8	82.5
F20	99±2.7	775±6.2	-2.2 ± 0.4	73±2.5	78.7±2.3	73.5
Pure drug	NA	NA	NA	19±1.3	55±2.2	42.5

For zeta potential, all formulations had a slight negative zeta potential (Table 3). The zeta potential of the diluted SEDDS formulations F4 and F19 is much larger than that of the other formulations. This could be explained by the small droplet size, which has a greater surface area and higher charge density. Therefore, compared to other SEDDSs, After emulsification, these formulas would result in a more stable emulsion.

3.4. Drug Dissolution for Liquid-SEDDS

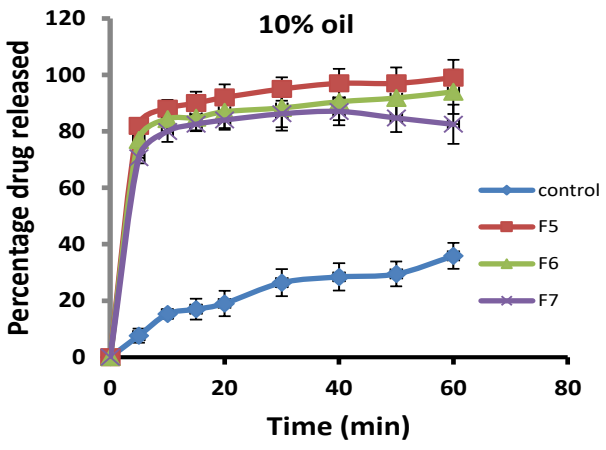
The drug dissolution from different formulations and pure CRV is illustrated as the % cumulative drug released versus time plots (Figure 2). The % drug released after 5 and 60

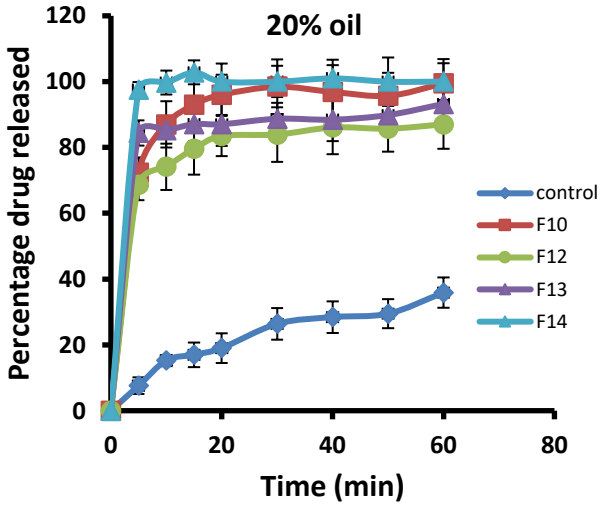
minutes (Q5 and Q60, respectively) were calculated and are presented in Table 3. Additionally, % of drug dissolution efficiency after 10 minutes (%DE10) was calculated. All liquid-SEDDS formulations improved drug dissolution significantly (P< 0.05) compared to the unprocessed drug, which is crystalline and dissolved slowly.

There was an increase in the initial drug release where Q5 ranged from 73 to 94% compared to only 19% of the unprocessed drug. %DE10 in the range of 6- to 10-folds, relative to the pure drug (Figure 2), indicating the marked improvement in the initial drug release. Though Q60 was about 2-to 3-folds higher than the control, the obtained rapid drug release would assume higher bioavailability, which supports the potential use of SEDDS. Formulations containing 30% oil (F19 and F20) showed the least enhancement. The drug release patterns for formulations prepared with 10% and 20% oil were comparable (P> 0.05), but they displayed a significant improvement (P< 0.05) in comparison to those prepared with 30% oil.

This might be attributed to the higher percentage of surfactant and co-solvents in the former systems and the high oil content in the latter. Additionally, there was a tendency for improved dissolution parameters from formulations containing a high ratio of PG compared to Tween 80. The presence of such hydrophilic surfactant (HLB=14) and effective solubilizing agent like PG resulted in the formation of small globules with a large surface area that permits fast diffusion of the drug into the aqueous dissolution medium.

Among all tested formulations, formula F14 showed the highest initial drug release of about 94% after 5 minutes with %DE10 of 95%. For poorly water-soluble drugs, especially those that suffer from first-pass metabolism, such a fast-release pattern is favorable. This could be explained by the high concentration of PG as the surfactant: the co-solvent ratio was 1:4. The surfactant concentration in F14 was only 16% which indicates the role of PG in improving the thermodynamic stability of the formed droplets. Moreover, the relatively smaller droplet size with higher surface charge could be considered a contributing factor to the superiority of F14 over other formulations. An additional advantage of F14 is its high oil concentration of 20%, with its known effect of increasing the amount of drug transport through the lymphatic system followed by absorption from GIT[31]. Therefore, F14 was considered the best formula and was selected to prepare the solid formulations.





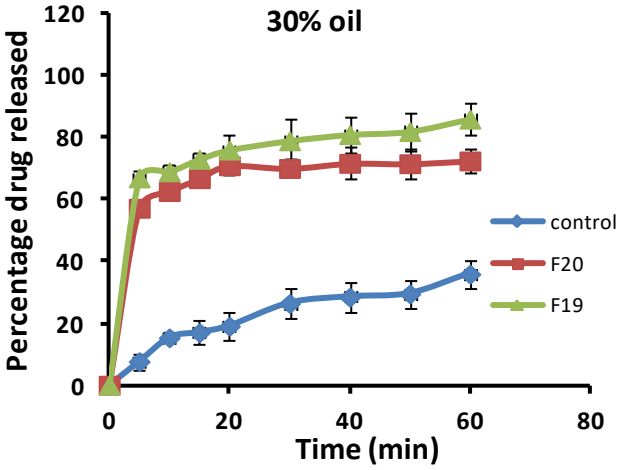


Figure 2: Dissolution profiles of carvedilol from its unprocessed form and different liquid-SEDDS formulations.

3.4. Solid formulation of Liquid-SEDDS (S-SEDDS)

Solid- SEDDS is mainly liquid-SEDDS transformed into solid by many methods such as spray drying, adsorption on a solid carrier, or freeze drying technique[32, 33]. S-SNEDDS improve drug stability, scalability, handling, and transportation. Therefore, the best L-SEDDS formula (F14) was converted to solid form using the solid carrier adsorption technique. Microcrystalline cellulose (Avicel PH101) and Fumed Silica and their mixture were used as a carrier at the different liquid-to-powder ratios (Table 4). The former was selected due to its porous particles and high absorption characteristics[34], and the latter for its large surface area[4]. Up to a 3:1 Liquid to powder, the ratio was feasible for fumed silica, while for Avicel, only a 1:1 ratio was prepared as a higher amount of liquid formulation resulted in the formation of paste.

Meanwhile, a lesser ratio was not practical due to the bulkiness of the formula.

3.5.1. Flow properties

The S-SEDDS will be formulated into either capsule or tablet. The manufacture of tablets and capsules requires the powder mix to have adequate flow to create a product with uniform dosing. Consequently, it was essential to investigate the flow characteristics of each S-SEDDS mixture. Powder flowability results are shown in (Table 4).

For Fumed silica, pure powder showed a passable flow. The addition of L-SEDDS at different liquid: carrier ratios inversely affects powder flow with high Carr's index and Hausnar ratio values (Table 4). The obtained poor flow will limit the suitability of such formulations for large-scale production. The reasons for a such bad flow could be due to

Table 4: Compositions of solid-SEDDS formulations (SF) and their flow behavior:

Formula	SEDDS: Carrier Ratio	Type of Carrier	Carr's index	Hausner ratio	Flow Carr's index	Flow Huasner ratio
Avicel (AV)	-	-	14.8±1.3	1.17±0.12	Good	Good
Fumed silica (FS)	-	-	20.9 ±1.8	1.26±o.22	passable	passable
SF1	1:1	FS	30.7 ±2.4	1.43±0.09	Poor	poor
SF2	1.5:1	FS	29.8 ±1.8	1.43±0.11	Poor	poor
SF3	2:1	FS	35.2 ±0.97	1.6±0.14	Poor	poor
SF4	1:1	Avicel	15.6 ±2.3	1.13±0.31	Good	Good
SF5	1:1	Avicel:FS 95:5	21.7 ±3.6	1.28±0.22	Fair	passable
SF6	1:1	Avicel:FS 90:10	20.9 ±1.8	1.26 ±0.20	Passable	Fair
SF7	1:1	Avicel:FS 85:15	21.9 ±1.9	1.29±0.24	passable	Fair

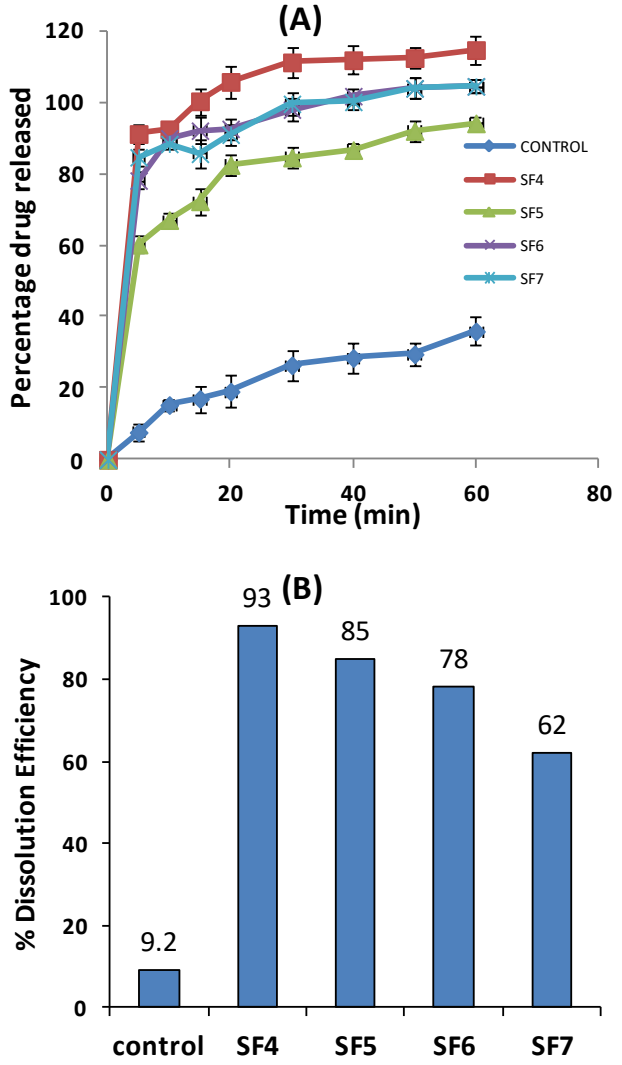
liquid on the surface of powder particles producing a slightly damped powder, with the possible formation of liquid bridges between particles that might hinder powder flowability.

Concerning Avicel PH101, pure powder showed good flow. The addition of L-SEDDS did not significantly affect powder flowability. This could be due to its high absorption property, producing a less damped powder mix[34]. The incorporation of fumed silica into Avicel reduced particle flow. However, it showed passable or fair flow characteristics that can be enhanced by adding a suitable glidant. Therefore, formulations SF4 through SF7 prepared using Avicel alone or in combination with silica were investigated for drug release behavior.

3.5.2. In-vitro dissolution results

Only formulations prepared using Avicel PH101 as a carrier were investigated for their dissolution behavior due to their good flow characteristics. Dissolution profiles and %DE10 are illustrated in Figure 3 A and B, respectively. All S-SEDDS improved drug dissolution ($P< 0.05$) compared to pure drug. The initial drug release after 5 minutes was about 91±2.6±, 82±3.7, 77 ±3.1, and 60±4.2% from SF4, SF5, SF6, and SF7, respectively. For %DE10, SF4 showed the highest value of 93% compared to only 9% for unprocessed drug (Figure 3B). Though there was no significant difference between different S-SEDDS ($P> 0.05$), there was a noticeable trend of reduced initial drug dissolution with increased fumed silica concentration. This might be attributed to the fact that fumed silica, with its large surface area and high adsorption properties, may be adsorbed on the surface of Avicel particles,

forming a coat[2]. For the drug to go into the solution, it should diffuse through this coating layer, which would delay drug dissolution. Increasing fumed silica concentration is expected



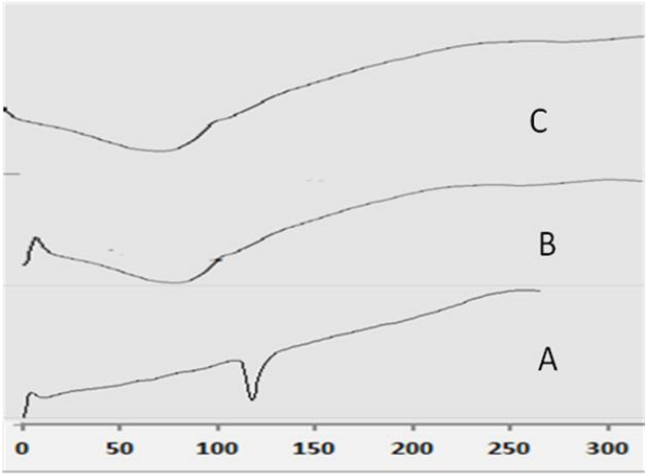
to increase the number of adsorbed layers producing multilayer coating over each Avicel particle. This would increase the pass length through which the drug should diffuse to reach the dissolution medium.

Figure 3: Dissolution profiles (A) and percentage dissolution efficiency after 10 minutes (B) of carvedilol from different Solid-SEDDS formulations and unprocessed form.

The dissolution parameters indicated the superiority of SF4 in enhancing drug dissolution and providing a potential for improved bioavailability. Comparing SF4 with the liquid formulation F14, there was no significant difference regarding drug dissolution parameters. This would signify the use of the S-SEDDS as it maintains the same benefits as the liquid formulations regarding drug dissolution, with the added advantages of the solid formulation.

3.5.3. Solid state characterization

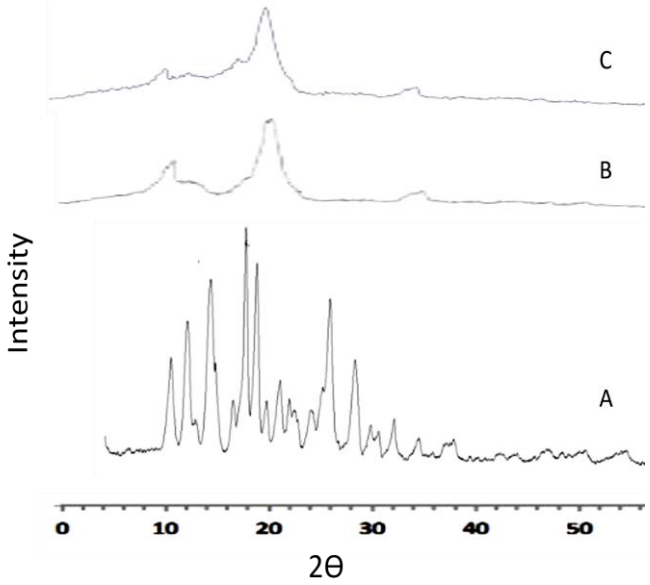
The DSC thermograms of unprocessed CRV, Avicel PH101, and S-SEDDS formula SF4 are illustrated in Figure 4. The thermogram demonstrates a sharp distinctive endothermic peak at 115°C, which corresponds to the melting point of CRV; such a sharp endothermic peak indicates that CRV used was in the crystalline state[35, 36]. The thermograms for Avicel



PH 101 showed a broad endothermic peak at 88°C as a result of the volatilization of adsorbed water and charring of the cellulosic material[37]. For the solid SEDDS formula SF4 there was an entire disappearance of the drug peak, and only a peak for the carrier can be seen; this would indicate the full transformation of the drug into an amorphous state.

Figure 4: Differential Scanning Calorimetry of Carvedilol (A), Avicel PH101 (B), and solid-SEDDS formula SF14 (C).

The XRPD patterns of the pure drug, Avicel PH101, and optimized solid formula SF4 are shown in Figure 5. Avicel PH101 has a characteristic diffraction angle of 2θ at about



22.0° [37]. For CRV, various diffraction peaks were observed at 2 θ of 12.8°, 15.62°, 17.46°, 18.56°, 20.1°, 24.3°, and 26.2°

demonstrating the crystalline nature of CRV and being in good accordance with published data[35]. For SF4, there was a complete vanishing of the drug's characteristic peaks, with the existence of the peak corresponding to the carrier.

Figure 5: X-ray powder diffractograms of carvedilol (A), Avicel PH101 (B), and solid-SEDDS formula SF14 (C).

4. CONCLUSION

In the current work, it can be concluded that the prepared SEDDS formulations showed good emulsification and improved Carvedilol dissolution. Additionally, the formation of solid-SEDDS of CRV can be obtained by employing an adsorption technique using Avicel PH101 as a solid carrier with good flow properties. The present study thus provided a promising potential for enhancing the bioavailability of carvedilol by improving the dissolution rate, reducing intestinal efflux, and bypassing hepatic first-pass metabolism.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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