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Original Article

ENHANCING ORAL BIOAVAILABILITY OF CARVEDILOL USING SOLID DISPERSION TECHNIQUE

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ABSTRACT

Objective: Carvedilol (CRV) is a beta blocker drug that is basically used for the treatment of hypertension, heart failure and arrhythmias. The objective of this study is to increase the oral bioavailability of CRV by using solid dispersions to enhance its solubility and dissolution rate.

Methods: Various preparations of CRV-solid dispersions (SDs) and physical mixtures (PMs) were prepared using different carriers; polyethylene glycol (PEG) 4000, polyvinyl pyrrolidone (PVP) K30 and tartaric acid. Effect of type and concentrations of carriers on solubility and dissolution of CRV were studied. Selected CRV-SDs and PMs that showed the best solubility and dissolution were exposed for further investigations e. g. Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) and X-ray diffraction (XRD). In addition, the oral antihypertensive activity of the optimized formula compared to pure CRV was evaluated in induced hypertensive adult albino male rats.

Results: All carriers enhanced the dissolution rate of CRV. Tartaric acid had the most persuasive effect on the rate and the extent of dissolution of CRV, followed by PEG4000 and PVP. FTIR, DSC and XRD diffraction revealed an interaction between CRV and tartaric acid with the possibility of a polymorphic change in CRV**.** The optimized formula CRV-tartaric acid (SD 1:0.3) causes a marked increase in the antihypertensive activity compared to pure CRV.

Conclusion: Tartaric acid is a promising and efficient carrier for improving the solubility, dissolution and oral bioavailability of CRV.

Keywords: Carvedilol, Solid dispersion, Physical mixture, Hypertension, Oral bioavailability

INTRODUCTION

Therapeutic effectiveness of a drug depends on upon the bioavailability and the solubility of drug molecules**.** The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often causes insufficient bioavailability. Therefore, it is necessary to enhance dissolution of these drugs to ensure maximum therapeutic utility [1].

The most promising method for promoting dissolution is the formation of a solid dispersion in a proper carrier. The solid dispersion reduces particle size and therefore increases the dissolution rate and absorption of drugs. The term "solid dispersion" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, a solvent method, or fusion solvent-method [2, 3].

Carriers commonly used in solid dispersions (SDs) are PEG's of high molecular weight, polyvinyl pyrrolidones, urea, cyclodextrins, sugars, cellulose derivative and others [4, 5].

Carvedilol (CRV) ((±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxy-phenoxy) ethyl] amino]-2-propanol) is a beta-blocker used to treat high blood pressure and heart failure. CRV is practically insoluble in water and exhibits pH dependent solubility. The solubility of CRV is limited because of its protonation, resulting in situ hydrochloride salt formation which exhibits less solubility in acidic medium [6].

Many studies showed significant enhancement in the solubility of CRV by using solid dispersions, for example; Cyclodextrins [7], Gelucire 50/13 [8], PVP K30 [9] and Poloxamer 188 [10].

Most of the previous literature on CRV concerned with the *in vitro* study, and nearly none of them give an interest with studying oral bioavailability of the CRV-SDs.

The Aim of the present work was to enhance aqueous solubility of CRV by solid dispersion technique using carriers such as PEG 4000, polyvinylpyrrolidone PVP K30 and tartaric acid. Effect of variables e.g. type and concentration of carriers will be studied. The carrier that showed highest solubility and dissolution of CRV would be exposed to further investigations e. g. FTIR, DSC and XRD. Oral bioavailability of the optimized formula of the selected carrier of CRV SDs would be evaluated by measuring the antihypertensive activity in induced hypertensive adult albino male rats.

MATERIALS AND METHODS

Materials

CRV (kindly supplied by Amoun Co., Egypt), Methanol, polyethylene glycol (PEG) 4000, polyvinyl pyrrolidone (PVP) K30 and tartaric acid (kindly supplied by Nasr Pharmaceuticals Chemicals Co., Egypt). All other chemicals were of analytical grade.

Solubility studies

Solubility studies were carried out according to the method of Higuchi and Connors, 1965 [11]. An excess of CRV (10 mg) was placed into 25-ml glass vial containing various concentrations of each carrier in 10 ml distilled water. All glass vials were closed with stopper and cover sealed with cellophane to avoid solvent loss. The content of the suspension was equilibrated by shaking in a thermostatically controlled water bath at 25 ^{o}C for 24 h.

After attainment, the equilibrium, the content of each vial was then filtered through a double filter paper (Whatman 42). The filtrate was suitably diluted and assayed spectrophotometrically at 242 nm to measure the amount of dissolved drug. There was no interference from all used carriers at this wavelength. The solubility of CRV in water at the same temperature was also determined following the same procedure mentioned above [12].

Preparation of physical mixtures (PMs)

Physical mixtures (PMs) were prepared by triturating appropriate quantities of CRV and carriers using a mortar and pestle and then transferred to a vacuum desiccator until use [9].

Preparation of solid dispersions by solvent evaporation method

The solid dispersion of CRV using (PEG) 4000, (PVP) K30 and tartaric acid were prepared by dissolving CRV and weighed carrier corresponding to the chosen ratio in methanol (table 1). The solution was stirred at room temperature and methanol was then removed under vacuum at a maximum temperature of 40 °C. The solid residue was dried in a vacuum oven for 24 h at room temperature [13].

The dried mass of PMs and SDs was pulverized and passed through 355 µm sieve. The powder was dried at 40 °C for 3hs in a tray drier, and then the powder was stored in a desiccator for further studies.

Table 1: Types of carriers and their ratios in CRV solid dispersions and physical mixtures

Carrier	Drug: Carrier W/W
Polyethylene glycol (PEG) 4000	1:1, 1:3 and 1:5
Tartaric acid	1:0.1, 1:0.2 and 1:0.3
polyvinyl pyrrolidone (PVP) K30	1:0.5, 1:1, 1:2 and 1:3

***In vitro* dissolution studies**

The dissolution of CRV from the prepared (SDs) and (PMs) was carried out according to the USP-24 rotating paddle method [13]. Dissolution medium consisting of 200 ml of distilled water was used. The reason for choosing distilled water as the dissolution medium is that CRV has a low solubility in water than in acidic or basic media [14]. The stirring rate was 100 rpm and the temperature was maintained at 37±0.5 °C. A sample of 10 mg of CRV or its equivalent of the (SDs) or the (PMs) was placed on the surface of the dissolution medium. At appropriate time intervals (5, 10, 20, 30, 45, 60, 90 and 120 min.), 5 ml samples were withdrawn and replaced with an equivalent amount of the fresh dissolution medium kept at 37 °C. The samples were filtered rapidly through a double layered filter paper (Whatman 42), diluted with dissolution medium and assayed spectrophotometrically at λ_{max} (242 nm) without interference from the carriers.

The amount of CRV dissolved at different time intervals was calculated using a standard calibration curve developed in the same medium. Each experiment was carried out in triplicate.

A cumulative correction factor was applied to compensate for the previously withdrawn samples according to the following equation [15]:

$$C_n = C_{n\,obs} + (5/865)\, C_{n-1}$$

Where:

$C_{n\,obs}$: observed concentration of n^{th} sample

C_{n-1}: concentration of n^{th} sample

C_n: corrected concentration of n^{th} sample

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrophotometer using KBr disk method. The scanning range was 400–4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential scanning calorimetry (DSC)

The DSC thermograms were recorded on a Shimadzu-DSC 50. Samples (2.5 mg) were heated in hermetically sealed aluminium pans over the temperature of 30-300 °C at a constant rate of 10 °C/min under a nitrogen purge (30 ml/min).

X-ray diffraction (XRD)

X-ray diffraction patterns were obtained using a Siemens Kristallofex D-5000 powder diffractometer with CuKα radiation. Diffractograms were run at a scanning speed of 8°/min the 2Θ of 0-80°.

***In vivo* study**

Calculated amount of either CRV powder or solid dispersion (CRV–tartaric acid 1:0.3 w/w) was suspended in 2% gum mucilage. Adult albino male rats weighing (200~250 gm) were used. Rats were obtained from animal breeding center, Faculty of Veterinary Medicine, Zagazig University, Egypt and treated according to Ethical Committee of animal handling in faculty of pharmacy Zagazig University "ECAHZU"

All groups (table 2) received an equivalent of 12 mg CRV per kg body weight of rats [16].

Table 2: Animals groups and route of administration

Group No.	Received formulation
Group I	(control): rats were subjected to operation but not received any drug
Group II	CRV alone
Group III	Solid dispersion (CRV–tartaric acid 1:0.3 w/w)

Induction of hypertension

The rats were anesthetized with urethane (ethyl carbamate) in a dose of 2.0 gm/kg body weight which was injected I.P as 25% freshly prepared aqueous solution [17].

After shaving of hair and sterilization of skin, 2 cm long incisions was made in the left side just below the ribs and 0.5 cm away from the vertebral column. The left renal artery was exposed and completely ligated with 4-0 sterile surgical silk as close as possible to the aorta. The incision was closed by careful continuous suturing of the muscle layer of 4-0 silk with a non-cutting needle; then the skin was approximated and closed with interrupted sterile surgical 0-silk sutures (fig. 1).

Postoperatively, the rats were given penicillin G (100,000 units I. M) per rat for 3 successive days; and were allowed free access to food and water for 28 d. The rats were anesthetized again as before and the blood pressure of rats was determined employing the method of Parasuraman and Raveendran, 2012 and Zheng *et al.*, 2008 [17, 18].

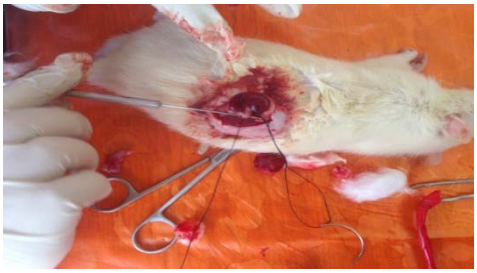

Fig. 1: Exposed left renal artery

Statistical analysis

Two-way analysis of variance (ANOVA) was employed to assess the significance difference between the formulations using GraphPad Prism version 5.04 (Windows, GraphPad software, San Diego, CA). p

Values of >0.05, >0.01 and >0.001 will be considered statistically significant, highly significant and very highly significant, respectively.

RESULTS AND DISCUSSION

Effect of different carriers on the solubility of CRV

In the present study, the solubility of CRV in distilled water at 25 °C was found to be 0.013 mg/ml, a finding that is approximately half the value (0.028 mg/ml) reported by Rehab *et al.*, 2013 [19].

Table 3, summarizes the effect of various carriers on the solubility of CRV in distilled water. In the case of tartaric acid, PVP and PEG 4000, the solubility of CRV linearly increased as the carrier concentration increased, showing the feature of an A_L-type solubility phase diagram [12]. This illustrates that a complex may be formed which is soluble and did not form a precipitate over the range of carrier concentration. These results are in agreement with Navneet *et al.*, 2015 [20] who stated that the solubility of glibenclamide linearly increased as the carrier concentration (PEG 4000) increased.

These carrierse arranged descendingly according to their effect on increasing the solubility of CRV as tartaric acid>PVP>PEG 4000. The increased solubility of CRV in carrier's solution may be attributed to both complex formation and reduction in interfacial tension of water and hence intermolecular forces and polarity occurred by the presence of these carriers [21].

Table 3: Solubility enhancement data of CRV in various carrier solutions at 25 °C

Item	Phase solubility diagram	Optimum carrier concentration (%)	Solubility (mg/ml)	Solubility factor
CRV	A_L	---------	0.013±0.001	--------
Tartaric acid	A_L	0.057	1.161±0.03	89.3
PVP	A_L	10	0.1652±0.01	12.70
PEG 4000	A_L	10	0.0433±0.003	3.33

Solubility factor = (total solubility/intrinsic solubility), A_L = type of phase solubility diagram, Mean of solubility±SD (n=3).

Dissolution studies

The dissolution profiles of pure CRV and SDs with different carriers are shown in table 4. The shapes of the dissolution profiles were examined using the following parameters:

I) The initial dissolution rate (IDR) calculated as percent dissolved of the drug over the first 20 min per minute.

II) The percentage of the drug dissolved after 20, 60 and 120 min ($PD_{20,}$ PD_{60} and PD_{120}).

III) The dissolution efficiency (DE %) parameter after 120 min (enhancement factor) [22, 23].

The dissolution efficiency can be defined as the area under the curve up to a certain time. It is measured using the trapezoidal method by certain equation through Microsoft office Exell and is expressed as =(b1+b2)/3*(a2-a1)

The dissolution efficiency (enhancement factor) is expressed as (AUC a/AUC b) where a is PM or SD, b is pure drug

The calculated dissolution parameters revealed that at 120 min pure CRV yielded the slowest dissolution rate with only about 7.8% of the drug is dissolved. The hydrophobic property of CRV prevented its contact with the dissolution medium which led to a slow dissolution rate [24].

As shown in table 4, all (PMs) showed higher dissolution rate than pure CRV as reflected by higher (IDR) and greater extent of dissolution after 60 min. These results can be explained on the basis that the dry mixing brings the drug in close contact with the hydrophilic polymer [25].

It is also apparent that the rate and the extent of dissolution of CRV from (SDs) exceeded those of pure CRV. The PD_{120} was 91.42 %, 25.46 %, 17.55 % and 7.8 % for tartaric acid (1:0.3), PEG4000 (1: 3), PVP K30 (1:3) CRV-SDs and pure drug, respectively. Their enhancement factor was 1473.7, 369.5, 257.4 and 100.

Table 4: Dissolution parameters of CRV in distilled water from different CRV–tartaric acid, PEG 4000 and PVP K30 systems

Composition (w/w)	IDR (% dissolved/min)	PD20 (%)	PD60 (%)	PD120 (%)	Enhancement factor
CRV Powder	**0.23±0.01**	**4.69±0.3**	**5.39±0.96**	**7.8±0.4**	**100**
CRV-to-D-tartaric acid					
PM 1:0.1	1.22±0.07	24.5±1.49	36.6±0.91	42.25±0.73	615.19
SD 1:0.1	2.12±0.01	42.47±0.38	49.26±0.65	53.43±0.54	841.3
PM 1:0.2	1.5±0.01	30.12±0.30	44.3±0.82	48.36±2.32	686.2
SD 1:0.2	2.43±0.08	48.62±1.66	56.18±2	59.22±1.86	956
PM 1:0.3	1.95±0.09	39.11±1.94	50.26±0.56	58.93±1.15	853.7
SD 1:0.3	3.52±0.17	70.75±3.54	87.11.68±3.6	91.42±4.61	1473.7
CRV-to-PEG 4000					
PM 1:1	0.38±0.02	7.63±0.26	11.74±0.68	14.67±0.03	199.2
SD 1:1	0.51±0.08	10.52±1.96	14.58±1.58	19.77±0.07	263
PM 1:3	0.67±0.02	13.57±0.48	17.13±0.71	18.89±2.46	287.1
SD 1:3	0.86±0.01	17.2±0.28	21.5±0.69	25.46±0.03	369.5
PM 1:5	0.6±0.04	12.06±0.99	51.43±0.69	18.20±0.09	266.5
SD 1:5	0.67±0.05	13.41±1.18	16.79±1.6	18.33±0.1	288.9
CRV-to-PVP K30					
PM 1:0.5	0.47±0.009	9.5±0.19	12.68±0.5	14.54±0.58	213.1
SD 1:0.5	0.6±0.01	12.11±0.25	15.64±0.24	18.35±0.53	266.7
PM 1:1	0.43±0.01	8.77±0.3	11.26±0.2	12.65±0.43	190.3
SD 1:1	0.74±0.02	14.83±0.46	17.9±0.37	21±0.94	310.1
PM 1:2	0.45±0.008	9.06±0.17	11.13±0.12	12.32±0.31	189.8
SD 1:2	0.55±0.01	11.15±0.21	41.32±0.3	17.90±0.41	251.5
PM 1:3	0.46±0.02	9.16±0.47	11.01±0.17	11.75±0.2	187.9
SD 1:3	0.57±0.005	11.38±0.1	14.68±0.59	17.55±0.64	257.4

IDR = Initial dissolution rate, PD20, PD60, PD120 = Extent of dissolution after 20, 60, 120 min, DE = Dissolution efficiency (enhancement factor) after 120 min=AUC a/AUC b, (a: PM or SD, b: pure drug), mean±SD (n=3).

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness and to improve the apparent solubility of the drug [26-28]. Tartaric acid had the most influential effect on the rate and the extent of dissolution of CRV. It was found to decrease the pH of the solution, thus enhancing CRV solubility [26].

PEG showed increase in drug dissolution behavior due to an increase in the drug solubility by its entrapment in the helical interstitial space of PEG molecules [29,30], On the other side, PVP showed increase in drug dissolution by drug incorporation into its linear chain, thus retarding the crystallization of poorly water soluble drug [30, 31].

The carrier concentration was found to play a significant role in the solubility and the dissolution of dispersions, particularly with tartaric acid. As regard to tartaric acid SDs, it was observed that peak solubility increased and time is taken to achieve this peak decreased on increasing concentration of tartaric acid. In addition, pH values were dependent on the concentration of tartaric acid. A marginal change in pH may be sufficient to influence the solubility of CRV owing to its strong pH-dependent solubility [26].

PEG4000 and PVP also demonstrated an increased dissolution as the proportion of the polymer increased. This is in agreement with that reported by Kumar *et al.*, 2011 and Mudgal and Pancholi, 2012 [31, 32]

Hence, tartaric acid SDs showed the highest solubilization and the most powerful effect on the rate and the extent of dissolution of CRV. It is selected for further investigations

Fourier transform infrared spectroscopy (FTIR)

FTIR spectrum for CRV, PM and SD were depicted in fig. 2 (a-d). The characteristic shoulders of CRV were traced at 3342 cm^{-1} (N-H stretching), 3063 cm^{-1}(C-H aromatic),2919 $cm^{-1}$and 2989 cm^{-1}(C-H aliphatic stretching), 1597 cm^{-1}(C=C aromatic) and 1254 cm^{-1}(C-O stretching).

The spectra of tartaric acid PM indicated that all the characteristic bands of drug and the polymer appear except the disappearance of the carbonyl group band of tartaric acid which may be due to the intermolecular hydrogen bond with N-Hand O-H. This reflected that there were little interactions between the drug and the polymer.

The spectra of tartaric acid SD indicated the appearance of new peak at 1601 cm^{-1}due to interaction between COOH of polymer and OH of drug lead to formation C=C with elimination of molecule of water, the disappearance of O-H band and C=O band of the polymer and N-H band of the drug which may be due to the intermolecular hydrogen bond between them. This reflected that there were significant interactions between the drug and the polymer.

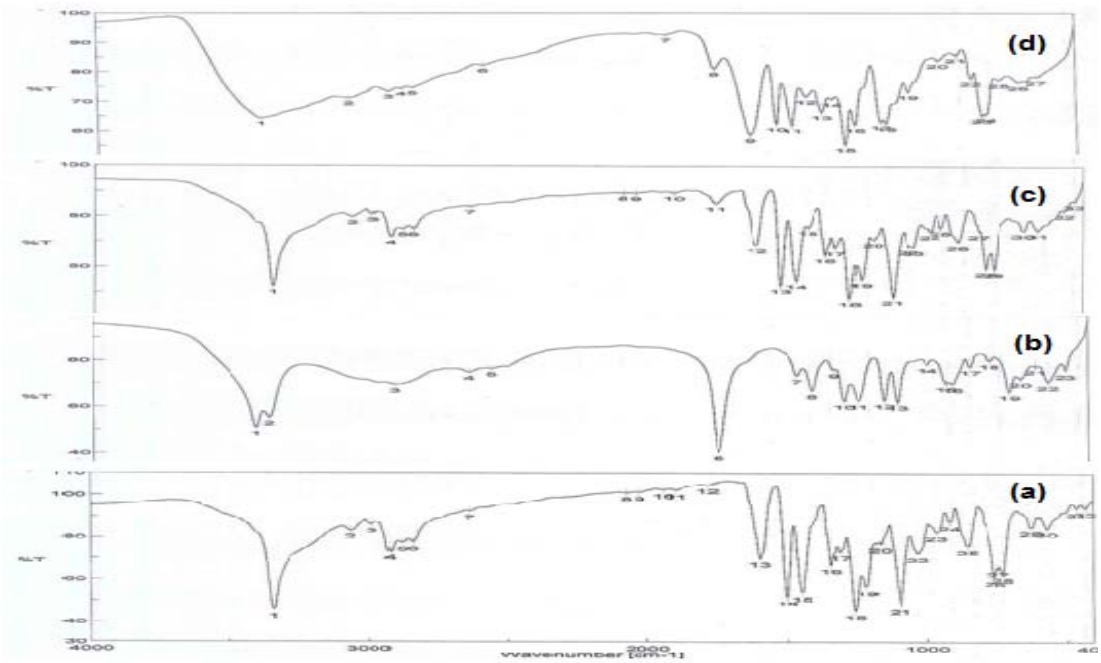

Fig. 2: FTIR spectra of CRV-tartaric acid systems. a) CRV alone, b) Pure tartaric acid, c) CRV-tartaric acid PM, d) CRV-tartaric acid SD

Differential scanning calorimetry (DSC)

In order to get evidence on the possible interaction between CRV and the investigated carrier (tartaric acid), DSC studies were performed. The DSC thermograms are shown in fig. 3. DSC curves of pure CRV exhibited a sharp endothermic peak at 113 ^{o}C, which is corresponding to its melting point.

The DSC thermogram of CRV–tartaric acid SD showed new endothermic peaks at temperatures different from that of pure drug and the carrier. This result indicated the interaction of the two components without miscibility, thus proving formation of an amorphous solid suspension.

The DSC thermogram of the CRV-tartaric acid physical mixture showed CRV two endothermic peaks, one at the same position of pure CRA but with decreased intensity and another at 162^{o}C due to the fusion of the carrier.

This result indicated that some of CRV powder might be still in crystalline state, and this reflected the immiscibility of the two components, thus proving formation of an amorphous solid suspension [19]. This result is in agreement with Shamma RN *et al.*, 2013 [19].

In DSC, changes in the melting endotherm of the drug and single *T*g at a temperature between *T*g values of both components is evidence for the formation of a miscible system (18). SDs can thus be classified as an amorphous solution (with single *T*g), amorphous suspension (two *T*gs) or crystalline suspension (*T*g and melting event) [26, 33].

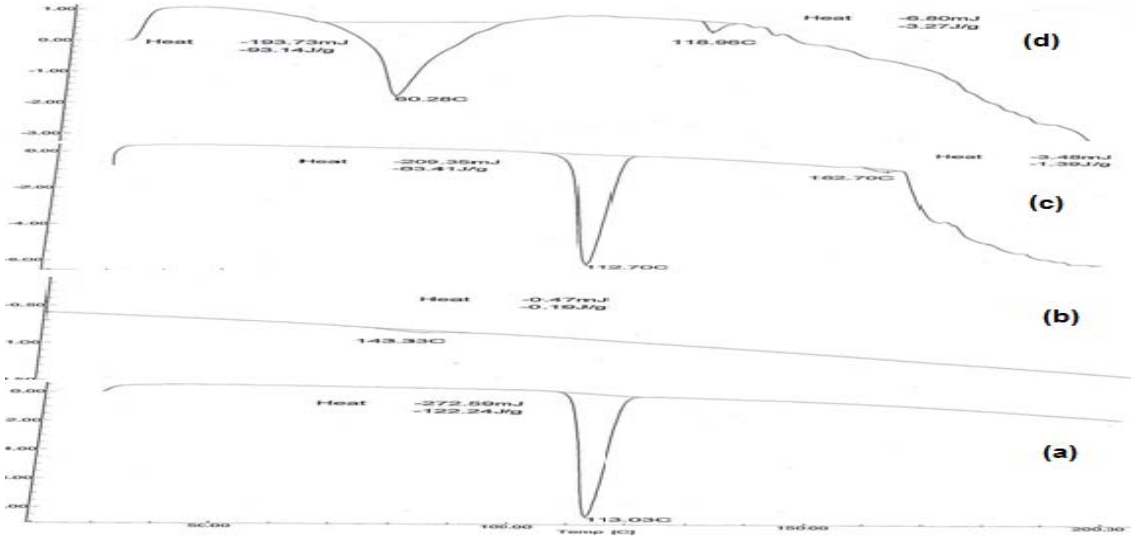

Fig. 3: DSC spectra of CRV–tartaric acid systems, a) CRV alone, b) Pure tartaric acid, c) CRV–tartaric acid PM, d) CRV–tartaric acid SD

X-ray diffraction

The x-ray diffraction patterns of CRV and tartaric acid PMs and SDs were illustrated in fig. 4. CRV was a powder with characteristic diffraction peaks at 2θ of 13.62°, 17.46° and 18.56°; in addition, there were some other peaks of lower intensity.

In the case of untreated tartaric acid, there were peaks at 19.23°, 21.29° and 36.28°. The diffraction pattern of the tartaric acid physical mixture showed the peaks for both CRV and the carrier, thus indicating that there was not a strong interaction between the drug and the carriers.

On the other hand, the diffraction pattern of tartaric acid solid dispersion showed a change in the 2θ and the intensity of the peaks of CRV and tartaric acid, thus indicating that there was an interaction between the drug and the carriers. These results were in line with our findings from DSC and FTIR analysis.

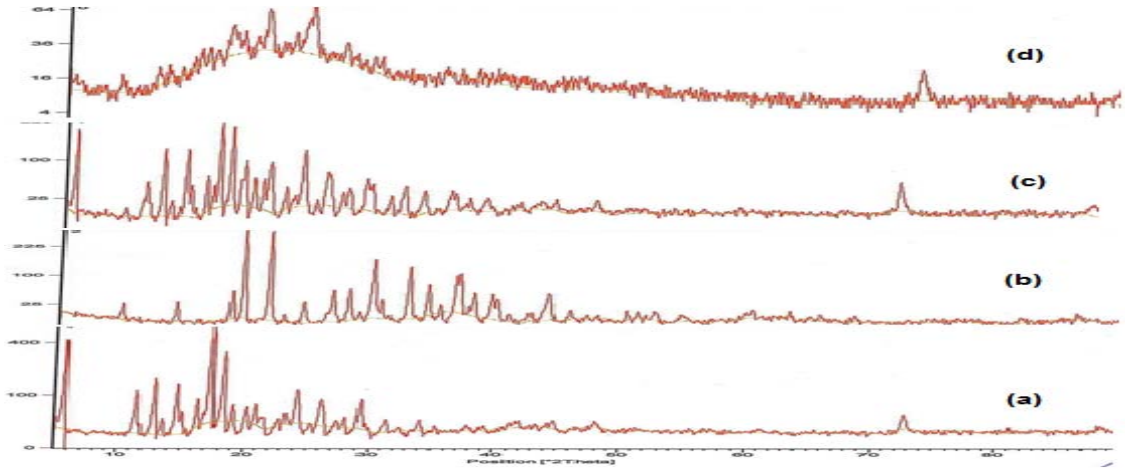

Fig. 4: X-ray spectra of CRV–tartaric acid systems, a) CRV alone, b) Pure tartaric acid, c) CRV–tartaric acid PM, d) CRV–tartaric acid SD

***In vivo* study**

The mean arterial blood pressure (MAP) values obtained after administration of plain CRV and the tested formulation are illustrated in table 5. The results showed a very highly significant difference between the tested formulation and the plain drug.

CRV-tartaric acid SD showed a decrease in MAP of hypertensive rats to normal values for about 5 h and then increased in the sixth hour. On the other side, with the plain CRV in the same dose (12 mg/kg), the decrease in MAP was continued for only 2 h. The antihypertensive effect difference clearly demonstrated that tartaric acid solid dispersion causes a significant increase in the bioavailability of the pure CRV. This is matching with Sherif *et al.*, 2013 [34], who stated that the solid dispersion causes an increase in the relative bioavailability of the plain Sulpiride by 1.8 times.

Also, Kalaiselvan *et al.*, 2007 [35], reported that ternary inclusion complex (prepared by using albendazole, hydroxypropyl-beta-cyclodextrin and L-tartaric acid at 1:1:1 molar ratio) showed a bioavailability enhancement for albendazole by 3.2 fold increase compared to a commercial suspension.

Statistical analysis of CRV from different formulations showed that the drop of MAP between the third and the end of the six hours after administration of CRV solid dispersions was highly significantly lowered compared to that obtained after oral suspension of the plain drug (all results showed P value less than 0.001).

Table 5: Mean arterial blood pressure of different CRV formulations

	Group 1 control	Group 2 CRV alone	Group 3 Tartaric acid SD	P value
0 h	132.1±5.45	127.2±15.12	138.3±6.01	P>0.05
0.5 h	131.1±4.8	109.4±12.5	111.7±16.41	P>0.05
1 h	128.9±7.69	94.44±6.94	102.2±12.61	P>0.05
2 h	130.9±2.3	79.33±2.4	72.22±8.39	P>0.05
3 h	137.8±1.92	111±9.76	64.55±8.69	P<0.001 ***
4 h	135.0±5.77	121.2±4.5	53.33±5	P<0.001 ***
5 h	133.9±8.66	119.2±0.84	44.44±5.09	P<0.001 ***
6 h	135.6±7.7	127.8±6.73	80.00±10.93	P<0.001 ***

The results expressed as MAP±S. D (n=3).

CONCLUSION

This study demonstrated the ability of SDs prepared from (PEG) 4000, (PVP) K30 and tartaric acid to enhance the solubility and dissolution of CRV. Tartaric acid can be considered as a promising carrier for improving the solubility, dissolution and oral bioavailability of CRV as SDs compared to pure CRV. This effect can be explained by FTIR, DSC and XRD diffraction which clarified the physical state of CRV and tartaric acid in the sample. The amorphous solid suspension was obtained in which the contribution of the tartaric acid carrier was concentration dependent.

CONFLICTS OF INTERESTS

All authors have none to declare

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