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Original Article

ENHANCEMENT OF THE RELEASE OF CURCUMIN BY THE FREEZE DRYING TECHNIQUE USING INULIN AND NEUSILIN AS CARRIERS

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ABSTRACT

Objective: Curcumin (CUR), the active ingredient in turmeric has been proven to possess many therapeutic activities chiefly as anti-inflammatory and antioxidant. Unfortunately, CUR suffers from low bioavailability and dissolution due to its poor water solubility. The aim of this work was to enhance the dissolution of CUR by converting it into an amorphous form by freeze-drying and using different carriers.

Methods: Different solid dispersions of CUR with Inulin and Neusilin US2 at different ratios using the freeze-drying technique were prepared. The various prepared formulas were characterized using differential scanning calorimetry, X-ray diffraction studies, fourier transform infrared and scanning electron microscopy. Release studies, as well as stability studies of CUR from different formulas, were done.

Results: Formulation containing CUR, Inulin and Neusilin US2 at a ratio of 1:5:1 showed the highest CUR release during dissolution testing. The percent CUR release was 98% in comparison with that of 2% from the reference raw material. Physical stability testing showed that CUR remained in the amorphous state for 3 mo.

Conclusion: Inulin and Neusilin US2 combinations were found to be effective in enhancing the solubility and dissolution rate of CUR, and stabilizing the amorphous form in the prepared solid dispersion.

Keywords: Curcumin, Inulin, Neusilin US2, Freeze-drying, Enhancement of solubility

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INTRODUCTION

CUR is the main curcuminoid of the turmeric spice (curcunin longa), which is a member of the Ginger family (Zingiberaceae). Other curcuminoids present are desmethoxycurcumin and bis-desmethoxy curcumin. These curcuminoids which are polyphenols gave turmeric the yellow color. That is why turmeric is used as a yellow food colorant and food additive [1]. CUR has been used for many years due to its therapeutic activities, such as anti-inflammatory, antioxidant, antimicrobial, peptic ulcer healing and anti-cancer [1-7]. CUR suffer from low aqueous solubility due to its lipophilicity. Its solubility is about 3.12 mg/l at 25 °C. As consequence of its low solubility, CUR exhibits poor dissolution and bioavailability properties limiting its clinical use and enlarging the administered dose to 8-12g daily. Despite of the high administered dose, CUR plasma concentration was less than 1 µg/ml and this concentration has no therapeutic activity [8-10]. CUR structure present in fig. 1a demonstrates the lipophilic nature of CUR.

Many attempts were carried out to enhance the aqueous solubility of CUR. For example, solid dispersion of CUR with PVP using the spray drying technique was carried out. This led to an increase in the dissolution rate as compared with pure CUR [11]. Other methods include freeze-drying of CUR with Eudragit solution [12], formulation of oil in water nanoemulsion (o/w) [13], the use of nanoparticles [14] and the use of antisolvent technique [15]. Most of these techniques have many limitations such as the use of expensive solvents, the high production cost, poor stability, and the leaky nature of some of the carriers use. These findings the need to further enhance the dissolution properties of CUR that overcome the drawbacks of the previous methods.

One of the most promising techniques to improve CUR solubility is preparing it in the amorphous form by freeze drying [10, 16]. It is well known that the amorphous form has higher aqueous solubility and dissolution characteristics than the corresponding crystal form. In addition, spray drying produces a very small particle size product. The main drawback of this method is the physical instability due re-crystallization. Several additives have been used to stabilize the amorphous form of CUR such as Maltodextrin [17],PVP [10], HPMC [16], Gelucire–Aerosol combination [18]. The use of such additives showed some enhancement in stability. However, stability enhancement was not sufficient with some agents or the improvement of CUR solubility was limited.

One of the most valuable carriers that shows to be the high capability of stabilizing the amorphous form of many drugs is Neusilin US2. Neusilin US2 is a highly porous synthetic amorphous polymer with large surface area. It consists of a tetrahedron of silicon, octahedron of magnesium and either tetra or octahedron of aluminum. Fig. 1b shows the structure of Neusilin. Because of the high surface area and the porous structure, it can adsorb high amounts of oils or water and can be compacted into tablets or used as a carrier in solid dispersions by forming hydrogen bonds with the adsorbate [19-24].

Another substance that has been used to improve the solubility and dissolution of many drugs is Inulin. Inulin is a surfactant capable of improving the solubility of many drugs and has been used as carrier in solid dispersion. In addition, Inulin was used to stabilize amorphous drug by acting as coating additive. Inulin is a natural polysaccharide prebiotic that can be obtained from many plants such as *Cichorium intybus* (Chicory) and *Helianthus tuberosus* (artichoke). It does not get metabolized in the GIT of human as glucose, sucrose and lactose. The structure of inulin is shown in fig. 1. C. since Inulin is a prebiotics, it stimulate the growth of beneficial bacteria in the colon. Because of this, Inulin has been proven to be a flexible substance in different applications [25-30].

The main objective of this research is to prepare a stable amorphous form of CUR to enhance its dissolution and bioavailability properties using the freeze-drying technique. Because the amorphous form is not stable and tends to recrystallize due to its high internal energy, two carriers were used to prevent recrystallization namely: Inulin and Neusilin US2. Neusilin US2 has a high surface area and a porous character, it will entrap CUR and prevent its crystallization. Inulin is proposed to enhance the pharmacological effect of CUR by increasing its solubility and stabilization of the amorphous form through surface coating. The influence of carrier concentration on the dissolution and physicochemical properties were investigated, and the optimum formula having the highest dissolution rate was selected for further tests.

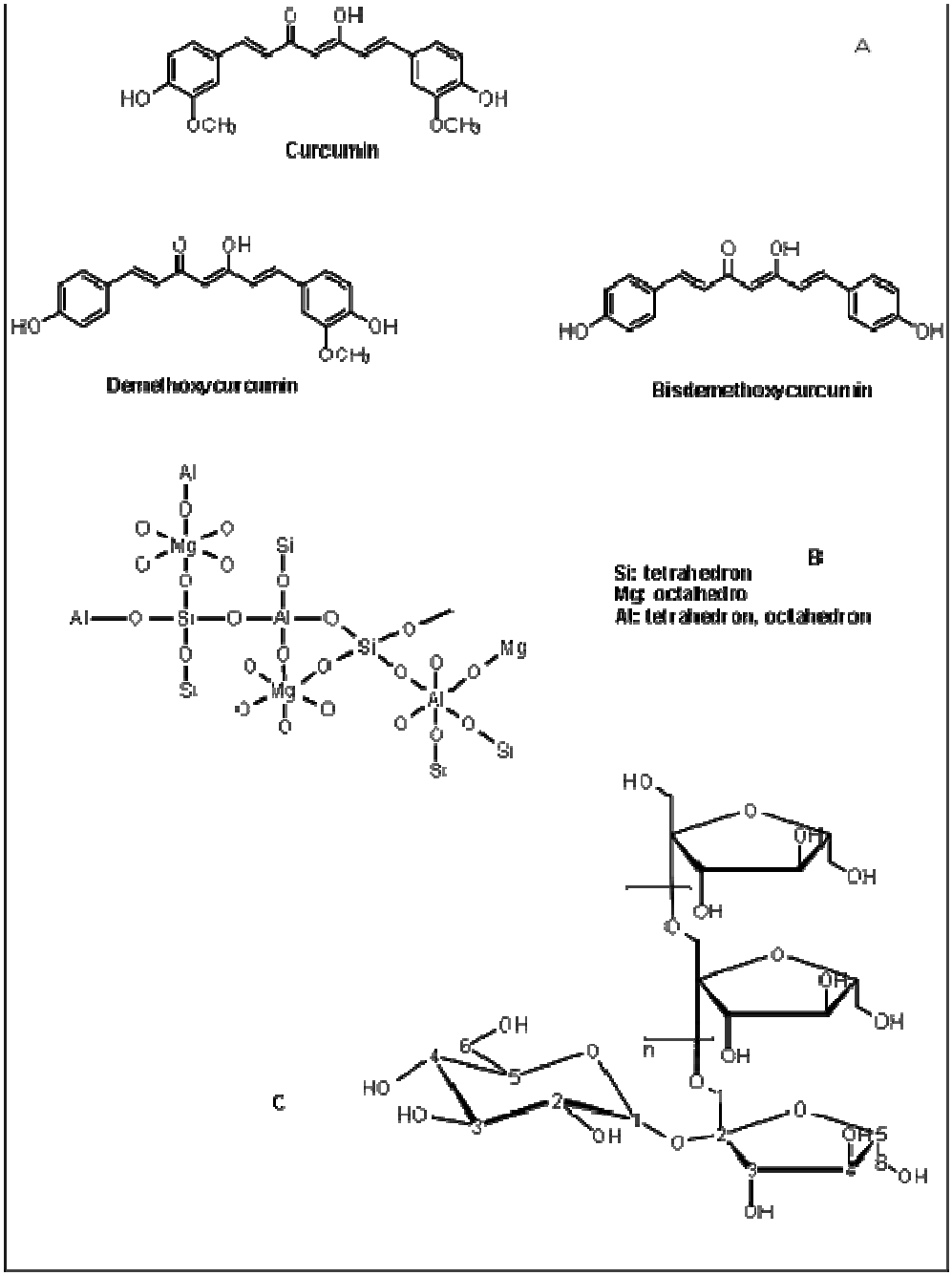

Fig. 1: A) Curcuminoids structure, (B) Neusilin US2 structure, (C) Inulin structure

MATERIALS AND METHODS

CUR was obtained from Acros Organics-Fisher, Belgium (Purity: 98%, melting point: 180 °C). Neusilin US2 was obtained from Fuji Chemical, Japan. Inulin Dahila Tubers was obtained from Santa Cruz Biotechnology, USA. Absolute ethanol was obtained from Carlo Erba-Italy. DPPH (2, 2-diphenyl-1-picrylhudrazyl) free radical was obtained from Sigma, Aldrich, USA. Distilled water used in all experiments and all chemicals were used as received without further modification.

Preparation of the solid dispersion

CUR sample of 150 mg was dissolved in 50 ml absolute ethanol and stirred at room temperature. The mixture was then added stepwise to 50 ml aqueous solution containing the carrier (Neusilin US2 and/or Inulin). The concentrations of the carriers were varied as present in table 1.

The mixture was stirred for 5 min. Then, ethanol was removed from the suspension by Heidolph rotary evaporator. Evaporation was carried out at 70 °C under vacuum and the rotational speed of 30 round/min for 10 min. Telstar lyo Quest freeze-dryer was then used to get rid of water. Freeze drying was performed at temperature of-80 °C and pressure of 0.3 mTorr Pressure. The product remained in the freeze dryer for 2 d. After processing, the prepared solid dispersions were kept in the dry state and stored in tightly closed amber containers.

Preparation of the physical mixture

A physical mixture of CUR with Neusilin and Inulin were prepared by mixing a specific amount of CUR with the carriers as shown in table 1. The samples were stored in a tightly closed amber container.

Table 1: The prepared CUR dispersions and physical mixtures that contain Inulin and/or Neusilin at different ratios

Formulation	Preparation method	CUR (mg)	Inulin (mg))	Neusilin (mg)	CUR: Inulin: Neusilin ratio
SD (1:1;0)	Freeze-dry	30	30	0	1:1:0
SD (1:0:1)	Freeze-dry	30	0	30	1:0:1
SD (1:5:0)	Freeze-dry	30	150	0	1:5:0
SD (1:0:5)	Freeze-dry	30	0	150	1:0:5
SD (1:1:1)	Freeze-dry	30	30	30	1:1:1
SD (1:5:1)	Freeze-dry	30	150	30	1:5:1
PM (1:5:0)	Physical mix	30	150	0	1:5:0
PM (1:1:1)	Physical mix	30	30	30	1:1:1
PM (1:5:1)	Physical mix	30	150	30	1:5:1
PM (1:0:1)	Physical mix	30	0	30	1:0:1
CUR	Pure	30	0	0	-

Note: Three batches were prepared from each formulation

Characterization of solid dispersion

X-ray diffraction (XRD)

XRD was performed at room temperature using Ultima XRD (Rigaku, Japan) with cobalt radiation (CuKa) at 40kV and current of 30 mA. The scan range was set from (0-40 °) 2θ diffraction angle at step size of 0.02 °.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was done using (Netzsh-DSC, Netzsh, Germany) connected to a liquid nitrogen chamber for cooling. The entire enthalpy process was calibrated by indium. Sample of 5 mg of raw materials, physical mixture or solid dispersion was accurately weighed and heated in a sealed aluminum pan under stream of nitrogen gas. The sample scan range was 40-200 °C at a rate of 5 °C/min.

Fourier transform infrared (FTIR)

FTIR spectra of all raw materials, the physical mixture and the solid dispersion were acquired using FTIR (Shimadzu, Japan) and KBr as a reference. About 5 mg of each sample was mixed with KBr and then scanned. The FTIR scan range was between 400 and 4000 cm^{-1}.

Dissolution tests

Dissolution tests of pure CUR, the physical mixture and the solid dispersion were performed in Apparatus II dissolution tester (RC-8DS, Tianjin Guoming medicinal equipment, China). The rotational speed of the paddles were set at 50 rpm. The volume of dissolution media was 900 ml. The dissolution medium was 0.25% w/v sodium lauryl sulfate (SLS). This media was selected to maintain the sink condition. The temperature was kept at 37±0.05 °C. Samples containing an equivalent amount of 30 mg CUR were tested. At predetermined time intervals, samples of 5 ml were withdrawn and an equal volume of fresh media was added to maintain the volume of the dissolution media. The withdrawn samples were filtered through cellulose membrane then diluted with the dissolution media and the concentration of CUR was determined using UV/VIS 1800 spectrophotometer (Shimadzu, Japan) at λ_{max} 430 nm. All experiments were done in triplicate [31].

Physical stability testing

To evaluate the effect of temperature and humidity on the stability of the amorphous form, samples of the prepared solid dispersion were placed in vials and stored at 40±2 °C and 75% relative humidity in (Schutzart-Mermmert stability chamber, Germany). After 3 mo samples were withdrawn. The samples were analyzed using XRD, DSC to evaluate the stability of the amorphous form of CUR. Dissolution testing of the samples was also conducted as discussed earlier.

Antioxidant test

The antioxidant test was performed by DPPH free radical assay. The test was done for the prepared solid dispersion and raw CUR. This done to determine if CUR activity on scavenging free radicals was affected by the preparation method of solid dispersion. About 1.5 mg of DPPH (2,2-diphenyl-1-picrylhudrazyl) was dissolved in ethanol and analyzed using UV spectrometer at λmax 517 nm to obtain the absorbance of the blank. Then 0.5 ml of the blank solution was added to 1.5 ml of ethanolic solution of CUR at different concentrations (20-100 µg/ml) (n=3), incubated in the dark for 15 min and then analyzed at λmax 517 nm to obtain the absorbance of the mixture. The antioxidant activity was expressed as AA% based on the following equation:

$$AA\% = \frac{(\text{absorbance of the blank} - \text{absorbance of the mixture})}{\text{absorbance of the blank}} \times 100\%$$

RESULTS AND DISCUSSION

Preliminary dissolution testing studies were conducted on the various formulation mentioned in table 1. Of the solid dispersion formulations, solid dispersion formula (SD 1:5:1) was found to produce the highest CUR release. Almost complete dissolution (98%) was achieved within one hour. The release of the other formulations was substantially less than that. The range of percent release within one hour was (26.55%-90.6%). The percent release of pure CUR within one hour was 22.9%. Solid dispersion formula (SD 1:5:1) was considered the best formula and selected for thorough investigations.

X-ray diffraction

XRD patterns for the raw materials and the prepared solid dispersion (SD 1:5:1) are shown in fig. 2. In fig. 2, pure CUR showed several characteristic peaks between 10 and 30 (2-theta) which indicate a highly crystalline material. The major peaks of CUR were observed at angles 14.56, 17.16 and 21.05 ° which is similar to what was previously reported [32]. Inulin shows peaks between 10 and 25 (2-theta) which is related to its crystalline nature. Meanwhile, Neusilin did not show any peaks as it is an amorphous substance.

By comparing the same ratios of the two formulas of CUR, one prepared by solid dispersion while the other is the physical mixture of the same components, it appears that the physical mixture retained the same crystalline peaks of its components while in the solid dispersion CUR peaks disappeared. This indicates that CUR prepared by freeze drying and dispersed in the carrier is present in the amorphous form.

Differential scanning calorimetry (DSC)

The DSC thermograms of raw materials are shown in fig. 3. CUR shows a sharp endothermic peak at 180 °C. These findings are in agreement with previously reported study[33]. This sharp melting peak indicates that pure CUR exists in the crystalline state. Inulin showed an endothermic peak at 169.5 °C. This peak is related to the melting of the substance. Meanwhile, Neusilin did not have any endothermic peak due to it amorphous nature.

Fig. 3 also shows the DSC thermogram for the prepared solid dispersion (1:5:1). CUR in this formulation did not show any endothermic peak at 180 °C. This finding suggests that CUR is present in its amorphous form. On the other hand, the corresponding physical mixture of the same ratio showed two endothermic peaks. The first peak at 169 °C corresponds to the melting point of Inulin while the other peak at 169.5 corresponds to the melting of the CUR. The presence of these peaks in the physical

mixture indicates that CUR is present in crystalline form. The DSC Data support the results obtained by XRD data.

Finally, based on the XRD and DSC tests, it was concluded that CUR in the prepared solid dispersion was in the amorphous state.

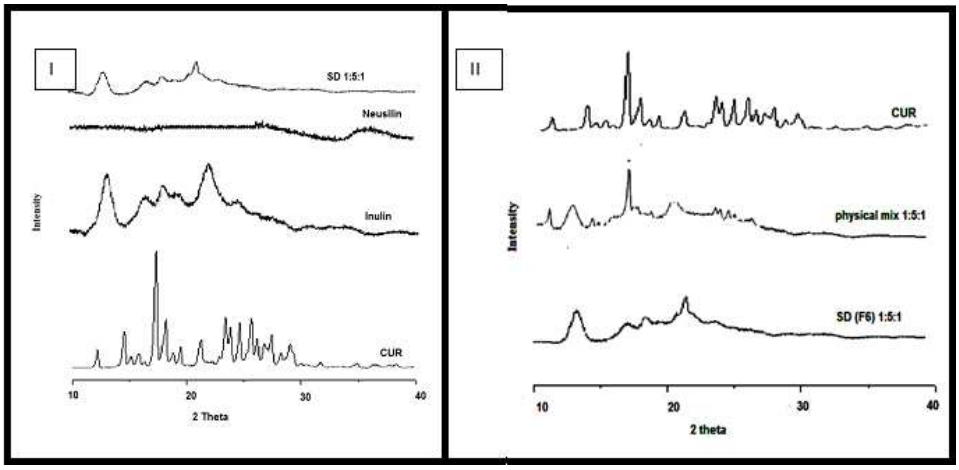

Fig. 2: I-shows the XRD pattern for the prepared solid dispersion (SD 1:5:1), Neusilin, Inulin and pure CUR. II-shows the XRD of pure CUR, physical mixture and solid dispersion (SD 1:5:1)

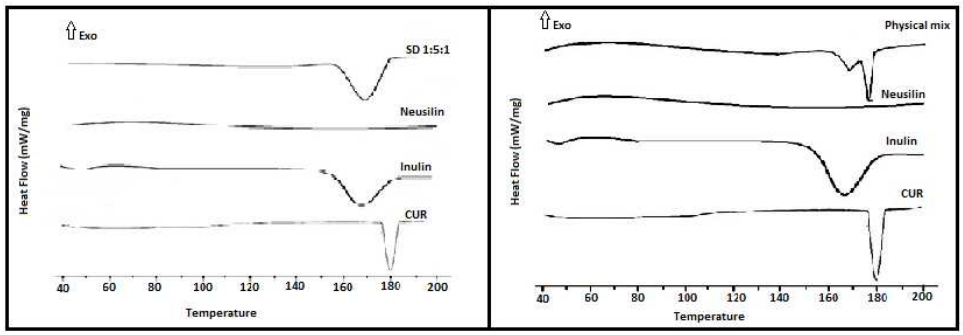

Fig. 3: DSC thermograms of pure CUR, Neusilin, Inulin and solid dispersion (SD 1:5:1) and the corresponding physical mixture

Fourier transform infrared (FTIR)

FTIR analysis was performed to provide structural information about the used materials and to detect the presence of any possible interactions between the drug and the carriers. These interactions are detected by any changes in the position or disappearance of a characteristic vibration or stretching region of the compound. FTIR spectra of CUR is shown in fig. 4. CUR shows a characteristic peak at 3450 cm^{-1} due to OH group stretching and a peak at 1650 cm^{-1} due to carbonyl functional group (C=O). Any interaction between CUR and the carriers is revealed by changing in the carbonyl peak position. FTIR of raw materials and solid dispersion (SD 1:5:1) are presented in fig. 4. The FTIR analysis of the physical mix and the solid dispersion shows that the C=O stretching of CUR was slightly shifted to a lower wavelength and the OH stretching peak disappeared. This change is attributed to the dilution effect of the carriers and hydrogen bonding between CUR and both carriers. Meanwhile, the physical mixture shows no change compared to the pure CUR other than dilution by the carriers.

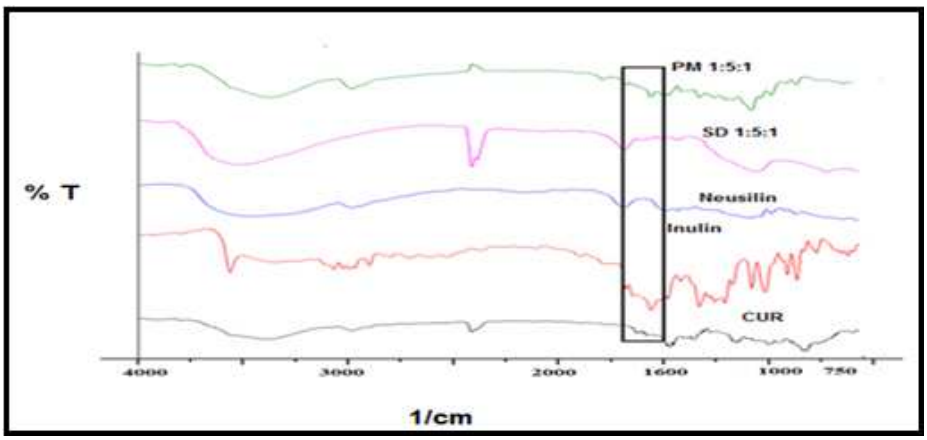

Fig. 4: FTIR spectra of CUR, Inulin, Neusilin, solid dispersion (SD 1:5:1) and the corresponding physical mixture

Dissolution tests

An *in vitro* study was performed to find out if the amorphous form of CUR in a mixture of Inulin and/or Neusilin US2 can improve the dissolution rate and enhance the total amount of drug dissolved in the media. The dissolution profile of the optimum solid dispersion (SD 1:5:1) was compared with the corresponding physical mixture and the pure crystalline CUR. Fig. 5 shows the dissolution profiles of pure CUR, the solid dispersion (SD 1:5:1) and the corresponding physical mixture. During the dissolution testing, freshly prepared samples were studied. After 1 hour in the dissolution media, the order of percent release was as follows; pure CUR<physical mixture<solid dispersion where pure CUR samples were able to release only 23% in comparison with 37.8% for physical mixture and 98% for the solid dispersion. Many factors could contribute to this result. Primarily, CUR is present in the amorphous state in the solid dispersion. XRD and DSC results confirmed the amorphous state of CUR in the prepared solid dispersion. Secondly, the prepared solid dispersion showed better flowability and lower agglomeration potential. This is attributed to the fact that Neusilin US2 is a highly porous spherical particle with a large surface area. This leads to more contact points with the dissolution media and the drug. In addition, the solid dispersion formula had better wettability due to the fact that Inulin is a surface active agent. Inulin was also reported to enhance the dissolution and solubility of drugs by coating drug particles and enhancing wettability [26, 28-30]. Thus, it was concluded that preparation of CUR solid dispersion in a carrier combination of Inulin and Neusilin by freeze drying has resulted in a vast improvement in the dissolution properties of CUR. This formula is expected to improve the oral bioavailability of CUR as compared with the raw CUR.

Physical stability testing

Most amorphous drugs in solid dispersions tend to recrystallize at high temperature and humidity. To evaluate the effect of aging on the performance of amorphous CUR in the solid dispersion formula, a three-month accelerated stability study was performed. It is known that the stability of the amorphous state is affected by the storage temperature and the humidity, which can influence and affect the recrystallization rate [34]. The rate of recrystallization usually accelerated with the increase in temperature and humidity. Consequently, storage conditions were selected to be 40 °C/75%RH to evaluate their influence on the solid state stability of the prepared solid dispersion. These conditions are frequently used during accelerated stability studies of pharmaceutical products.

The optimum solid dispersion formula (SD 1:5:1) was selected to be tested for aging as it has the fastest dissolution rate and contains an amorphous form of the drug. DSC and XRD were used to evaluate the influence of the storage conditions on the stability of solid form of CUR in the solid dispersion. The influence of aging on the *in vitro* drug release was also evaluated.

XRD, DSC, and dissolution profile results after storage for 3 mo in the stability chamber are shown in fig. 6 along with the results for the freshly prepared samples. Fig. 6-I shows the XRD data for the freshly prepared and aged sample of solid dispersion (SD 1:5:1). The two XRD profiles are identical. No peak has appeared. These findings indicate that CUR in the solid dispersion remained in the amorphous form and there is no sign of any crystallization is taking place. DSC data after aging, presented in fig. 6-II, did not show any endothermic peak at 180 °C related to the melting point of crystalline CUR. This indicates that CUR in solid dispersion remained in the amorphous form. These results go along with XRD data. The DSC thermogram of aged solid dispersion sample shows a broad peak around 90 °C. This peak is linked to the evaporation of water present in the sample as it was stored in the humid environment. Water uptake by the samples verifies the high hydrophilicity and wettability of the prepared solid dispersion. The results of the *in vitro* dissolution testing exist in fig. 6-III for the solid dispersion formula (SD 1:5:1) before and after storage in the stressed condition for 3 mo. The results showed that the percent drug release after one hour of dissolution testing was 97.5% for the aged sample in comparison with 98% for the freshly prepared solid dispersion. Statistical testing reveals that the difference between the two values was insignificant.

Overall, it can be concluded that CUR in the solid dispersion formula (SD 1:5:1) was physically stable and Inulin and Neusilin were capable of preventing the conversion of CUR from the amorphous state into the crystalline state and were capable of preserving the dissolution profile of CUR for three months under the harsh condition of elevated temperature and humidity.

Antioxidant test

Antioxidant test by DPPH free radical assay was performed on both pure CUR and the selected optimum solid dispersion formula (SD 1:5:1). This test determines if the solid dispersion technique and the additives used during preparation have any effect on the free radical scavenging activity of CUR. In general, DPPH (1,1-Diphenyl-2-picryl-hydrazyl) is a free radical that act as a trap "scavenger "for other chemicals. Interactions of DPPH with other chemicals are used as an indicator of the antioxidant activity of the chemical. DPPH has a strong absorption peak at 517 nm, giving it a deep violet color in solution. Interaction of DPPH with other compounds leads to change of the color from violet to pale yellow during antioxidant activity tests due to the neutralization of the free radical. CUR is used as an antioxidant to treat many inflammatory diseases. To ensure that the antioxidant activity of CUR in the solid dispersion formulation, antioxidant activity test was performed using DPPH. The intensity of color of the solution was estimated by measuring the absorbance using UV at 517 nm. Fig. 7 shows the antioxidant test for the prepared solid dispersion (SD 1:5:1) and pure CUR. Fig. 7. I, compares the absorbance of the ethanolic solution of DPPH in the presence of different concentrations of CUR as a pure form and in the solid dispersion formulation. The profiles of the two CUR forms were identical indicating the same interaction with DPPH. Fig. 7. II, compares the antioxidant activity of CUR present as pure form and in the solid dispersion formulation with varying concentrations of CUR. The same conclusion was obtained that CUR activity in the solid dispersion formulation did not altered by preparation method of additives used.

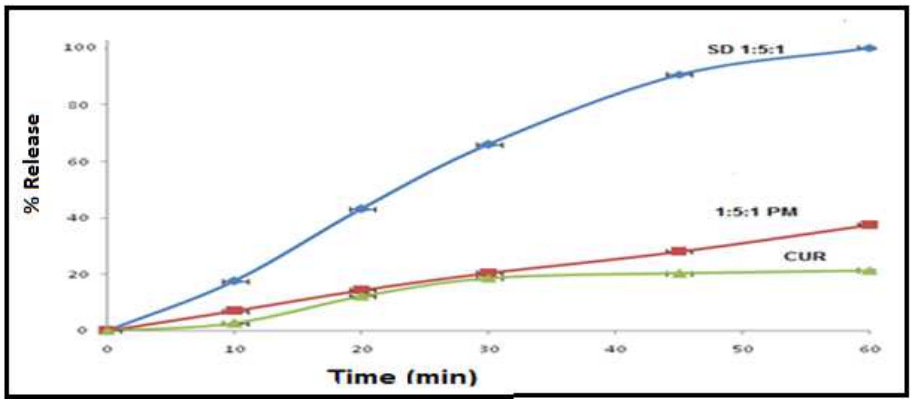

Fig. 5: Dissolution profiles of CUR, physical mixture and solid dispersion (SD1:5:1) (mean±SD, n=3)

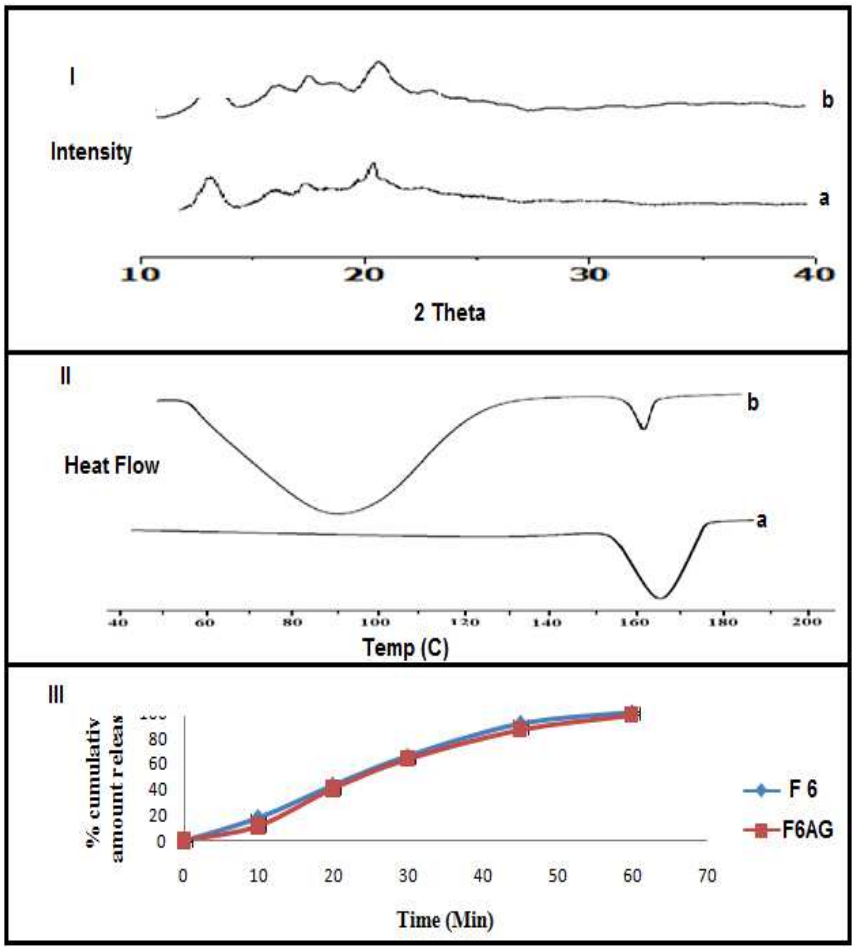

Fig. 6: (I) XRD pattern of (a) freshly prepared solid dispersion (SD 1:5:1) (b) aged solid dispersion (SD1:5:1) after 3 mo of storage in 40 °C and 75%RH. (II) DSC thermograms of (a) Freshly prepared solid dispersion (SD 1:5:1) (b) Aged solid dispersion (SD 1:5:1) after 3 mo of storage in 40 °C and 75%RH. (III) Release profile of freshly prepared solid dispersion (SD 1:5:1) and aged solid dispersion (SD 1:5:1) after 3 mo of storage in 40 °C and 75% RH (mean±SD, n=3)

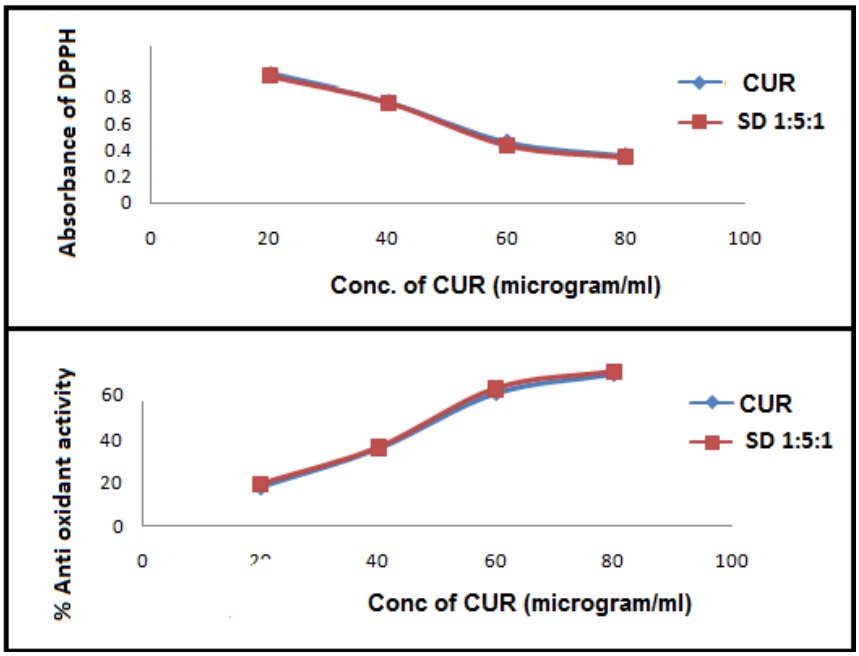

Fig. 7: (I) Effect of different concentrations of CUR pure or in solid dispersion (SD 1:5:1) on absorbance of DPP.(II)Scavenging effect of pure CUR pure or in solid dispersion (SD 1:5:1) on DPPH at different concentrations (mean±SD, n=3)

CONCLUSION

The findings clearly show that preparing CUR in solid dispersion by the freeze-drying technique was successful in improving the dissolution properties of CUR. Combinations of Inulin and NeusilinUS2 in the solid dispersion were capable of preserving the amorphous form of CUR in the formulation. The optimized solid dispersion did not only preserve the release properties but also maintained the antioxidant activity of CUR. This formulation is expected to be an effective delivery system for CUR.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICTS OF INTERESTS

The authors declare no conflict of interest

REFERENCES

1. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Altern Med Rev 2009;14:141-53.
2. Banerjee S, Singh SK, Chowdhury I, Singh R. Combinatorial effect of curcumin with docetaxel modulates apoptotic and cell survival molecules in prostate cancer. Front Biosci (Elite Ed) 2017;9:235-45.
3. Bar Sela G, Epelbaum R, Schaffer M. Curcumin as an anti-cancer agent: a review of the gap between basic and clinical applications. Curr Med Chem 2010;17:190-7.
4. Moghadamtousi SZ, Kadir HA, Hassandarvish P, Tajik H, Abubakar S, Zandi K. A review on the antibacterial, antiviral, and antifungal activity of curcumin. Biomed Res Int 2014. Doi:10.1155/2014/186864.
5. Noorafshan A, Ashkani-Esfahani S. A review of therapeutic effects of curcumin. Curr Pharm Des 2013;19:2032-46.
6. Sharma S, Saraogi GK, Kumar V. Development of spectrophotometric methods for simultaneous determination of artesunate and curcumin in a liposomal formulation. Int J Appl Pharm 2015;7:18-21.
7. Abbas SH, Abdulridha MK, Najeb AA. The potential benefit of curcumin adjuvant therapy to the standard helicobacter pylori eradication therapy in patients with peptic ulcer disease. Asian J Pharm Clin Res 2017;10. Doi:10.22159/ajpcr.2017.v10i5.17462.
8. Shelat P, Mandowara VK, Gupta DG, Patel S. Formulation of curcuminoid loaded solid lipid nanoparticles in order to improve oral bioavailability. Int J Pharm Pharm Sci 2015;7:278-82.
9. Phongpradist R, Chaiyana W, Anuchapreeda S. Curcumin-loaded multi-valent ligands conjugated-nanoparticles for anti-inflammatory activity. Int J Pharm Pharm Sci 2015;7:203-8.
10. Kaur J, Bawa P, Rajesh SY, Sharma P, Ghai D, Jyoti J, *et al.* Formulation of curcumin nanosuspension using box-behnken design and study of the impact of drying techniques on its powder characteristics. Asian J Pharm Clin Res 2017;10:43.
11. Paradkar A, Ambike AA, Jadhav BK, Mahadik KR. Characterization of the curcumin-PVP solid dispersion obtained by spray drying. Int J Pharm 2004;271:281-6.
12. Hu L, Shi Y, Li JH, Gao N, Ji J, Niu F, *et al.* Enhancement of oral bioavailability of curcumin by a novel solid dispersion system. AAPS PharmSciTech 2015;16:1327-34.
13. Wang X, Jiang Y, Wang YW, Huang MT, Ho CT, Huang Q. Enhancing anti-inflammation activity of curcumin through O/W nanoemulsions. Food Chem 2008;108:419-24.
14. Allijn IE, Schiffelers RM, Storm G. Comparison of pharmaceutical nanoformulations for curcumin: enhancement of aqueous solubility and carrier retention. Int J Pharm 2016;506:407-13.
15. Sadeghi F, Ashofteh M, Homayouni A, Abbaspour M, Nokhodchi A, Garekani HA. Antisolvent precipitation technique: a very promising approach to crystallize curcumin in presence of polyvinyl pyrrolidon for solubility and dissolution enhancement. Colloids Surf B 2016;147:258-64.
16. Wong JJL, Yu H, Lim LM, Hadinoto K. A trade-off between solubility enhancement and physical stability upon simultaneous amorphization and nanonization of curcumin in comparison to amorphization alone. Eur J Pharm Sci 2018;114:356-63.
17. Donsì F, Wang Y, Li J, Huang Q. Preparation of curcumin sub-micrometre dispersions by high-pressure homogenization. J Agric Food Chem 2010;58:2848-53.
18. Teixeira CCC, Mendonça LM, Bergamaschi MM, Queiroz RHC, Souza GEP, Antunes LMG, *et al.* Microparticles containing curcumin solid dispersion: stability, bioavailability and anti-inflammatory activity. AAPS PharmSciTech 2016;17:252-61.
19. Raymond C Rowe PJs. Handbook of pharmaceutical Excipients. fifth edition ed. London; 2006.
20. Allgeier MC, Piper JL, Hinds J, Yates MH, Kolodsick KJ, Meury R, *et al.* Isolation and physical property optimization of an amorphous drug substance utilizing a high surface area magnesium aluminometasilicate (Neusilin((R)) US2). J Pharm Sci 2016;105:3105-14.
21. Gupta MK, Vanwert A, Bogner RH. Formation of physically stable amorphous drugs by milling with Neusilin. J Pharm Sci 2003;92:536-51.
22. Shah A, Serajuddin AT. Conversion of solid dispersion prepared by acid-base interaction into free-flowing and tabletable powder by using Neusilin(R) US2. Int J Pharm 2015;484:172-80.
23. Sruti J, Patra Ch N, Swain SK, Beg S, Palatasingh HR, Dinda SC, et al. Improvement in dissolution rate of cefuroxime axetil by using poloxamer 188 and neusilin US2. Indian J Pharm Sci 2013;75:67-75.
24. Khanfar M, Al-Nimry S. Stabilization and amorphization of lovastatin using different types of silica. AAPS PharmSciTech 2017;18:2358-67.
25. Amorij JP, Saluja V, Petersen AH, Hinrichs WL, Huckriede A, Frijlink HW. Pulmonary delivery of an inulin-stabilized influenza subunit vaccine prepared by spray-freeze drying induces systemic, mucosal humoral as well as cell-mediated immune responses in BALB/c mice. Vaccine 2007;25:8707-17.
26. Mensink MA, Frijlink HW, van der Voort Maarschalk K, Hinrichs WL. Inulin, a flexible oligosaccharide. II: a review of its pharmaceutical applications. Carbohydr Polym 2015;134:418-28.
27. Mensink MA, Frijlink HW, Van der Voort Maarschalk K, Hinrichs WL. Inulin, a flexible oligosaccharide I: review of its physicochemical characteristics. Carbohydr Polym 2015;130:405-19.
28. Visser MR, Baert L, Klooster G, Schueller L, Geldof M, Vanwelkenhuysen I, *et al.*,Inulin solid dispersion technology to improve the absorption of the BCS class IV drug TMC240. Eur J Pharm Biopharm 2010;74:233-8.
29. Fares MM, Salem MS. Dissolution enhancement of curcumin via curcumin-prebiotic inulin nanoparticles. Drug Dev Ind Pharm 2015;41:1785-92.
30. Fares MM, Salem MS, Khanfar M. Inulin and poly (acrylic acid) grafted inulin for dissolution enhancement and preliminary controlled release of poorly water-soluble Irbesartan drug. Int J Pharm 2011;410:206-11.
31. Rahman S, Telny T, Ravi T, Kuppusamy S. Role of surfactant and pH in the dissolution of curcumin. Indian J Pharm Sci 2009;71:139-42.
32. Li J, Lee IW, Shin GH, Chen X, Park HJ. Curcumin-eudragit(R) E PO solid dispersion: a simple and potent method to solve the problems of curcumin. Eur J Pharm Biopharm 2015;94:322-32.
33. Athira GK, Jyothi AN. Preparation and characterization of curcumin loaded cassava starch nanoparticles with improved cellular absorption. Int J Pharm Pharm Sci 2014;6:171-6.
34. Kojo Y, Matsunaga S, Suzuki H, Sato H, Seto Y, Onoue S. Improved oral absorption profile of itraconazole in hypochlorhydria by self-micellizing solid dispersion approach. Eur J Pharm Sci 2017;97:55-61.