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Different Approaches for Enhancement of Curcumin Aqueous Solubility and Dissolution rate

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Abstract

Curcumin (CUR) is a nature polyphenolic phytoingredient. CUR showed anti-inflammatory, anti-oxidant, anti-fungal and anti-cancer activities. The therapeutic efficacy of CUR was limited due to its poor aqueous solubility, poor oral bioavailability. Poor solubility of drugs is the major challenge associated with formulation development. Therefore, the aim of present work was to enhance CUR aqueous solubility and dissolution rate using Physical mixture and its solid dispersion. CUR solid dispersions were prepared by solvent evaporation and Freeze drying techniques using different polymers, such as β-cyclodextrins, polyvinyl pyrrolidone (PVP K30), polyethylene glycol 6000 and Pluronic®F-127. The prepared physical mixtures, solid dispersions were characterized using different techniques such as (DSC), (FTIR) and (XRD). Furthermore, the solubility and the dissolution rate of the drug in its different systems were explored. The results of physical characterization of the different systems show no interaction between them. Dissolution studies of CUR solid dispersions showed that the highest drug dissolution rate was achieved at CUR/ Pluronic®F-127 weight ratio of 1:3. Also, complete drug dissolution was obtained for CUR/Pluronic F-127 solid dispersion after 30 min compared to 35 % dissolution for CUR alone after the same time. Also, CUR permeability coefficient through rat skin for Pluronic®F-127 micelles and solid dispersion were two times higher than that of the CUR alone. The obtained results concluded that, the preparation of solid dispersion of Pluronic®F-127 solid dispersions by freeze drying method is a promising one to overcome CUR shortcomings through enhancing its aqueous solubility, dissolution rate and skin permeability.

Key words
Curcumin , Freeze drying, Solid dispersions, Solubility, dissolution rate

1. Introduction

Water solubility of drugs is a critical factor in the drug development. Approximately half of new active pharmaceutical ingredients (API) were not successfully developed because of their hydrophobicity [1]. Reduced drug dissolution rate and limited aqueous solubility result in low oral bioavailability, reduced patient compliance and subsequent suboptimal therapy [2]. Actually, only solubilized drug molecules can be absorbed through the membranes to subsequently reach the site of drug action. So, for the drugs to be absorbed they should be present in the form of an aqueous solution at the site of absorption [3]. Therefore, one of the major challenges of drug development is to improve the dissolution rate and aqueous solubility of poorly soluble drug candidates as well as improve their bioavailability [4]. The literature shows tremendous endeavor to overcome the drug poor aqueous solubility through several approaches [5-7]. Such methods include complexation with cyclodextrins [8], polymeric nanoparticles[8], self-emulsifying drug delivery systems [9], pH adjustment and salt formation [10], micronization, use of co-solvents, emulsions and microemulsion, nanosuspensions, micellar solubilization and solid dispersions [11].

Formation of solid dispersion is an interesting solubilization approach that has shown promising results in improving the dissolution profile of poorly water soluble drugs [4]. Solid dispersion is defined as the molecular dispersion of a drug in an amorphous polymer matrix [12]. The mechanism of increasing the solubility and dissolution rate of drugs in solid dispersions includes particle size reduction, reduced agglomeration, improved wettability and solubility, or dispersion of the drug as micro-fine crystals or amorphous materials [13]. Complexation with cyclodextrins (CDs) is another technique that has been widely studied to enhance aqueous solubility of several drugs [14, 15]. The incorporation of hydrophobic guest molecules in the hollow cyclodextrins central cavity has been the basis for most of their pharmaceutical applications [16, 17]. A number of molecules are solubilized in cyclodextrin solutions through formation of an inclusion complex. The solubilizing capacity of CDs depend on many factors such as, size of the CD cavity, degree of substitution on CD molecule, intrinsic solubility of the drug and whether there are specific interactions between the drug and the CD molecule [18]. Micellar solubilization is a powerful method to improve the aqueous drug solubility using surfactants or amphiphilic polymers above their respective critical micelle concentration (CMC) [19]. In addition to enhancing the aqueous solubility of hydrophobic drugs,

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incorporation into the micelle core also improves drug efficacy and enhances permeability across the physiological barriers [20].

Curcumin (CUR), bis (4-hydroxy-3-methoxyphenyl)-1,6-diene-3,5-dione, is a low molecular weight polyphenol yellow compound derived from the rhizome of the plant Curcuma longa. It has been widely used in different pharmacological applications such as anti-inflammation, anti-microbial, anti-oxidant, and anti-cancer with low or no intrinsic toxicity [21, 22]. However, the potential of curcumin in treating the various diseases is limited mainly owing to their poor bioavailability; this is due to its low solubility in aqueous solutions. In fact, the solubility of curcumin has been reported to be very low (0.0004 mg/mL in water at pH 7.3) [23, 24].

The current work is an attempt to enhance CUR aqueous solubility and improve its dissolution rate using different techniques including formation of solid dispersion. The preparations were evaluated using different techniques and the ability of the optimum formulation to enhance CUR permeability across rat skin was tested.

2. MATERIALS AND METHODS

2.1. Materials

Curcumin (purity > 95 %)was purchased from SD Fine-Chem limited Mumbai India. Polyethylene glycols (PEG 6000, 400 and 600) fromAdwic, EL-Naser Pharmaceutical Co., Cairo, Egypt; Pluronic® F-127(PluF127)& F-68 from Sigma-Aldrich Chemie GmbH, Germany; polyvinylpyrrolidone (PVPK30), Fluka chemie GmbH; hydroxypropyl- β-cyclodextrin(HPβ-CD),Alpha Chemica, India;β-cyclodextrin (β-CD), Fluka, Japan**;** polyoxyethylene lauryl ether (Brij®35), Merk, Germany; All other material are pharmaceutical grades.

2.2. Methods

2.2.1. Measurement of (CUR)Equilibrium Solubility

The equilibrium solubility of CURin water was determined by adding excess amount of the drug (5 mg) to 10 ml of distilled water in stoppered conical flasks. The flasks were agitated in a thermostatically controlled water bath **(Gesellschaft Labor Technik M.B.H.&Co., GFL. Germany)** at 50 RPM and 37 °C for 48 h. Samples were withdrawn at timeintervals (0.25, 0.5, 1, 2, 4, 6, 8, 12, 24 and 48h), properly diluted with water and filtered using membrane filter (0.45 µm).Drug concentration in the samples was determined at λ_{max}430 nm using UV/Vis spectrophotometer **(Jenway Model 6305, U.K)** [25].

2.2.2. Phase Solubility of CUR in the Presence of Cyclodextrins

The phase solubility studies were performed according to the method developed by Higuchi and Connors [26]. Excess amounts of CUR were added to screw-capped tubes containing 10 mL aqueous solutions of β-CD or HPβ-CD having different concentrations (0, 0.25, 0.5, 1, 3, 5, 7, 10 mM). The mixtures were shaken at room temperature under constant agitation rate (50 RPM) for 48 h. Subsequently, aliquots were withdrawn, filtered using membrane filter (0.45 µm) and assayed spectrophotometrically for drug content at λ_{max} 430 nm. Each experiment was carried out in triplicate. The molar concentration of solubilized CUR was plotted versus that of CDs and the apparent stability constant Kc was calculated from the initial straight line portion of the phase solubility diagram using equation 1 [26].

$$Kc = \frac{\text{slope}}{\text{intercept}(1-\text{slope})} \qquad (1)$$

2.2.3. Assessment of CURSolubility in the Presence of DifferentAdditives

Aqueous solubility of curcumin in presence of some carrires and cosolvents at different concentrations was performed. The selected additives were PEG 6000 and PVPK 30 at concentration (0, 0.25, 0.5, 1, 3, 5, 10 and 15 mM). In addition, the solubility in presence of different concentrtions (0, 0.25, 0.5, 1, 3, 5, 10 and 15 mM) of nonionic surfactants and triblock copolymers (Brij® 35, PluF-127 and F-68) was also studied. Also, solubility of CUR in presence of different concentrations (0.1, 2 and 3 %) of cosolvents (PEG 400, PEG 600, Tween 80 and propylen glycol (PG) was investigated.An excess amount of CUR was added to 25-ml stoppered glass bottles containing 10 ml additive solutions. The bottles were shaken in a mechanical shaking water bath equilibrated at 37 ^{o}C. Aliquotes were withdrawn after 48 hr, filtered using membrane disc filter (0.45µm) and assayed spectrophotometrically at λ_{max} of 430 nm after appropriate dilution employing the same concentration of carrier or surfactant as a blank. Each experiment was carried out in triplicate and the results are expressed as mean ±SD.

2.2.4. Prepration of CUR/Carriers Physical Mixtures

CUR and different carriers were sieved through a 150 µm sieve. The physical mixtures containing CUR and different carriers (HPβ-CD) in molar ratio 1:1, (PEG 6000 , PVPK30 and PluF-127) in the ratio of 1:1, 1:2 and 1:3 w/w were prepared by simple, gentle mixing using spatula and paper method.

2.2.5. Prepration of Solid Dispersions by Coprecipitation Method

Carriers used for this experiments were (HPβ-CD at molar ratio of 1:1, PEG 6000, PVPK30 and PluF-127 at weight ratios of 1:1, 1:2 and 1:3 Drug/carrier). The calculated amounts of CUR and carrier were dissolved in a minimum amount of acetone. The solvent was allowed to evaporate at room temperature and the residue was dried at 40 °C in a hot air oven until constant weight of the residue was obtained. The dried solid mass was placed in the desiccator containing anhydrous calcium chloride for further 24 h. The obtained solid mass was grounded and passed through a sieve (150 µm pore size).

2.2.6. Preparation of Solid Dispersions by Freeze Drying

Drug/carriers (HPβ-CD) at molar ratio of 1:1, PEG 6000, PVPK30 and PluF-127) weight ratios of 1:1, 1:2 and 1:3

(drug:carrier) were used to prepare freeze dried solid dispersions according to to the method reported byYallapu, et alwith modification [27]. Calculated amount of CUR was dissolved in an appropriate volume of acetone (5ml) while the polymer was dissolved in sufficient amount of water (5 ml). The drug solution was added to the polymer solution and the whole mixture was stirred over a magnetic stirrer for 15 min. The solution was frozen over night at -80 ±1 ^{o}C and then lyophilized over a period of 48 h using a FreeZone freezedrier (Labconco Inc., Kansas City, MO, USA). The CUR content in the freeze dried powder was determined spectrophotometrically at λ_{max} 430 nm.

2.2.7. Solubility Studies of Prepared Solid Dispersions

Excess of curcumin solid dispersion(equivalent to 5 mg) were dispersed in 25 ml of distilled water in screw-capped bottles. These bottles were shaken continuously for 2 h at room temperature until equilibrium was attained **[28]**. Supersaturated solution was filtered using membrane disc filter (0.45 µm)and further diluted with methanol and absorbance was measured at λ_{max} 430 nm. Solubility studies were also performed for pure drug.

3. Characterization of CURSolid Dispersions

3.1. Differential Scanning Calorimetry (DSC)

The DSC thermograms of CUR alone, individual carriers (PluF-127, PVPK30 and HPβ-CD),CUR freeze dried solid dispersions and physical mixtures of CUR with all studied carriers at a 1:1, w/w ratio were obtained using a differential scanning calorimeter (Shimadzu, Seisakusho Ltd, Kyoto, Japan). Samples (4-5 mg) were weighed and sealed in aluminum pans and heated at a scanning rate of 10 °C/min over the temperature range of 25-200 °C under constant flow of nitrogen gas. Indium was sealed in an aluminum pan and used to calibrate the instrument.

3.2. Fourier-Transform Infrared Spectroscopy (FT-IR)

The FT-IR spectra of CUR alone, individual carriers (PluF-127, PVPK30 and HPβ-CD), CUR freeze dried solid dispersions and physical mixtures of CUR with different carriers at a weight ratio of 1:1 were record using Shimadzu IR-470 spectrophotometer(Shimadzu, Seisakusho Ltd, Kyoto, Japan) at a range of 4000-400 cm^{-1}. Potassium bromide (KBr) disc method was used. The samples were ground, mixed thoroughly with KBr and compressed into discs using IR compression machine.

3.3. Powder X-ray Diffraction Method (P-XRD)

The Powder XRD patterns was performed on CUR alone, individual carriers (PluF-127, PVPK30 and HPβ-CD), CUR freeze dried solid dispersions and physical mixtures of CUR with all studied carriers at a 1:1, w/w ratio. Each powder sample was carried out with Philips (PW-1050, Bragg-Brentano) diffractometer; Cu K α radiation (35Kv, 40mA, slit 1.5418 A^{o}).

4. Dissolution Studies

The dissolution of CUR alone, coprecipitate CUR solid dispersions, freeze dried CUR solid dispersions and the corresponding physical mixtures was studied using USP XXIV type II dissolution apparatus**(Electrolab, India)**. Samples equivalent to 5 mg of CUR were dispersed in the dissolution medium consisting of 500 mLphosphate buffer pH 5.5 maintained at 37 °C and stirred at 50 RPM. At predetermined time intervals of 5, 15, 30, 60, 90 and 120 minutes, 5 mL samples were withdrawn and replaced by an equal volume of fresh dissolution medium. The samples were filtered using a 0.45 µm membrane filterand assayed spectrophotometrically at λ_{max} 430 nm.

4.1. *Ex-vivo*Permeability Studies

Ex-vivo permeability of CUR through rat skin was studied using optimum samples of CUR loaded into PluF-127 and CUR solid dispersion with PluF-127. Male Wister rats weighing 200–250 g were used in this study. All experimental procedures were in accordance with the guidelines of the Institutional Animal Ethical Committee of Assiut University. Rats were sacrificed immediately before the start of the experiment. A full thickness of skin was excised from abdominal site of dead rat and then was washed with water. The fatty tissue layer was removed as thoroughly as possible to minimize variation between the tissue specimens. The skin was washed with cold phosphate buffer saline (PBS) (pH 5.5). The membrane was stored in cold (PBS) (pH 5.5) and used within 1 hour after removal. The skin samples were firmly stretched using rubber bands over one end of glass tubes opened from both sides and having an internal diameter of 2.4 cm. The stratum corneum was facing upwards (donor side) and the dermal surface was facing downwards and allowed to be in contact with receptor compartment. Tested formulations (5 mL of aqueous CUR micelle solution, or CUR solid dispersion dispersed in (PBS pH 5.5) were placed in the tubes over the skin membrane (donor compartment). As a comparison, the permeability profile of CUR alone through rat skin was also examined where an equivalent amount of CUR was dispersed in 5mL of buffer and placed on the skin (donor compartment). The tubes having the skin and samples were immersed in a beaker containing 100 mL of PBS (receptor compartment) containing (1%) Tween® 80. The tubes were adjusted so that the tissue was below the surface of buffer but not touching the bottom of the beaker. The beakers with the tubes were placed into a shaking water bath maintained at 37±0.5 °C and 50 RPM. Samples of 5 mL were withdrawn from the receptor compartment at time intervals of 0.5, 1, 2, 3, 4, and 6 h and were replaced by the same volume of fresh buffer maintained at the same temperature. Samples were analyzed for CUR content spectrophotometrically at λ_{max}430 nm against blank. All experiments were carried out in triplicates and the mean± SD were calculated. The cumulative percent of curcumin, which permeated to the rat skin was plotted against time. The drug flux was calculated from the slope of the linear portion of the plot.

4.2. Calculation of Apparent CUR Permeability Coefficients (P_{app})

The apparent permeability coefficients (P_{app}, cm/s) of CUR were calculated using Equation (2):

$$Papp = \frac{1}{AC0} x \frac{dQ}{dt} \qquad (2)$$

Where: dQ/dtis the rate of appearance of CUR in the receptor compartment (nmol/s), A is the surface area of the skin, and C_0 is the initial CUR concentration (nM) in the tested sample at t = 0. Permeability rates (dQ/dt) were obtained from the permeation profiles of each tested sample. The regression coefficients (r^2) obtained from the curve was generally between 0.80 and 0.99.

Permeability enhancement ratios (R) for each compound were calculated using Equation (3):

$$R = \frac{Papp\ (sample)}{Papp\ (control)} \qquad (3)$$

5. Statistical Analysis

The differences between the mean values were analyzed using Graph Pad Prism software version 5. One-ways analysis of variance (ANOVA) was used to analyze the differences between experimental groups. Newman–Keuls method was used as a post-hoc test. A probability of less than 0.05 ($p < 0.05$) was considered statistically significant.

6. Results and Discussion

6.1. Equilibrium Aqueous Solubility of Curcumin

The solubility of CUR alone in water increased over time and equilibrium solubility of 2.0 µg/mL (0.005 mM) was obtained after 6 h.

6.2. CUR Phase Solubility Studies in the Presence of Cyclodextrins

When drugs are incorporated into cyclodextrins they generally form inclusion complexs at a drug/CD molar ratio of 1:1 [29]. The effect of cyclodextrins on the aqueous solubility of curcumin was evaluated using the phase solubility method. The equilibrium phase solubility of CUR in the presence of different concentration of HP-β-CD is shown in **Figure 1S (S: Supporting information)**. This figure shows that aqueous curcumin solubility increases linearly with increasing HPβ-CD concentration. The addition of 10 mM HP-β-CD resulted in a dramatic increase in CUR aqueous solubility from 0.005 to around 0.5 mM (about 85-fold improvment)., this indicates AL-type phase solubility diagram, which is in agreement with the results obtained previously by Brewster *et al.* [30]. Also, the presence of an AL profile with a slope less than 1, suggested that a 1:1 CUR/CD complex has been formed [31]. On the other hand, the phase solubility diagram for CUR/β-CD exhibits B_S type corresponding to the formation of poorly soluble complex at higher concentration of β-CD **(Figure 2 S).**The linear portion of the curve reflects the increase of CUR solubility to 0.055 mM (9-fold improvement in CUR aqueous solubility). The CUR aqueous solubility reached a plateau, which is the limit of complex solubility at β-CD concentration of 5 mM, after which the solubility started to decrease due to formation of insoluble inclusion complex. This resultcould be attributed to the lower aqueous solubility of β-CD (18.5 mg/ml, 16.29 mM) compared to that of HPβ-CD (400 mg/mL, 286.5 mM) [32]. The stability constants (Kc) of inclusion complexes were calculated from the straight line portion of the curves and found to be 6094.40 and 185.8 M^{-1} for HPβ-CD and β-CD, respectively. These results indicate that β-CD derivatives, such as HPβ-CD form a thermodynamically favourable inclusion complex with CUR and indeed enhance its aqueous solubility.

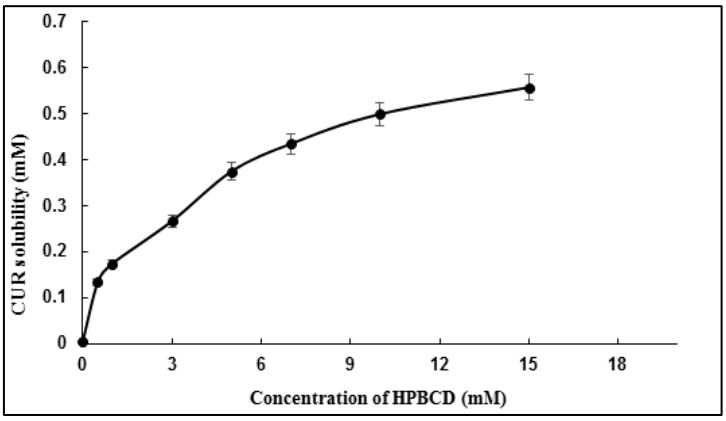

Figure 1s : Solubility diagram of CUR in the presence of different concentrations HP-β- CD in water at 25°C. Each value represents the mean ±SD (n=3)

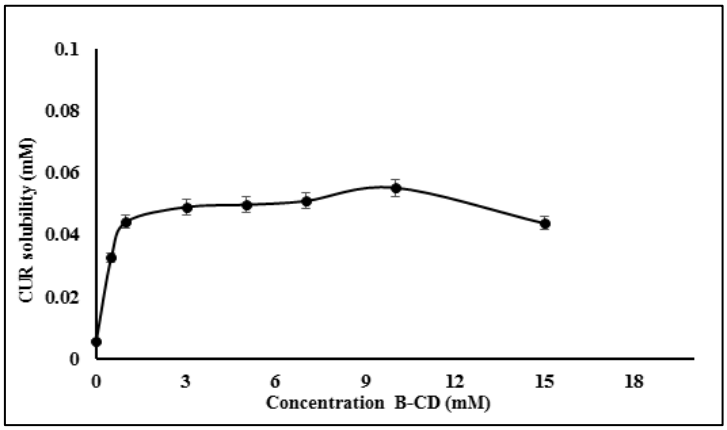

Figure 2s : Solubility diagram of CUR in the presence of different concentrations β- CD in water at 25°C. Each value represents the mean ±SD (n=3)

6.3. Assessment of CURAqueous Solubility in the Presence of Different Additives

The effect of different concentrations of various additives, such as PEG 6000 and PVP K30 at concentrations ranging from 0.25 - 15 mM on the water solubility of CUR are showed in **(Table 1)**. All additives displayed an increase in CUR solubility as their concentration increased and there was a direct relationship between the solubility and the concentration of theadditives used. Among the studied additives, PVPK30 was the most

Table 1: Solubility of CUR (mM) in presence of different carriers at different concentrations. Each value represents the mean ±SD (n=3)

Polymer Concentration (mM)	Brij 35	Plu 127	Plu f-68	PEG 6000	PVP	HPβ-CD	β-CD
0	0.005 ± 0.7	0.005± 0.7	0.005± 0.7	0.005± 0.7	0.005± 0.7	0.005± 0.7	0.005± 0.7
0.25	0.057 ± 0.6	0.143±0.54	0.104±0.54	0.020±0.56	0.099±0.7	0.1333±0.87	0.032±0.8
0.5	0.11667 ±0.21	0.192±0.74	0.149±0.35	0.027±0.47	0.135±0.8	0.174±0.56	0.044±0.6
1	0.17267 ± 0.34	0.268±0.56	0.190±0.54	0.045±0.8	0.168±0.65	0.266±0.76	0.049±0.8
3	0.23431± 0.32	0.376±0.76	0.279±0.7	0.099±0.7	0.214±0.76	0.374±0.54	0.0497±0.56
5	0.27469 ± 0.45	0.456±0.43	0.359±0.57	0.139±0.8	0.225±0.74	0.434±0.45	0.050±0.45
10	0.2825 ± 0.5	0.550±0.65	0.398±0.45	0.141±0.45	0.232±0.47	0.480±0.56	0.055±0.45
15	0.28467 ± 0.9	0.559±0.54	0.422±0.65	0.146±0.56	0.243±0.65	0.557±0.85	0.043±0.76

effective inincreasingthe aqueous solubility of CUR. This is probably due to hydrophobic interactions between the drug and the amphiphilic tetraethylene moiety of the PVP [33]. Also this might be explained by the lower surface tensioneffect of PVP and the improved drug wetting in the dissolution medium [34, 35]. It was noted that the presence of PEG 6000 enhanced aqueous solubility of CUR. This couldbe explained on the basis of the hydrophilic effect of the additive [36]. Similar results were obtained with carbamazipine [33].

The solubilizing effect of different concentrations of nonionic surfactants such as polyoxyethylene alkyl ether (Brij®35), PluF-127 and F-68 was studied. The solubilization of CUR in different surfactants solutions at 37 ^{o}C is shown in **(Table 1)**. The solubility of the drug in these solutions increased linearly by increasing the surfactants and polymers concentration. It was found that at 5mM concentration, PluF-127(HLP 22) showed the highest CUR solubility of 0.45 mM (80-fold) while PluF-68 (HLP 29) enhanced CUR solubility up to 0.35 mM (60-fold). The higher solubility achieved for PluF-127 compared is probably due to the higher lipophilicity of the former due to its larger number of propylene oxide (PPO) units [37, 38]. It is well established that PluF-68 and F-127 copolymers self-aggregate in aqueous solution forming spherical micelles above their critical micelle concentration[39, 40]. For Brij®35 it was observed that the effect of Brij®35 at concentration 5 mM (CUR concentration was 0.27 mM, 40-fold enhancement). This is because of the fact that the ether type surfactants (Brijs) have higher solubilizing capacity due to the relative linear structure of ether type that favor the formation of a more hydrophobic environment [41].

6.4. Characterization of solid dispersions

6.4.1. Differential Scanning Calorimetry (DSC)

DSC thermo-grams obtained for CUR, various polymers, their freeze dried solid dispersion and corresponding physical mixtures are overlaid and shown in **(Figures 1, 3S, 4S)**. The investigated carriers were HPβ-CD, PVPK30 and PluF-127, respectively.The complex formation with a guest molecule may result complete disappearance of endothermic peak or shifting of peak to the other temperatures indicating changes in crystal lattice and melting points. Since HPβ-CD has shown to have the highest complexation efficiency, HPβ-CD-curcumin complex was used for DSC analysis. DSC thermogram of curcumin shows an endothermic peak at 180◦C indicating the melting of curcumin [42]. DSC curves of HPβ-CD **(Figure 1)** show peaks corresponding to the evaporation of water at 50-120◦C. These endothermic peaks were attributed to the loss of the water molecules inside the cavity of the cyclodextrins [43]. The DSC thermograms of CUR/HPβ-CD physical mixture shows peaks corresponding to the melting of curcumin confirming the absence of interactions with CD **(Figure 1)**. However, shift in peak position is observed in this case and the melting peak is not very sharp. The dilution effect by HPβ-CD contributed to the sharp decrease in intensity of the melting peak. Thermogram of freeze dried complex appears exactly like that of HPβ-CD(CUR characteristic peakdisappeared), this probably due to the inclusion of CUR into the CD cavities The total absence of melting endotherm of curcumin indicates that changes occurred in the molecular level [27].

The DSC curve of CUR, PVPK 30, their freeze dried solid dispersion and physical mixture are shown in **(Figure 3 S)**. DSC thermogram of PVPK 30 exhibited a broad endothermic ranging from 50 and 120 °C, which indicates the loss of water due to the extremely hygroscopic nature of PVP polymers [44]. Similar to HP-β-CD, the endothermic peak of CUR disappeared in the thermogram of freeze dried sample while it existed in the physical mixture. DSC curves of solid dispersion and freeze dried systems of CUR with PluF-127 are shown in **(Figure 4 S)**. The thermogram of PluF-127exhibited single endothermic peaks at 56.4 °C which is corresponding to the melting of polymer. Physical mixture of CUR with PluF-127 shows one endothermic peaks, corresponding to the melting points of the polymer. The melting peak of CUR disappeared probably due to

its solubility in the melted carrier during heating [45, 46]. Similar behavior was observed for freeze-dried solid dispersion of CUR with PluF-127, which could be explained by drug solubilization in the molten polymer, formation of a molecular solution, or through the drug being dispersed in an amorphous state [47, 48].

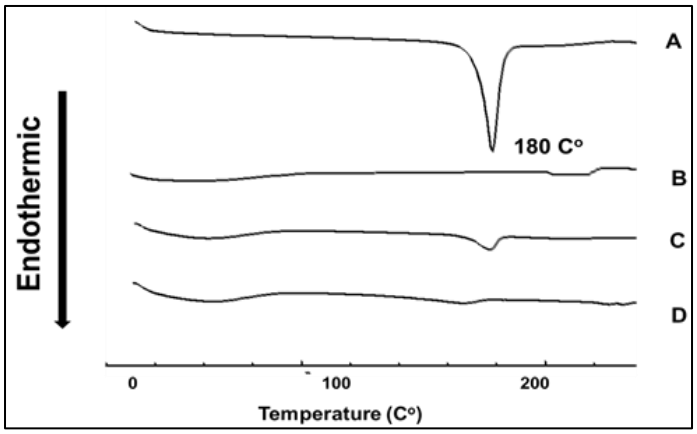

Figure 1: DSC thermogram of CUR (A), HPβ-CD (B), their physical mixture (C) and freeze dried solid dispersion (D) at ratio 1:1.

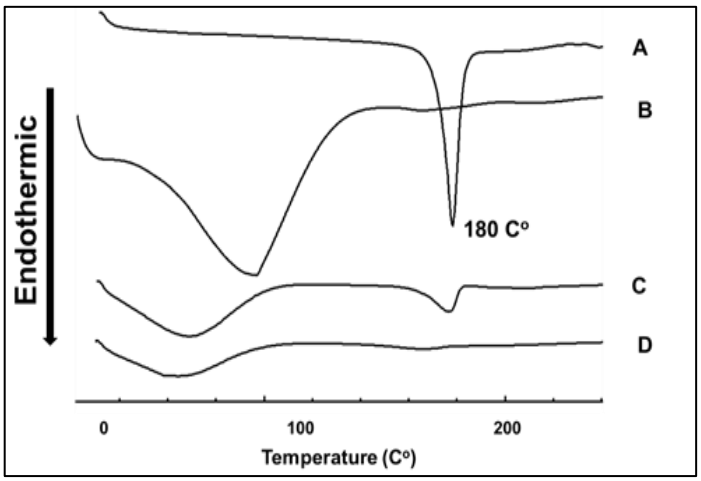

Figure 3s: DSC thermogram of CUR (A), PVPK30 (B), their physical mixture (C) and freeze dried solid dispersion (D) of CUR and PVPK30 at ratio of 1:1.

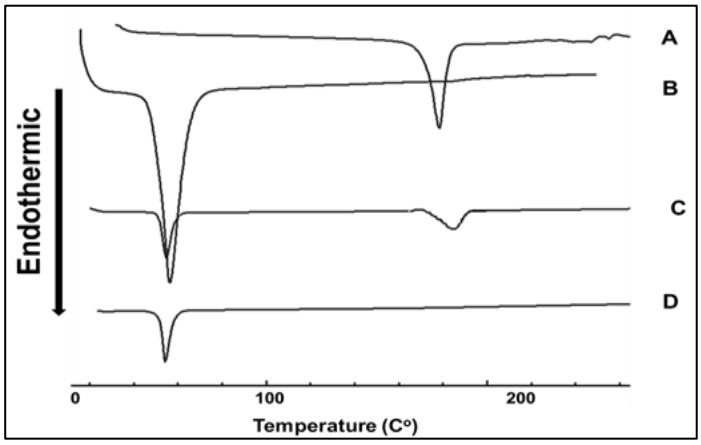

Figure 4s: DSC thermogram of CUR (A), PluF-127 (B), their physical mixture (C) and freeze dried solid dispersion (D) of CUR and PluF-127 at ratio of 1:1.

6.4.2. Fourier-Transform Infrared Spectroscopy (FT-IR)

Infrared spectroscopy was employed to investigate the nature of the interactions between the drug and different carriers. Pure HPβ-CD **(Figure 2)** (**B)** spectra show vibration bands of free –OH groups between 3100 and 3800 cm^{-1} (a rounded broad band) while those of the bound -OH groups appear between 2800 and 3100 cm^{-1}. The FTIR spectrum of curcumin **(Figure 2) (A)** exhibited an absorption band at 3512 cm^{-1} attributed to the phenolic O–H stretching vibration. Also, sharp absorption bands at 1605 cm^{-1} (stretching vibrations of benzene ring of CUR), was observed [27]. Spectra of physical mixtures showed some of CUR characteristic peaks with decreased intensity of the peaks, probably due to dilution effect. In contrast, the FT-IR spectrum of the freeze dried complexes indicated an altered environment all the sharp peaks belonging to CD have appeared and only few characteristic peaks of CUR are visible. Because of CUR complexation with CD. This data confirmed the presence of CUR in CD-CUR complexes. The formation of intermolecular hydrogen bonds between the C=O group of the drug and the hydroxyl groups of HPβ-CD is a possible explanation for this, These observations are in agreement with those of Trapani G, *et al*. [49] who reported the shifts of the carbonyl groups of zolpidem upon complexation with HPβ-CD. These results are also in accordance with those attained in the DSC studies. **(Figure 5 S)** shows the IR spectra of PVPK30 with CUR in freeze dried solid dispersions. The spectrum of PVP exhibited broad peak at about 3440cm^{-1} due to the presence of moisture. Moisture is known to promote drug dispersion in PVP, which is very hydroscopic, hence it was expected that the polymer can also form a hydrogen bond with water [50]. PVPK30 has a peak at1645 cm^{-1} which represents the stretching of carbonyl in the amide group [33]. The CUR characteristic peaks were disappeared in the spectrum of freeze dried solid dispersion probably due to the formation of intermolecular interactions such as ion dipole and van der Waals forces between CUR and PVP[51]. **(Figure 6 S)** shows the FT-IR spectra of solid dispersions and physical mixtures of CUR with PluF-127. The spectra of PluF-127 copolymer display broad bands at 3245-3745 cm^{-1}. The spectra of freeze dried solid dispersions and physical mixtures show the characteristic bands of polymer and the disappearance of CUR bands was observed, probably due to molecular interaction between CUR and PluF-127 such as the hydrogen bonding which could be expected between the hydroxyl group of Poloxamers and the carbonyl group of CUR [48, 52].

6.4.3. X-ray Diffraction Studies

The X-ray diffraction patterns of pure curcumin, HPβ-CD, PluF-127, CUR/ PluF-127 solid dispersion, CUR /HPβ-CD solid dispersion and their physical mixtures are shown in **(Figures 3 and 7 S)**. CUR shows the characteristic peaks at 7, 12, 18, 22 and 25 2θ which are displayed in the wide-angle regions pointing to its crystalline nature [28]. CUR/HPβ-CD–complex and CUR/ PluF-127 solid dispersion did not contain any peaks associated with crystals of the drug, suggesting that

the drug may have formed interaction and solid dispersions with HPβ-CD and with PluF-127; thus, there is reduction in the number of peaks. Reduction in the number of peaks also indicates that the solid dispersions may have been converted from crystalline into amorphous form. X-ray diffraction study only allows differentiation between crystalline data and amorphous material. In case of the physical mixtures, the characteristic peaks of CUR were observed; however, there was a reduction in the intensity of the peaks. These results confirmed that obtained from DSC and FTIR studies.

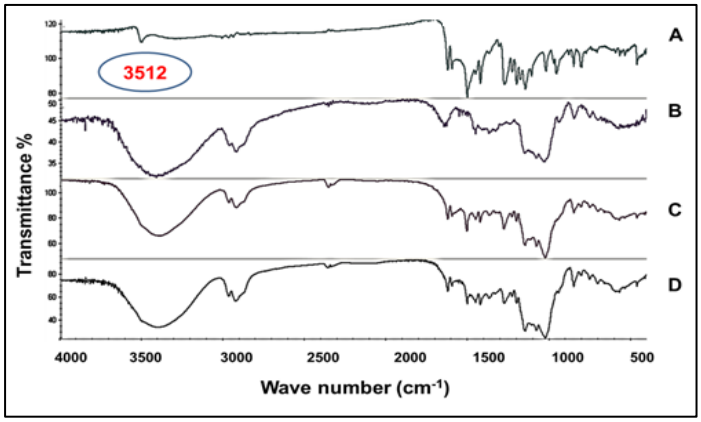

Figure 2: FT- IR spectra of CUR (A), HPβ-CD (B), their physical mixture (C) and freeze dried solid dispersion (D) of CUR and HPβ-CD at ratio of 1:1.

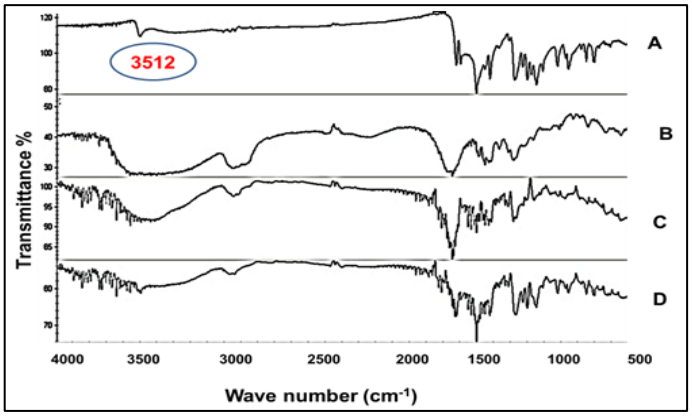

Figure 5s: FT- IR spectra of CUR (A), PVPK30 (B), their physical mixture (C) and freeze dried solid dispersion (D) of CUR and PVPK30 at ratio of 1:1.

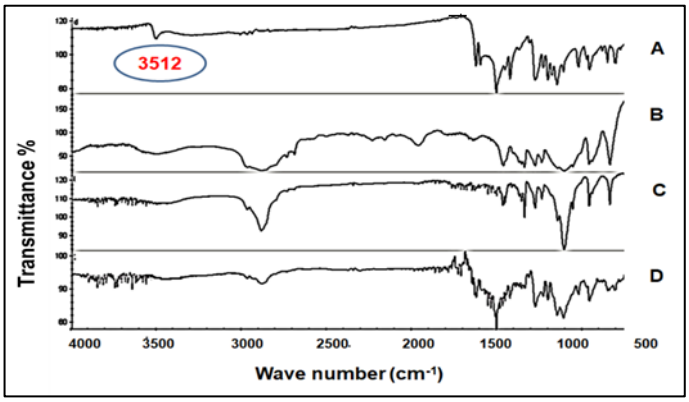

Figure 6s: FT- IR spectra of CUR (A), PluF-127 (B), their physical mixture (C) and freeze dried solid dispersion (D) of CUR and PluF-127 at ratio of 1:1.

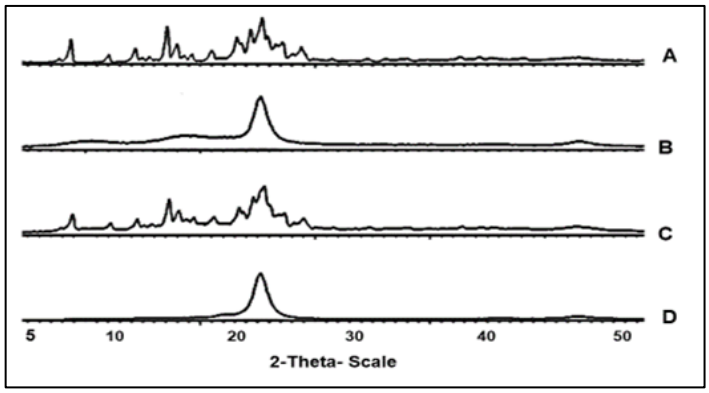

Figure 3: XRD spectra of CUR (A), HPβ-CD (B), their physical mixture (C) and freeze dried solid dispersion (D) at ratio 1:1.

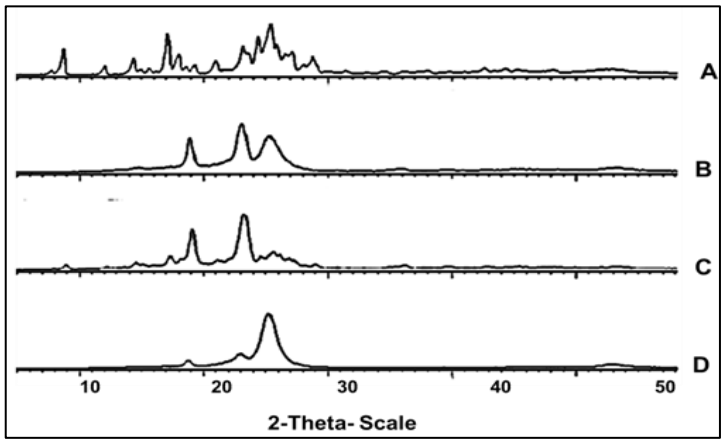

Figure 7s: XRD spectra of CUR (A), PluF-127 (B), their physical mixture (C) and freeze dried solid dispersion (D) at ratio 1:1.

6.4.4. Dissolution Studies of CUR Physical Mixture and its Solid Dispersions

The percents CUR dissolved as a function of time for CUR alone, its solid dispersions and physical mixtures with different carriers are shown in **Figures (4-7 and 8 S – 10 S**). The solid dispersions were prepared at CUR/polymer ratios of 1:1 with HPβ-CD, and at CUR/polymer weigth ratio of 1:1, 1:2 and 1:3 with PEG 6000, PVPK30and PluF-127. Dissolution of CUR alone was rather slow wehere 35% only of the drug was dissolved after 30 min. Dispersion of CUR in the above polymers considerably enhanced its dissolution rate. For instance, after the same time CUR/HPβ-CD solid dispersion exhibited CUR dissolutions of about 95 % (**Figure 4).** The observed increase in the dissolution rate of CUR could be attributed to the formation of inclusion complexe with HPβ-CD where the drug is being incorporated into the interior CD cavity [16, 53]. Dissolution CUR from the physical mixture was faster than the drug alone for CUR/HPβ-CD due to increased drug wettability by this hydrophilic carrier. **(Figures 5, 6)** show the dissolution of CUR from its physical mixtures and solid dispersions with PVP K30 at weight ratio 1:1, 1:2 and 1:3.The solid dispersion at a weight ratio of 1:1, 1:2 and 1:3 exhibited significantly higher dissolution of about 91% after 30 min.compared with CUR alone (p<0.05). This may be attributed

to surface tension-lowering effect of PVP and the reduced particle size, as well as prevention of drug aggregation, in addition to the improved wetting of CUR in the dissolution medium by PVP K30 [35]. The increased CUR dissolution observed for the physical mixtures (PM) at three ratios compared to pure drug is attributedto the wetting properties of the polymer which increase the wetting of the drug particles. These results are in agreement with those obtained by Tantishaiyakul V *et al.* [54] who reported a similar finding forthe enhancement of dissolution rates of piroxicam from its solid dispersion with PVP.

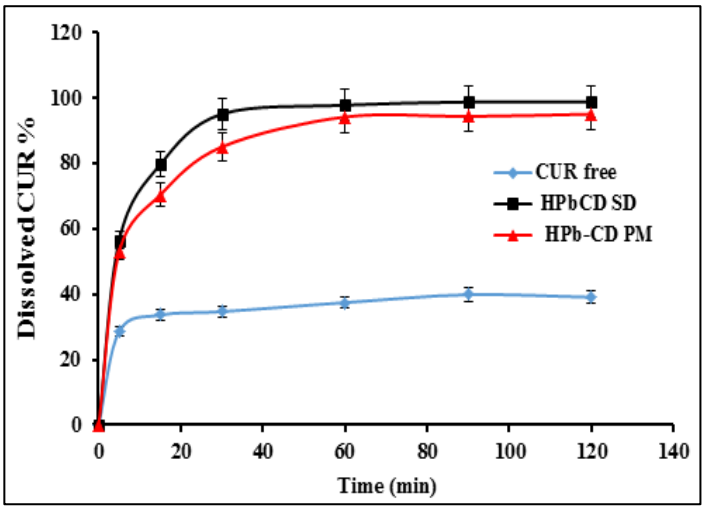

Figure 4: Dissolution profile of CUR from its physical mixture (PM) and solid dispersions with HPβ-CD in phosphate buffer pH 5.5 and 37 °C. Each value represent the mean ±SD (n=3).

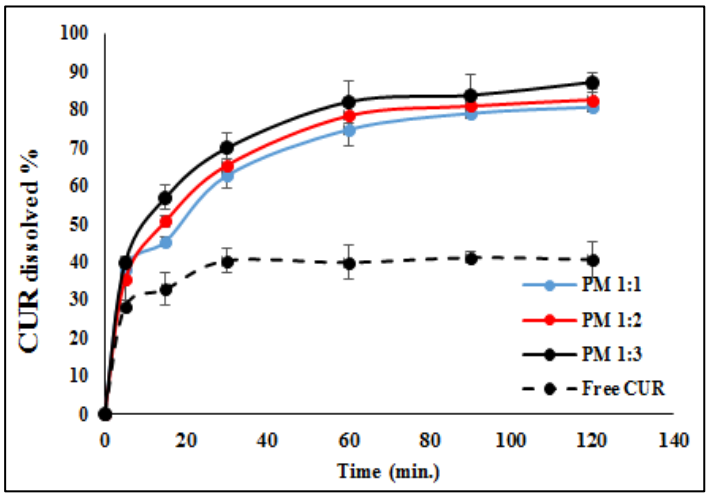

Figure 5: Dissolution profile of CUR from its physical mixtures (PM) at different ratios with PVPK30 in phosphate buffer pH 5.5 and 37 °C. Each value represent the mean ±SD (n=3).

The results of dissolution studies of CUR from physical mixturesand its solid dispersions and with Plu F-127 are shown in **Figure 7, 8 S**. CUR/PluF-127 solid dispersion showed highest dissolution rate among all the studied carriers where ~99% CUR dissolution was achieved after 30 min., for the solid dipersion prepared at a weight ratio of 1:3.This could be attributed to the higher hydrophilicity and solubilization capacity of PluF-127 due to the presence of large number of propylene oxide units (65) and with an HLB (hydrophilic-lipophilic balance) value of 18-23 [37, 55]. CUR physical mixtures with PluF-127 also showed enhanced drug dissolution compared to the drug alone **(Figure 8 S**. This could be attributed to the ability of pluronic to form micelles where hydrophobic drugs are incorporated into the hydrophobic micelle core [37]. Taken together the above results indicate the ability of CUR solid disperion with diffferent polymers to improve the drug dissolution rate compared with the free curcumin.

(Figure 9 S and 10 S) show the dissolution of CUR from physical mixtures (PM) and its solid dispersion and with PEG 6000. The solid dispersions exhibited significantly (p<0.05) higher dissolution of about 73, 76 and 78 % for weight ratio 1:1, 1:2 and 1:3, respectively after 30 min. compared with pure drug. The observed increase in dissolution may be attributed to improved wettability, local solubilization at the diffusion layer surrounding the particles [56].Similar results were obtained by Lin C-W and Cham T-M for nifedipine solid dispersion with PEG6000 [57].

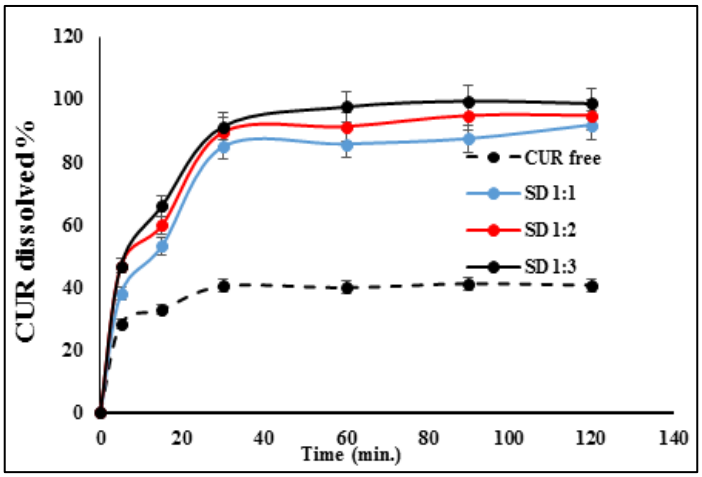

Figure 6: Dissolution profile of CUR from its solid dispersions (SD) at different ratios with PVPK30 in phosphate buffer pH 5.5 and 37 °C. Each value represent the mean ±SD (n=3).

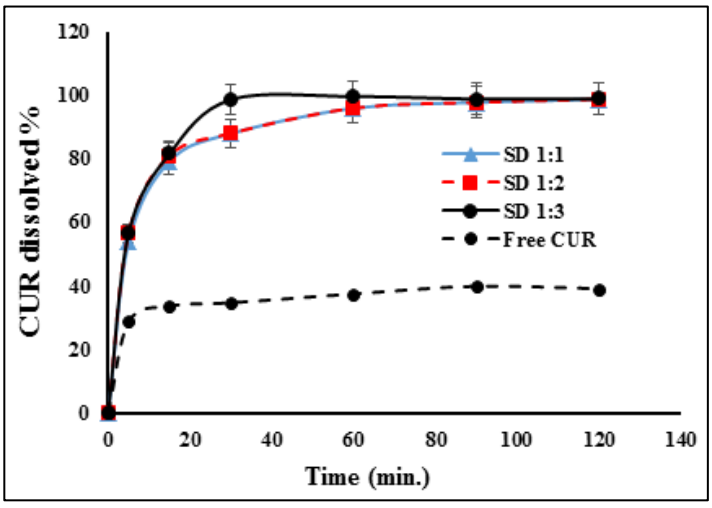

Figure 7: Dissolution profile of CUR from its solid dispersions (SD) with Plu F-127 in phosphate buffer pH 5.5 and 37 °C. Each value represent the mean ±SD (n=3).

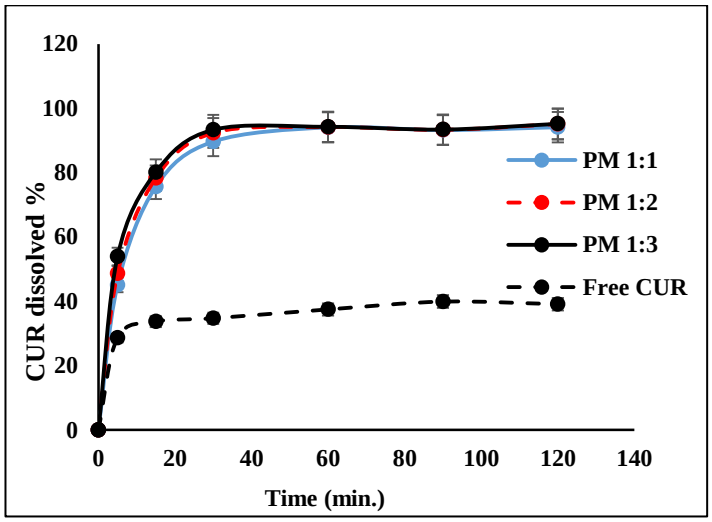

Figure 8s: Dissolution profile of CUR from its physical mixtures (PM) with Plu F-127 at pH 5.5 and 37 ^{o}C. Each value represent the mean ±SD (n=3).

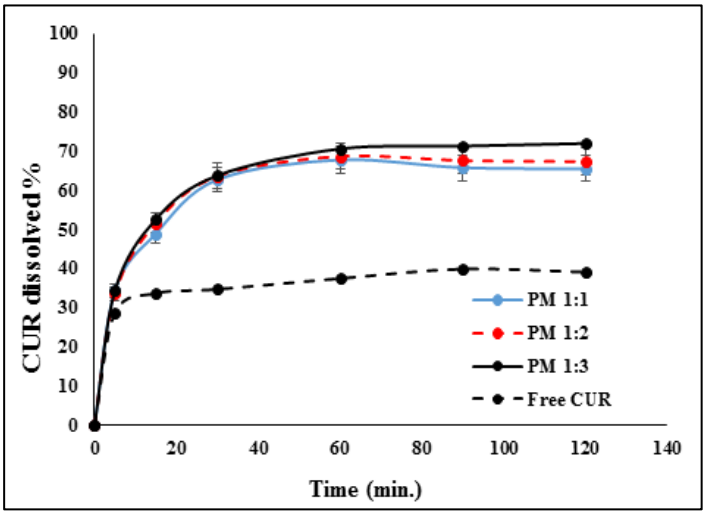

Figure 9s: Dissolution profile of CUR from its physical mixture (PM) with PEG6000 in phosphate buffer pH 5.5 and 37 ^{o}C. Each value represent the mean ±SD (n=3).

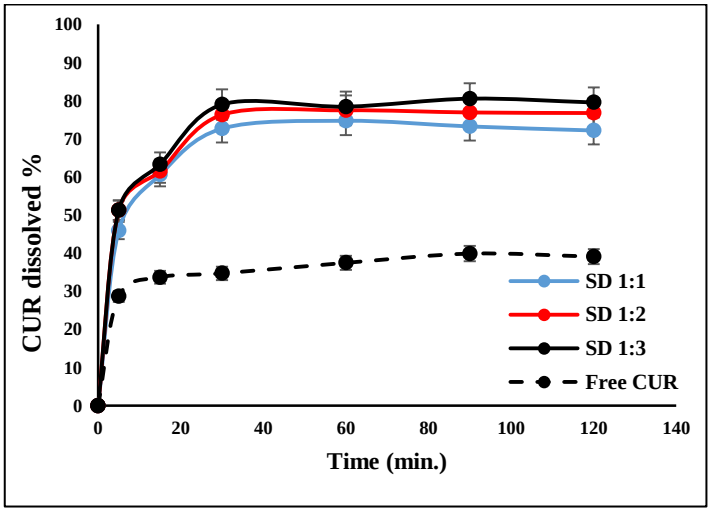

Figure 10s: Dissolution profile of CUR from its solid dispersions (SD) with PEG 6000 in phosphate buffer pH 5.5 and 37 ^{o}C. Each value represent the mean ±SD (n=3).

The faster dissolution rate (RDR) of PMs compared to pure drug was observed for both of carriers **(Table 2)** and could be attributed to the improvement of wettability of drug particles due to the presence of highly hydrophilic polymers. Dissolution rates for SDs were greater than those for PMs and drug alone.

6.4.5. *Ex-vivo* Permeability Studies

The skin forms an attractive and accessible route for delivery of CUR because of its limitations, which include bioavailability challenges, low skin penetration and limited aqueous solubility. Lower permeability of curcumin which may dramatically reduce the partition coefficient between the skin and curcumin thereby decreasing the flux values of free CUR [58]. Therefore, the potential of the selected CUR formulations in this work to increase drug permeability through rat skin was tested. The samples tested were CUR/PluF-127 micelles and CUR/Plu F-127 solid dispersion.

(Figure 11 S) shows the permeability profile of CUR loaded into different formlations through rat skin. The cumulative amount of CUR found in the receptor compartment increased over time for the tested samples. The cumulative CUR permeated increased by a factor of 3.35 and 2.9 for CUR/PluF-127 micelles and CUR/PluF-127 solid dispersion, respectively when compared to CUR alone. The permeability coefficient (P_{app}) values of CUR/PluF-127 micelle solution(6.824 x10^{-6} cm/sec) and CUR/PluF-127 solid dispersion (6.036 x10^{-6} cm/sec) were significantly higher than that of pure drug (2.25 x10^{-6} cm/sec), (p<0.05). Thus, the drug permeability coefficients of CUR/PluF-127 and CUR/PluF-127 solid dispersion were 3 and 2.5 times higher than that of CUR alone, respectively. The lower permeability for CUR/PluF-127 freeze dried solid dispersion compared to the micelles could be attributed to the presence of un-complexed insoluble drug in the medium, which was unable to permeate through skin. Only dissolved drug molecules are able to permeate skin. Similar observation was previously reported where PluF-127 micelles improved the effective permeability of paclitaxel through rat small intestine

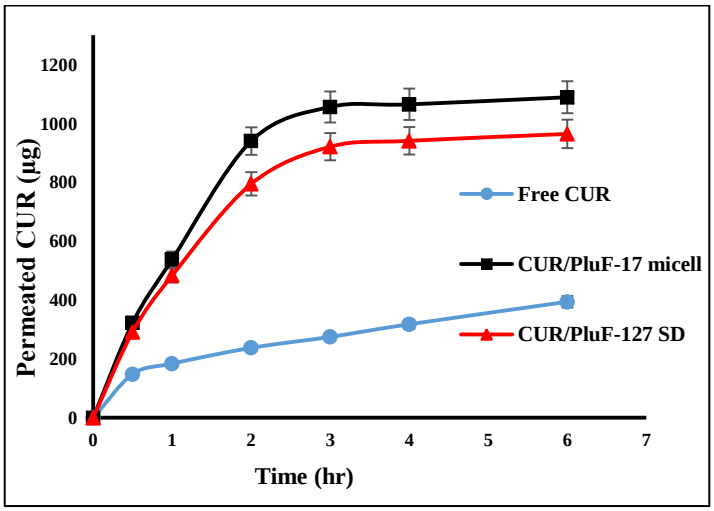

Figure 11s: Cumulative amount of CUR permeated across rat skin for CUR/PluF-127 micelles and CUR/PluF-127 solid dispersion (Plu F-127 SD). Each value represents the mean ±SD (n=3).

Table 2: The percent of drug dissolved after 30 and 60 min (PD) and relative dissolution rate (RDR) after the same times of physical mixture and its solid dispersions in HPβ-CD, PVPK30, PluF-127 and PEG 6000 prepared at different drug: polymer ratios.

Polymer	System	PD_{30}	RDR_{30}	PD_{60}	RDR_{60}
drug alone	-	35	1.00	36	1.00
HPβ-CD	PM 1:1	85	2.42	94	2.6
	SD 1:1	95	2.71	97	2.70
PVPK30	PM 1:1	62	1.77	74	2.10
	PM 1:2	65	1.85	78	2.16
	PM 1:3	70	2.00	83	2.30
	SD 1:1	85	2.42	86	2.40
	SD 1:2	89	2.54	91	2.52
	SD 1:3	91	2.60	97.5	2.70
Plu F-127	PM 1:1	89	2.54	92	2.55
	PM 1:2	92	2.62	93	2.58
	PM 1:3	93	2.65	94	2.61
	SD 1:1	87	2.48	94	2.61
	SD 1:2	90	2.57	95	2.63
	SD 1:3	98	2.80	99	2.75
PEG 6000	PM 1:1	62	1.77	67	1.86
	PM 1:2	63	1.80	67	1.86
	PM 1:3	65	1.85	70	1.94
	SD 1:1	72	2.051	74	2.05
	SD 1:2	76	2.1	77	2.13
	SD 1:3	79	2.25	82	2.27

PD: percent of drug dissolved.
RDR: relative dissolution rate (ratio between CUR dissolved from PM, SD and that dissolved from free drug at specific time.

[59]. Surfactants have been shown to increase drug permeability by altering membrane properties, thus allowing drug absorption by passive diffusion through the paracellular pathway [60]. Pluronics were also found to be permeability enhancers acting through inhibition of efflux pumps and lowering membrane fluidity [61]. Based on these results, PluF-127 could find applications as effective permeability enhancer of curcumin in micelles and solid dispersion products.

7. Conclusion

CURCUMIN is a hydrophobic drug with poor aqueous solubility, which needs the development of effective solubilization approaches. Among them hydrophilic additives were added to enhance CUR solubility, formation of solid dispersions. The dissolution of CUR from its solid dispersions at different ratios with the investigated hydrophilic polymers, as well as cyclodextrins was clearly improved. CUR/Plu F-127 solid dispersions at different ratios that prepared by freeze drying method showed the fastest drug dissolution rate where complete CUR dissolution was obtained after 30 min. The improved drug dissolution was attributed to convert to amorphous one this as suggested by DSC, FT-IR and XRD studies. The cumulative of CUR permeated was increased in the presence of Plu F-127. It was concluded that the most effective carrier for enhancement CUR solubility is PluF-127.

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