Application of dumping and transfer methods to study *in vitro* dissolution behavior and precipitate of the poor water soluble weak base drug: Carvedilol case

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Article Info:

Received Feb 2024
Revised May 2024
Accepted June 2024
Published May 2025
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DOI: https://doi.org/10.32947/ajps.v25i2.1163

Abstract:

This work intended to evaluate the dissolution of poor water soluble weakly basic drug like carvedilol (Carv) via two methods used to study and assess the effect of pH changes from the stomach to the small intestine on the drug dissolution and precipitation (ppt): dumping and transfer.

Three approaches were used to increase solubility and decrease the precipitation of carvedilol; first, the acid modification principle was by incorporating Carv with fumaric acids (FA) to keep the drug at a low pH in the intestine. The second approach was solvent evaporation, which converted the drug from a low soluble crystalline form to a highly soluble amorphous form, and the last approach was forming a slow-release floating dosage form. The prepared samples were investigated by FESEM and FTIR. There is a slight shift in the peaks related to the hydroxyl group in approaches (acid modification and solvent evaporation) compared to the peak's position in the Carv spectrograms, and the FESEM shows a decrease in particle sizes of prepared samples. The Carv prepared samples *in vitro* dissolution of dumping, and the transfer showed different *in vitro* dissolution profiles with enhanced dissolution profiles and lower ppt amount. The amorphization technique's ppt was highly decreased in both dissolution dumping and transfer methods compared to the *in vitro* dissolution of the control of Carv.

Keywords: Carvedilol, transfer method, dumping method, poor water soluble weak base drug, precipitate

تطبيق طرق الإغراق والنقل لدراسة سلوك الذوبان وترسيب الدواء القاعدي الضعيف القليل الذوبان في الماء في المختبر: حالة كارفيديلول

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خلاصة

يهدف هذا العمل إلى تقييم ذوبان القاعدة الضعيفة القليلة الذوبان في الماء لدواء كارفديلول عبر طريقتين تستخدمان لدراسة وتقييم تأثير تغيرات الاس الهيدروجيني (pH)من المعدة إلى الأمعاء الدقيقة على ذوبان الدواء والترسيب: الإغراق والنقل. تم تطبيق ثلاثة أساليب لزيادة الذوبان وتقليل ترسب دواء كارفديلول؛ أولاً، كان مبدأ تعديل الحامض من خلال دمج كارفديلول مع حامض الفوماريك للحفاظ على الدواء عند درجة حموضة منخفضة في الأمعاء. كان النهج الثاني هو التبخر بالمذيبات، والذي يحول الدواء من شكل بلوري منخفض الذوبان إلى شكل غير متبلور عالي الذوبان، وكان النهج الأخير هو تشكيل شكل جرعة عائمة بطيئة الإطلاق. تم فحص العينات المحضرة بواسطة FESEM وFTIR. هناك تحول طفيف في القمم المتعلقة بمجموعة الهيدروكسيل في طريقتي (تعديل الحامض وتبخر المذيبات) مقارنة بموضع الذروة في مخططات كارفديلول الطيفية، ويظهر

FESEM انخفاضًا في أحجام الجسيمات او الذرات للعينات المحضرة. تم اعداد عينات من كارفديلول في إذابة الإغراق في المختبر، والنقل أشكالًا مختلفة في الذوبان في المختبر مع زيادة في ذوبان الكارفديلول وقلة في ترسب الدواء. كمية الكارفديلول المترسبة من عملية التبخر بالمذيبات جدا قليلة في طريقتي الاغراق والنقل مقارنة مع التحلل المختبري لدواء الكارفدلول لوحده.

الكلمات المفتاحية: كارفديلول، طريقة النقل، طريقة الإغراق، دواء قليل الذوبان في الماء لقاعدة ضعيفة، راسب

Introduction

A poor-water weakly base (PWWB) drug solubility is frequently pH-dependent since acidic pH media ionizes and improve water solubility. Hence, with the rise in pH, the PWWB becomes deprotonated and un-ionized, and its solubility falls. As a result, a basic drug in solid dosage forms may dissolve fully in the stomach, but due to a significant pH increase in the intestine, the drug may precipitate (ppt) (1, 2). Tremendous applicable methods increase the PWWB solubility; herein, the focus first by acidic modification through incorporating acidic excipients such as organic acids into formulations, which is a popular strategy for enhancing the solubility of a PWWB (3). The acids aid in limiting the dramatic pH change of the stomach to the intestinal media, allowing the drug to remain soluble (4-6). The second approach is amorphization using the solvent evaporation technique, which assists crystalline material converting into an amorphous state (7). The last one is the gastroretentive approach by the floating system. This system incorporates the medicine in a slow-release buoyant dosage form that persists in the stomach for several hours, letting the transfer of PWWB slowly to the intestinal media, decreasing the drug ppt (8). In this study, the formulation's dissolution behavior is essential to examine, two methods were applied; first, the dumping method, which is a soluble PWWB in the acidic buffer to be poured directly into intestinal media, whereas, the transfer method takes into consideration both the stomach and intestinal compartments, mimics the *in vivo* condition, in which the drug and the formulation were exposed to a continually changing environment during transit in the gastrointestinal system (9, 10). The proposed methods tested Carvedilol (Carv), a class II weak base drug, a highly effective β-adrenoceptor blocker for treating cardiovascular disorders (6, 11)**.** The purpose of this study was to evaluate the dissolution and precipitation of Carv, using dumping and the transfer multicompartment system for the 3 approaches that were selected to enhance PWWB solubility.

Materials and Methods

Materials

Carv was bought from Shanghai D&B Biological Science and Technology Co.Ltd /China, while fumaric acid was purchased from Triveni Interchem Pvt.Ltd /India). Also, Sodium Alginate and calcium carbonate were purchased from Meron Group /India and CALSPAR /India, respectively.

Methods

Sample preparation

The samples in this study were prepared according to each selected approach, as shown below, to be utilized in different dissolution methods.

Approach I using the acid modification

The procedure was by taking equivalent portions of the drug and fumaric acid (FA), 25 mg of each Carv and (FA), followed by mixing the combinations (3). After that, these complexes were dissolved in 100 ml of 0.1 N HCl pH 1.2 with stirring and controlled heating at 37℃ in the case of the dumping method or the complexes dissolved in 250 ml of HCl in the case of the transfer method.

Approach II using amorphization technique (Solvent evaporation)

Carv was put in a suitable container, and about 3-5 ml of methanol was added and shaken for a few minutes until the drug dissolved, followed by a methanol evaporation step then, weighing 25 mg Carv from the remaining powder to be used in the dissolution methods (12, 13). This was to be followed by dissolving the Carv in 100 ml of 0.1 N HCl pH 1.2 with stirring and controlled heating at 37 ºC in the dumping method, while in the transfer method, the Carv was solubilized in 250 ml of HCl pH 1.2 media.

Approach III using gastroretentive system (Floating system)

Boiling water of 10 ml was gradually added to 200 mg sodium alginate with continuous stirring and heating at 37 ℃. After that, the solution was left for cooling and incorporated with 25 mg of Carv by persistence heating at 37 ℃ and stirring at 100 rpm, waiting for 15 min. 100 mg of calcium carbonate was added to the mixture by stirring until a homogenous dispersion (in situ gel) (14).

Characterization of samples

Fourier transform infrared spectroscopy (FTIR)

A Carv powder sample was mixed with potassium bromide and pressed into the disc. The KBr discs were made by crushing the powders in a hydraulic press. The scanning range was from 400 to 4000 cm^{-1}. The disc was analyzed by Shimatzu FTIR spectroscopy (13, 15).

Field emission scanning electron microscopy (FESEM)

Selected prepared samples were subjected to be investigated for surface morphology using FESEM to capture an image of the sample surface that was already polished with argon ion beams in a highly vacuumed atmosphere (16) .

***In vitro* dissolution methods for evaluation of Carv behaviour in gastric media**

All the dissolution methods in this work exclude using surfactants in the buffer media that ensure the Carv sink condition to investigate the effect of the dissolution method technique and the selected approach. In addition, the intestinal media pH 7.2 that was used in this work was prepared by mixing equal volumes of HCl solution pH 1.2 and phosphate buffer pH 8.4.

Direct addition of 25 mg to 100 ml of HCl (pH 1.2) with continuous stirring at 100 rpm and temperature 37 ºC by dissolution apparatus; then, the sampling was according to the time frame (5, 10, 15, 20, 30, 45 and 60) min and the 5 ml volume of samples was replaced continuously to be read by UV spectrophotometer by substitution the absorbance values in the calibration curve equation (y= 0.0266x+0.0187) with R^2 equals 0.966 that was constructed from several Carv concentrations in the HCl pH 1.2 buffer versus absorbances (17). This dissolution method was done in triplicate.

***In vitro* dissolution of Carv in intestinal media**

The 25 mg of Carv was directly added to 900 ml of intestinal media pH 7.2 that was prepared by mixing 450 ml HCl solution pH 1.2 and 450 ml of phosphate buffer pH 8.4 with continuous stirring at 50 rpm and temperature 37 ℃ using dissolution apparatus and after that sampling was at (5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180 and 240) min and the 5 ml sample was taken to be replaced with equal volumes continuously and then samples were read by UV spectrophotometer depending on the equation (y= 0.0198x+ 0.0051 with R^2 = 0.9977) of the calibration curve that was built by many prepared dilutions of Carv in intestinal media pH 7.2 (18). The Carv dissolution in intestinal media was repeated 3 times. Then, the 900 ml was filtered using

Whitman filter paper to collect the ppt that was subjected to be dissolved in a measured suitable volume of HCl solution to be analyzed by UV spectrophotometer.

Dumping method

The dumping dissolution method was applied for the Carv for the approaches, the acid modification, and the amorphization by solvent evaporation. This method, as seen in Figure 1(A), started by taking out 100 ml of HCl solution pH 1.2, which represented a portion of the total intestinal buffer media, to dissolve the 25 mg Carv and pouring it directly into the 800 ml of intestinal media pH 7.2 that was composed of 350 ml HCl solution and 450 ml phosphate buffer in a suitable container, with a controlled temperature at 37 ºC by hot plate with a continuous stirring at 50 rpm. The sampling was according to a time frame of (5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180 and 240) min, and 5 ml samples were taken to be continuously replaced with equal volumes as this dissolution method was applied in triplicate (19). Then, these samples were read by UV to convert them as concentrations using the calibration equation that was built in phosphate buffer pH 7.2. This was to be followed by the final dissolution media filtrated using Whatman filter paper no. 0.45 µm to collect the drug's precipitate and dissolve it in an HCl solution to be quantified using the calibration curve of Carv in the acidic media.

Transfer method

The selected approaches to apply the transfer method for Carv were acid modification and amorphization by solvent evaporation. This method was accomplished using a peristaltic pump figure 1(B), which transferred fluid to compartments by tubes, as clarified in figure 1(C). The pump was equipped with three tubes controlling the fluid speed through the tubes at 5 ml /min, as the first tube ensured the transfer of the gastric media to the intestinal media. At the same time, the second one assisted in moving the fluids from the intestine to the sink/supersaturation compartment. The last one transferred the fluid from the reservoir to the intestine compartment. The gastric compartment contained 25 mg Carv dissolved in 250 ml HCl solution pH 1.2 with a rotating speed of 100 rpm to mimic the fasting stomach environment. Also, the intestinal compartment was filled with 250 ml of intestinal media with a pH of 7.2 (20). The third compartment, the sink/supersaturation compartment, started empty, as the filter paper was placed at the tip of the tube that transferred the fluid from the second compartment into the third jar to ensure the removal of undissolved drug from the intestinal compartment to the sink/supersaturation compartment, this compartment was under rotating speed 50 rpm. The fourth compartment, the reservoir, containing at first 50 min of experiment 250 ml of phosphate buffer pH 8.4, then replaced by another media that contained intestinal media pH 7.2, which was kept in water bath at 37 °C; as this part of the dissolution experiment started the transfer from the reservoir to the intestinal compartment, after the first 50 minutes of completed stomach media transfer (20). This method was repeated three times.

The samples were withdrawn from the sink/supersaturation compartment according to the timetable at (5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180, and 240) min and read by UV spectrophotometer according to the equation of the calibration curve that constructed by several dilutions of Crav in pH 7.2. The filtration of intestinal media was continuous alongside the dissolution process to collect and solubilize the ppt in HCl pH 1.2 to determine the exact amount of precipitated drugs (20).

Modified transfer method (Floating approach)

This is a modified transfer method to apply the floating approach as it was adapted from a previous study that used the multicompartment with a minor modification by adding the peristaltic pump (21); as shown in Figure 1(D) this method consisted of a gastric compartment containing 70 ml HCl pH 1.2 and an intestinal compartment filled with 400 ml pH 7.2. In addition, two reservoirs were completed with HCl pH 1.2 and intestinal phosphate buffer pH 8.4 and both of container kept in water bath at 37°C to ensure the continuous supply of the stomach and intestinal media to the gastric and intestinal compartments. The sink or supersaturation compartment started empty, and once the peristaltic pump was turned on, the fluid transferred from the gastric reservoir to the gastric compartment and the same for the intestinal compartment from the intestinal reservoir and from gastric compartment to the intestinal compartment at a rate of 2 ml/min. Concurrently, the transfer from the intestinal compartment to the sink or supersaturation compartment was controlled with a filter membrane at a flow rate (4 ml/min). The sampling from the sink/supersaturation compartment was at (5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180 and 240) min and read by UV spectrophotometer. Also, the intestinal media was filtered to collect the ppt, and the content was analyzed by a UV spectrophotometer (21).

Statistical analysis

All dissolution profiles and the ppt for all prepared formulations were statistically examined via Prism software utilizing ANOVA-one way with post hoc.

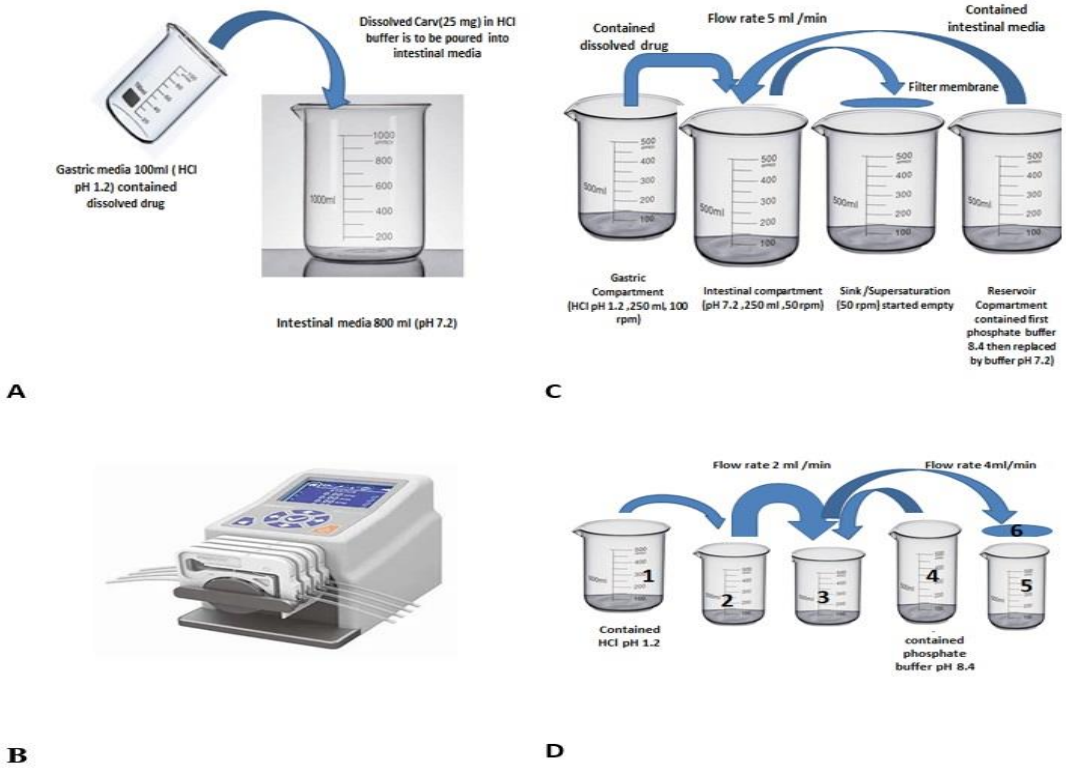

Figure (1): (A) Diagram depicts the dumping method (B) Peristaltic pump (3 tubes were used in the transfer method, while the 4 tubes were arranged in the floating release method) (C) The diagram depicts the transfer system showing the all compartments and the media

volumes (D) Modified transfer method of multicompartment dissolution apparatus as 1- gastric Reservoir 2- gastric compartment 3- intestinal Compartment 4-intestinal reservoir 5- sink/supersaturation compartment 6- filter paper.

Results and Discussion

Characterization of the prepared samples

Fourier Transform Infrared Spectroscopy (FTIR)

This study was applied to observe the peaks shifting in the Carv formulations and Carv spectrograms in the approaches used, as seen in Figure 2. The Carv prominent characteristic peaks are 2923.4 cm^{-1}, 1594.1cm^{-1}, 3060.2 cm^{-1}, 3344.9 cm^{-1}, 752.0 cm^{-1}, 1100.1cm^{-1} and 1217.6 cm^{-1} which are related to the chemical groups (C-H ,C=C ,-C-H- ,OH ,=C-H ,C-O-C and C-N) respectively (22). There is a slight shift in the peaks related to the hydroxyl group in both approaches (acid modification and solvent evaporation) to 3346 cm^{-1} and 3349 cm^{-1} compared to the peak's position in the Carv spectrograms 3353 cm^{-1}. As this shift indicated, the hydrogen bondings between Carv and FA (23-25). could be due to the solvent evaporation of the Carv with the methanol.

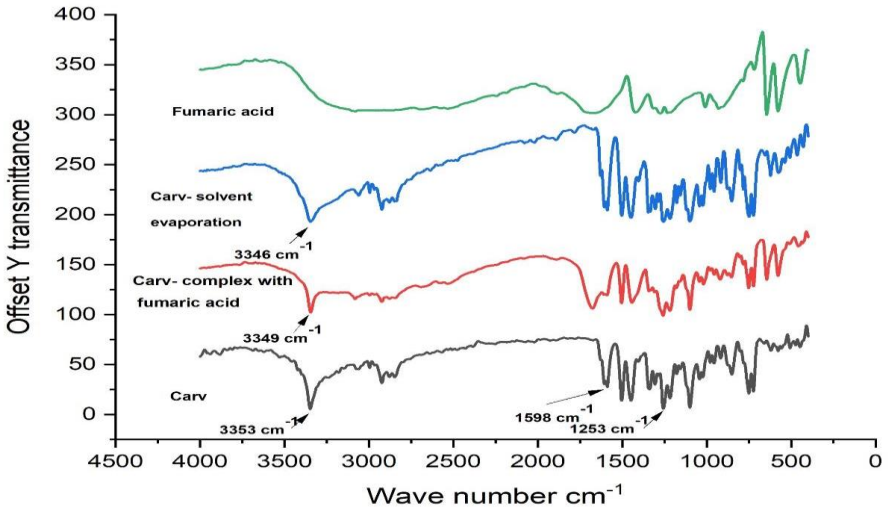

Figure (2): FTIR spectrograms of the Carv, Carv-FA complex, Carv solvent evaporation and FA

Field emission scanning electron microscopy (FESEM)

This technique was used to determine drug particle size and morphology. The images in figure 3 presented before and after sample preparation in both approaches revealed a decrease in particle sizes. This decrease might assist in changing or enhancing the dissolution of Carv due to the increased exposed surface area to the dissolution. Further, the complex of Carv with FA after trituration also presented a particle size reduction that might be for both Carv and FA, as this also helped to enhance the process of changing the surrounding Carv environments. The same was found by Thenge *et al* (22).

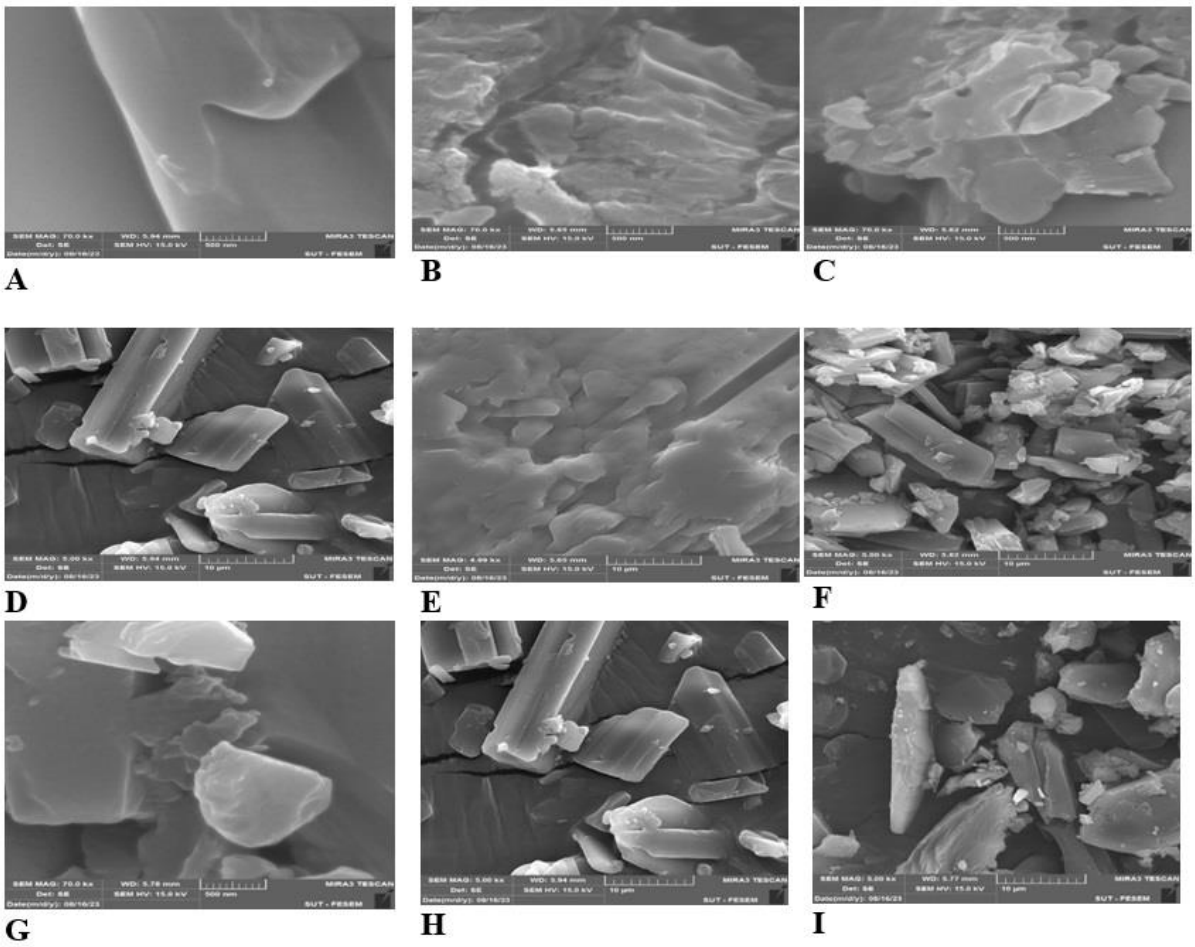

Figure (3): FESEM images A, B, and C were scaled against 500 nm, as A and B represent the Carv and FA before mixing, while image C represents the Carv complex with FA after mixing. Images D, E and F were scaled against 10µm, as D and E identify the Carv and FA before mixing, and image F identify the Carv complex with FA after mixing. Images G identifies Carv before applying solvent evaporation, while H and I represent the after-solvent evaporation with different scales against 500 nm and 10 µm, respectively.

In vitro dissolution of Carv in gastric and intestinal media

This dissolution application was to determine the behaviour of Carv in these media in isolation, as shown in figure 4; in gastric media, a rapid dissolution was about 99.79 % in 10 min as a maximum dissolution. This result agrees with a different study that showed Carv of 95.8–98.2% dissolution but within 60 min in 100 ml simulated gastric media as no precipitation occurred because Carv was highly soluble in the low pH of the gastric environment. In the same study, the dissolution of Carv in intestinal media presented very low dissolution. As presented in Table 1, it reached about 79.31 % after 1

hr and approximated 97.37 % after 4 hrs. The precipitated amount in this method was 3.19 %, while Hamed *et al* studied Carv *in vitro* dissolution in simulated intestinal media and found Carv dissolution started at 15.9 % and ended after 4 hrs at 86.2% (1). It was discovered that the buffer types, i.e. the pH of the dissolving fluid, affected the Carv dissolution.

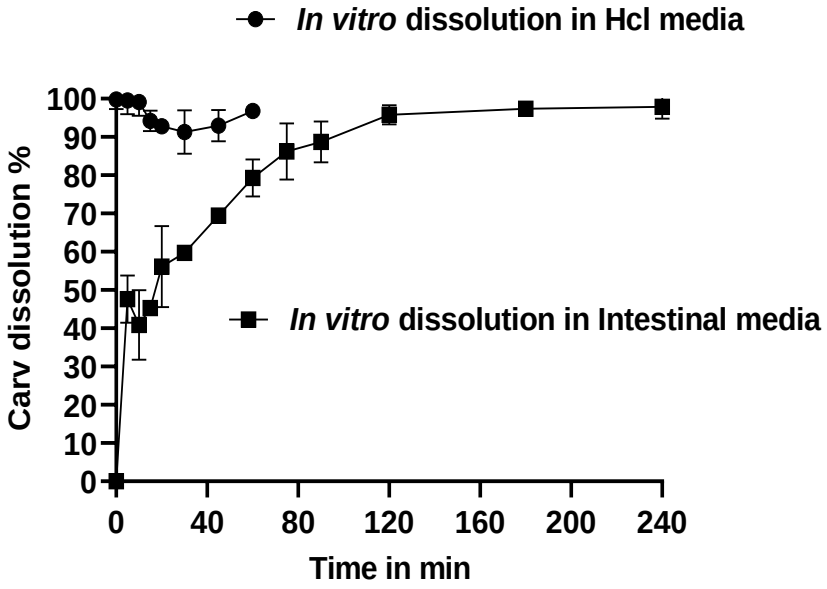

Figure (4): *In vitro* dissolution of Carv in gastric and intestinal media

Dumping and transfer method of Carv alone

As a control, this experiment was applied in order to study and evaluate the effect of the dissolution method single-handedly of the approach's impact on the dissolution and precipitation of the drug; the dumping and the transfer methods were presented in Figure 5(A). It is clear that the dumping method showed rapid Carv dissolution, as seen in Table 1, as after 1 hr of the dissolution study, the Crav dissolved and reached 94.16%, then Carv escalated to 98.34 % after 3 hrs, keeping this high average of Carv till the end of the study. The transfer method presented a Carv gradual increase from 39.94%, 74.53%, 90.83% and 96.78% after 1hr, 2hr, 3hr and 4 hr, respectively, as these increased values demonstrated and simulated the usual physiology attitude of the gastric and intestine fluid transfer. The ppt, as presented in Table 2, in the dumping method was 3.16%, which appeared rapidly at the first minutes of the dissolution, while the ppt from the transfer method was less and emerged gradually, around 1.27%. The Carv was evaluated by Hamed study in many dissolution media using the dumping and transfer methods, and their results disagreed with ours as they found the Carv dissolution after 2 hrs via dumping was 37.9 % in phosphate buffer pH 7.2. The acetate buffer in the Hamed study via transfer method presented an equivalent dissolved Carv amount to our result, 94.5%, while in the phosphate buffer, it was 90.3% (17).

Dumping and transfer methods for Approach 1 (Acid modifier)

This approach was found to increase the solubility and decrease ppt by adding an acid to be complexed with the base, such as verapamil, when complexed with the FA (26), led to an increase in verapamil

dissolution from 50 mg/ml to 100 mg/ml because of the acid keeping the drug formulation in the intestine at pH low; therefore the drug remains soluble (27).The dumping and the transfer were executed to the Carv- FA complex and the result is shown in Figure 5(B). The Carv dissolution in the dumping method was rapid, achieving 95.07 % after 1 hr (Table 1) and keeping a persistence value after 2 and 3 hrs at 95.13% and 95.98%, respectively. In comparison, the transfer method showed a gradual increase in the Carv dissolution at 42.6%, 80.47%, 92.1% and 98.23% after 1hr, 2hr, 3 hr and 4 hr, respectively. The ppt, as presented in Table 2, was lower in dumping method compared with the ppt from the transfer, as this approach of complexing Carv with the acid did not decrease the ppt amount compared with the ppt that came out from the control of Carv dissolution of the transfer method but it did in dumping method; however, the difference in ppt amongst the controls and the Carv-FA belonged to both dissolution methods were very significant ($p < 0.01$). The enhancement in the dissolution of the Carv-FA complex in the transfer method was observed, while this was not evident in the dumping method. Interestingly, Lim co-workers studied the *in vitro* dissolution of the Carv as a pure powder in gastric pH 1.2 directly and dissimilar to our results, as after 2 hr, the Carv dissolution was close to 40 % and found a dramatic increase close to 100 % after complexing Carv with the FA dissolution in acidic media (28).

Dumping and transfer methods for Approach 2 amorphization by solvent evaporation

The addition of methanol, the best solvent to solubilize Carv to convert less soluble crystalline form to more soluble amorphous form by using solvent evaporation technique (13, 29, 30) as its dissolution in both methods showed the same behavior and shown in figure 5(C); the ppt was the lowest in both dissolution methods and was very significantly different ($p < 0.01$) as illustrated in Table 2 compared with the ppt in other applied approaches. This approach was used in different works. However, the Carv dissolution was as usual in acidic media, revealing a 35-fold increase in Carv solubility after being combined with a PVP polymer and evaporating with methanol (13). Despite the low ppt Carv amount, the Carv dissolution in this approach in the dumping and the transfer methods was not enhanced in the first 3 hrs, as observed in Table 1, compared with the control of Carv in both dissolution methods but showed the same dissolved amount in the last 4 hrs.

Modified transfer of Approach 3 (Floating system)

This approach was investigated by transfer method only, as shown in Figure 5(D), as it is impractical and contraindicated with the gastroretentive system that the dosage form (*in situ* gel) needs to be retained in the stomach.

The release of Carv at the first hr was low, about 36.4 %, and reached, as exhibited in Table 1, the maximum release of 98.69% after 4 hrs, similar to the *in vitro* dissolution of Carv as a control. However, the ppt amount was close to the control of Carv, which indicates that this approach did not help decrease the amount of ppt. This result was not similar to the result of cinnarizine as a weak base model drug that showed the conventional tablet was dissolved entirely in gastric media, and about 50% of cinnarizine was ppt in intestinal media, while floating cinnarizine tablet showed complete release within 24 hr and non-ppt observed in the intestinal media (21).

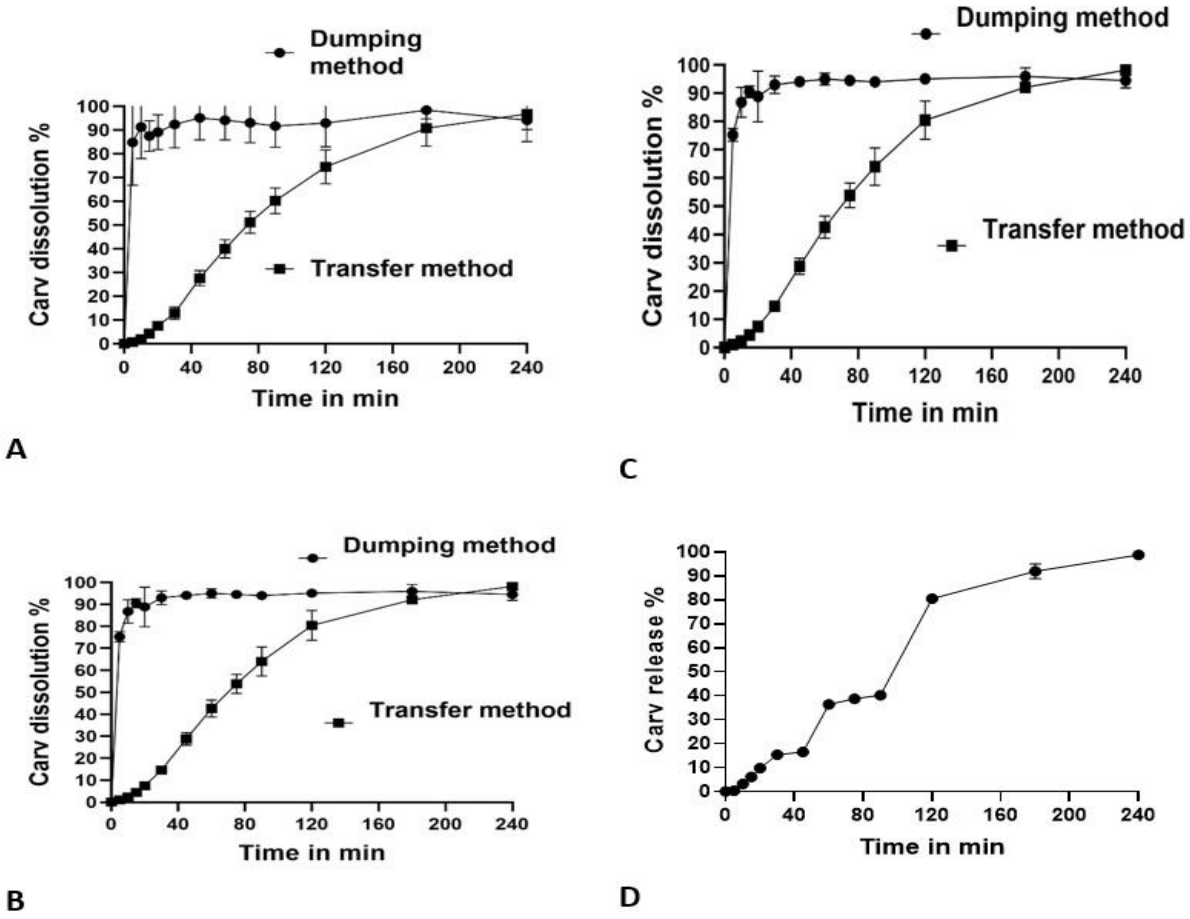

Figure (5): (A)The *in vitro* dissolution of Carv alone using the dumping and the transfer methods for 240 min (B) The *in vitro* dissolution of the Carv-FA complex using dumping and transfer methods for 240 min(C) The *in vitro* dissolution of dumping and transfer method of Carv by amorphization using solvent evaporation. (D) Carv *in vitro* release by the modified transfer method using the floating system for 240 min.

Table 1 shows there was an enhanced dissolution of Carv in both methods in all approaches; however, statistically, all *in vitro* dissolution of dumping and transfer in the three selected approaches were compared with the *in vitro* dissolution of dumping and transfer of Carv as a control were non-significant ($p > 0.05$).

Table (1): Summary of *in vitro* dissolution percentage of Carv in dumping and transfer method after 1hr, 2 hr, 3hr and 4 hr.

Method	Release % (1 hr)(±SD)	Release % (2 hr)(±SD)	Release % (3hr)(±SD)	Release % (4 hr)(±SD)
In vitro dissolution of Carv (intestinal media)	79.31(±4.83)	95.8(±2.49)	97.37(±1.94)	97.86(±3.04)
Dumping Carv control	94.16(±8.26)	92.95(±9.97)	98.34(±3.62)	94.1(±8.98)
Transfer Carv control	39.99(±3.89)	74.53(±7.06)	90.83(±7.65)	96.78(±6.59)
Dumping Carv - FA complex	95.07(±2.14)	95.13(±0.81)	95.98(±3.09)	94.52(±2.64)
Transfer Carv-FA complex	42.6(±3.94)	80.47(±6.73)	92.1(±0.63)	98.23(±1.78)
Dumping Carv (solvent evaporation)	87.84(±4.45)	89.12(±4.93)	89.00(±2.15)	93.88(±1.45)
Transfer Carv (solvent evaporation)	28.36(±2.95)	56.76(±6.3)	78.65(±5.51)	98.95(±2.53)
Transfer floating Carv	36.4(±1.55)	80.47(±1.39)	91.86(±3.12)	98.69(±1.07)

Table (2) Summary of ppt percentage of Carv in dumping and transfer method

Method	Dumping method % of ppt. (± SD)	Transfer method % of ppt. (±SD)
In vitro dissolution of Carv (intestinal media)	3.190 (±0.040)	-------
Carv	3.163 (±0.441)	1.27 (±0.123)
Carv – FA complex	1.23 (±0.021)	2.06 (±0.35)
Carv (solvent evaporation)	0.89(±0.005)	0.511 (±0.031)
Carv (Floating)	-------	7.09 (±0.081)

Conclusion

The dissolution and precipitation of (PWWB) Carv were studied by applying two methods, which were the dumping and transfer method, using three approaches to decrease precipitation amount in basic media were complex formation with fumaric acid, amorphization by solvent evaporation and the last approach floating preparation. All approaches showed non-significant enhancement in the *in vitro* dissolution of all approaches that applied compared with the control; however, the ppt in the dumping after executing the amorphization and the complex with FA decreased the ppt very highly significant and highly significant, respectively. Both these approaches showed a very significant decrease in the ppt amount. This outcome encourages the study to focus on the amorphization technique to improve the dissolution and decrease the ppt.

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