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Research Article

Agglomeration of Celecoxib by Quasi Emulsion Solvent Diffusion Method: Effect of Stabilizer

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Abstract

Purpose: The quasi-emulsion solvent diffusion (QESD) has evolved into an effective technique to manufacture agglomerates of API crystals. Although, the proposed technique showed benefits, such as cost effectiveness, that is considerably sensitive to the choice of a stabilizer, which agonizes from a absence of systemic understanding in this field. In the present study, the combination of different solvents and stabilizers were compared to investigate any connections between the solvents and stabilizers.

Methods: Agglomerates of celecoxib were prepared by QESD method using four different stabilizers (Tween 80, HPMC, PVP and SLS) and three different solvents (methyl acetate, ethyl acetate and isopropyl acetate). The solid state of obtained particles was investigated by differential scanning calorimetry (DSC) and Fourier transform infrared (FT-IR) spectroscopy. The agglomerated were also evaluated in term of production yield, distribution of particles and dissolution behavior.

Results: The results showed that the effectiveness of stabilizer in terms of particle size and particle size distribution is specific to each solvent candidate. A stabilizer with a lower HLB value is preferred which actually increased its effectiveness with the solvent candidates with higher lipophilicity. HPMC appeared to be the most versatile stabilizer because it showed a better stabilizing effect compared to other stabilizers in all solvents used.

Conclusion: This study demonstrated that the efficiency of stabilizers in forming the celecoxib agglomerates by QESD was influenced by the HLB of the stabilizer and lipophilicity of the solvents.

Introduction

Spherical crystallization technology which has been used to enlarge the size of the particles, has attracted the attention of pharmaceutical industry in the last decades, where small crystals are often produced by crystallization but their handing out is then very difficult and costly. The technology has the capability to agglomerates the crystals directly inside the reactor where the properties of agglomerates can be controlled.[1-3] However, this method is still not widely employed in pharmaceutical industry. This could be due to the lack of understanding and governing the process parameters that permit the efficient production of agglomerates.

In general, spherical crystallization methods for the preparation of agglomerates can be classified into two main categories spherical agglomeration and the quasi emulsion solvent diffusion (QESD). The spherical agglomeration consists of crystallization of fine crystals of a drug followed by the aggregation by employing water –immiscible solvents (e.g., methylene chloride or chloroform, as binder liquid.[4,5] Nonetheless, in case of using these solvents, they can increase ecological and human safety worries over solvents left in the samples, thus they are not suggested for the routine production process. Conversely, QESD is built on the miscibility of solvents with water. QESD technique consists of the emulsification of organic solution of drug which is miscible with water and it also contains stabilizers. On shifting a temporary O/W emulsion into water, droplets solidify promptly as a result of the diffusion of the organic solvent out of the droplets to the external phase. Indeed, in this method, the intermediate step of agglomeration is establishing an emulsion, which is turned into agglomerates. The process is reliant on sensitive to the selection of solvent and the stabilizer. The stabilizer plays the role of dispersing emulsion droplets and preventing the emulsion droplets from coalescence. This critical point distinguishes QESD from simple precipitation processes. Unfortunately, the selection is dependent on the empirical approaches. At present, the manufacture of drug agglomerates via QESD needs a number of trial and error experiments since the systematic knowledge about the process is absent. Despite the industrial significance of the process, the

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selection of a stabilizer in agglomeration techniques has not systematically been studied. Furthermore, as in previous studies each researcher has used different processing and characterization conditions, thus, it is extremely difficult to compare the results of previous reports. The main aim of the present study is to show that performing experiments under similar conditions can generate a knowledge which the crystallization process in a controlled fashion can be tailored to produce agglomerates.

In the present investigation, the combinations of 2 commonly used stabilizers (HPMC and PVP), 2 surfactants (Tween 80 and SLS) and 3 solvents (methyl acetate, ethyl acetate and isopropyl acetate) were investigated under constant processing and characterization conditions.

Materials and Methods

Materials

Celecoxib (CLX) was supplied by (Arastoo chemical company, Iran), solvents (Merck, Germany), HPMC (Colorcon, UK), povidon (PVP K30) (BASF, Ludwigshafen, Germany), Tween 80 (Merck Schuchardt OHG, Hohenbrunn, Germany), SLS (Scharlau Chemie SA, the
European Union) were used.

Preparation of agglomerates

Three different organic solvents as good solvent including methyl acetate (MA), ethyl acetate (EA), and isopropyl acetate (IPA) were employed as a dispersed phase for making oil-in-water emulsions (O/W). Crystallization was carried out in a cylindrical vessel equipped with three baffles. Celecoxib (CLX) was dissolved in 15 ml of good solvent. The solvent solutions were then poured dropwise during 3 min, under stirring (500 rpm), into 485 ml of water containing 0.1% w/v emulsifier. Tween 80, SLS, PVP or HPMC were used as emulsifiers. After 15 min agitation by a propeller type stirrer, the agglomerates were separated from the solution by filtration under vacuum and then were placed in a thin layer in an oven at 60°C for 3 h. The solubility of organic solvents in water was the basis of the selection of the solvents in making solvent-in-water emulsion.[6]

Determination of solubility

The solubility of CLX was investigated, by adding the excess drug particles in the solvents and shaking the glass vials for specific time until reaching equilibrium conditions. A 0.45 µ- membrane filter solution was used to filter the solutions. UV-Spectrophotometer was used to determine the absorbance of the filtrate solutions after suitable dilution. The experiments were undertaken at 25 ± 0.1°C. The mean of three determinations was used to calculate the solubility of the drug in the solvents.

The agglomerates characterization

Particle size:An optical microscope (Nikon Labophot, Tokyo, Japan) was used to determine the size of agglomerates and their primary crystals. To measure the initial size of crystals of the agglomerates, the agglomerates were fragmented in distilled water containing polysorbate 80 (Tween 80; 0.05%) using ultrasonicator (VC 130, Sonics and Materials Inc., USA) at 100W before determining the size of particles. Mineral oil was used to suspend a small amount of powder and the suspension was spread onto a microscope slide to measure the size of the particles by optical microscope via a miniature video camera. The largest diameter of at least 100 particles under the microscope was measured by the scion image analysis software. We confirmed that the dissolution of the drug in the dispersing medium was negligible for the measurement of particle size due to its extremely low solubility.

To measure the agglomerates size, light microscopy pictures of the particles were captured. The mean particle size of a single particle was denoted as the mean length of the distance determined at 2° intervals connecting two outline points passing through the center of gravity of the particle. Each determination was carried out on a minimum of 100 particles.

Sieving: It has been shown that the size of particles could affect the mechanical and dissolution performance of particles.[7] In order to minimize the effects of CLX particle size on friability and dissolution rate of obtained samples, the same sieved fraction of 250 - 500 µm was used to characterize all CLX samples. CLX crystallized samples were poured separately onto the top of 500 µm sieve which was placed above a 250 µm sieve. The vibratory mechanical shaker was then tightened closely and operated for 10 min, after which the particles retained on the 250µm sieve were collected.

Determination of agglomeration yield: In order to determine the percentage yield, the obtained agglomerates were dried at 60 °C for 3 h and the final weight was recorded after drying. Then the following equation was used to calculate the percentage yield (Eq. 1). The procedure was repeated for three batches of the samples.

$$\text{Agglomeration yield (\%)} = \frac{\text{Practical mass (agglomerates)}}{\text{Theoretical mass (drug)}} \times 100 \quad \text{Eq. 1}$$

Dissolution studies

The agglomerates with diameters between 250 and 500 µm was selected for dissolution studies. The dissolution was performed by the paddle method and the dissolution medium was distilled water. The paddle speed was set at 50 rpm and the bath temperature was kept at 37 °C. The sink conditions was maintained by adding 0.25% (w/v) SDS in 1000 ml distilled water.[8,9] Each vessel was introduced the amount of sample equivalent to 40 mg celecoxib. At pre-determined time

intervals, samples were withdrawn from the vessels through a 5 µm membrane filter (Millipore) followed by their spectrophotometric analysis employing a UV detector (UV-160A, Shimadzu, Japan) at 253 nm. The number of dissolution run was three. The initial results showed that SDS did not have any interference with celecoxib at 253 nm.

FT-IR spectroscopy

Infrared spectra were recorded using an FT-IR spectrophotometer (M-B-100, Bomem, Canada) utilizing potassium bromide discs. These KBr discs containing 2-3 mg drug were made by grinding 2-3 mg of sample with 25-50 mg of potassium bromide and compressed by a hydraulic press (Riken Seiki, Japan) at 10 MPa for 2 min. The data region was 4000–500 cm^{-1}.

Differential scanning calorimetery (DSC)

Different polymorphic composition of pharmaceutical powders with different melting points can be studied by DSC. The DSC was calibrated using indium and lead standards. Samples of the crystals (3–5 mg) were heated (range 25-250°C) at 10 °C/min in crimped aluminum pans under a nitrogen atmosphere. The enthalpy of fusion and melting point were automatically calculated using the software provided by Shimadzu (Japan).

Statistical evaluation of data

All data reported in the present study were the mean ± standard deviation (SD). ANOVA was used to compare the mean values (more than two groups) of the data obtained and comparison between the two means was determined using the Tukey's test with statistical significance evaluated at $P < 0.05$.

Results and Discussion

Mechanism of agglomeration of crystals

The production of agglomerates by QESD technique starts with the preparation of O/W emulsion (in this case, oil is an organic solvent which is also partially miscible with water and it contains the drug). The oil phase acts as an internal phase. MA, EA and IPA solvents with different water miscibility (4.3-25% v/v) and having low toxicity were employed to manufacture the primary emulsion.[6] Preliminary results showed that, there are a number of variables can have an impact on the globule size of the emulsions (internal phase) and possibly the behavior of the resulting solid particles. The parameters affecting the droplet size and properties of the particles could be phase ratio, the stabilizer type and its concentration, mixing technique, processing temperature, and technological conditions of manufacturing. In order to cut down the number of experiments, the emulsions were manufactured at a constant phase ratio using pure water as continuous phase and 0.1 % stabilizer in identical condition, while the influence of different stabilizers was investigated. Safe and efficient stabilizers (Tween 80, HPMC, PVP and SLS) were selected in the preparation of agglomerates. It should be mentioned that even when pure water was used as antisolvent, the size of agglomerates was larger compared to the starting material. This can be explained in terms of the phase separation created upon mixing of partially water miscible solvents and water. To explain the formation of the agglomerates, 3 steps must be taken into account to: formation of emulsion droplets, creation of supersaturation by mass transfer and crystallization of drug into droplets. It has been recognized that the size of the obtained particles is reliant on the size of droplets throughout the emulsification step.[10] It can be concluded that as the size of droplets controls the size of the final particles, therefore, smaller droplets can produce smaller particles.

During the emulsification of organic solution in the aqueous phase, a hydrophobic surface is formed and the energy of the system increases. In order for the system to have low surface free energy the droplets normally aggregate and consequently coarse particles with wide particle size distribution (PSD) are formed. If the added stabilizing agent has any affinity to the surface of the droplets, then, it can cover the newly formed surface spontaneously. Therefore, the surface energy and hence the enthalpy of the system are reduced.[11]

In fact, the adsorption of stabilizer to the surface of the formed droplets, once the optimum packing of the stabilizer has been reached, can hinder coalescence of droplets through steric or electrostatic stabilization and thus droplets with smaller size and tight distribution are produced.[12-15] As mentioned above, the formation of finer and more homogeneous droplets, in turn, allows the formation of smaller particles with narrower PSD.

It can be predicted that the nature of the stabilizer could be the main reason for the efficient formation of droplets and stabilization of the agglomerates. The stabilizer should show sufficient tendency to the droplet surface as well as they should form a s mechanical and thermodynamic barrier at the interface that retards the approach and coalescence of individual emulsion droplets.[16] If the stabilizer has a hydrophobic region, it will have a greater affinity to organic solution droplets (hydrophobic droplets), thus, more surface coverage will be achieved. On the other hand, in order to avoid the aggregation of particles and encourage segregation, it is necessary that a stabilizer should posses a hydrophilic moiety with sufficient kinetic energy.[17]

Particle size

Table 1 summarizes particle size results for agglomerates obtained in the presence of different stabilizers prepared with MA, EA and IPA. The presence of stabilizers in the antisolvent was able to considerably decrease the particle size of the made agglomerates due to inhibition of coalescence. The most successful decrease in particle size was observed for the sample obtained in the presence of HPMC. The smallest particles with a median diameter of 100 µm

were formed in the case of IPA solvent when HPMC was present in antisolvent. HPMC not only decreased the median particle size but also capable of formation the agglomerates with narrower PSD (smaller ϭ) compared to control sample. This is a general consideration for the entire agglomerates obtained with HPMC.

Table 1. Production yield and size of agglomerates

samples	Yield (%)	Median (µm)	ϭ (µm)
MA(SLS)	88±5	215	340
MA(TW80)	62±4	420	365
MA(PVP)	77±3	260	360
MA(HPMC)	84±3	180	300
MA	92±3	830	380
EA(SLS)	86±4	270	280
EA(TW80)	77±5	570	350
EA(PVP)	83±3	525	280
EA(HPMC)	84±3	135	130
EA	91±4	610	325
IPA(SLS)	81±4	815	180
IPA (TW80)	76±4	875	195
IPA(PVP)	88±5	810	330
IPA (HPMC)	75±3	100	85
IPA	89±3	840	265

Since the polymer solutions had a very low concentration (0.1%w/v), factors such as viscosity was unlikely to play an important role in the prepation of agglomerates. Therefore, the differences may be mainly related to the affinity of the stabilizers to the droplets surfaces. These data showed that HPMC chains are firmly stick to the droplets surface and form a stable and rigid layer which can have a strong protective effect. In contrast, PVP did not reserve the physical properties of the dispersion as effectively as HPMC. PVP reduced the median particle size, however, coalescence and aggregation of particles were always observed in these batches (Figure 1). Upon emulsion formation, the stabilizer can make it stable, probably by remaining at the liquid–liquid interface and making the emulsion droplets more rigid then to prevent coalescence of the droplets. This deliberation could be stretched to explain the changes between the polymers used as stabilizer (HPMC and PVP). PVP which has a higher solubility parameter and thus lower hydrophobicity than HPMC can provide weaker protection for the droplets, because it is more likely to be present in the aqueous phase rather than being absorbed on the particle surface. In contrast, HPMC can be adsorbed onto the surface of the droplets in order to lower the interfacial tension due to its surface activity.[18] As HPMC contains hydrophobic substituents (methoxyl group) and PVP is more hydrophilic, therefore, it is expected that HPMC particles should have higher affinity for hydrophobic droplets compared to PVP. These findings are in agreement with the results reported in other works associated with stabilization of drug crystals. Rasenack et al. showed that HPMC, methylhydroxyethyl cellulose (MHEC) and polyvinyl alcohol (PVA) most effectively inhibited crystal growth of ibuprofen.[19] They found out that the particle size of ibuprofen decreased as the hydrophobicity of excipient increased. It has also been reported that the adsorption of polymers on hydrophobic silicon dioxide increased with increasing hydrophobicity of the polymers.[20] In another work, it has been reported that cellulose ethers containing hydrophobic groups (as HPMC) adsorbed onto hydrophobic siramesine surfaces while more hydrophilic derivates (as HEC) show a lower tendency for adsorbing onto the solid–liquid interface.[21] Moreover, the stability of the polymeric nanoparticles was also correlated to the affinity of the stabilizers for the droplets surface.[22,23] In a few studies which PVP was used as a stabilizer, low efficiency of PVP was referred to no distinct hydrophobic units driving the adsorption of polymer chains.[24-26] This interpretation was also verified by other hydrophilic additives. For example, Eerdenb rugh et al. showed that PEG with a mainly hydrophilic molecule structure did not stabilize the formed crystals effectively for a range of drugs studied due to its high hydrophilicity.[27]

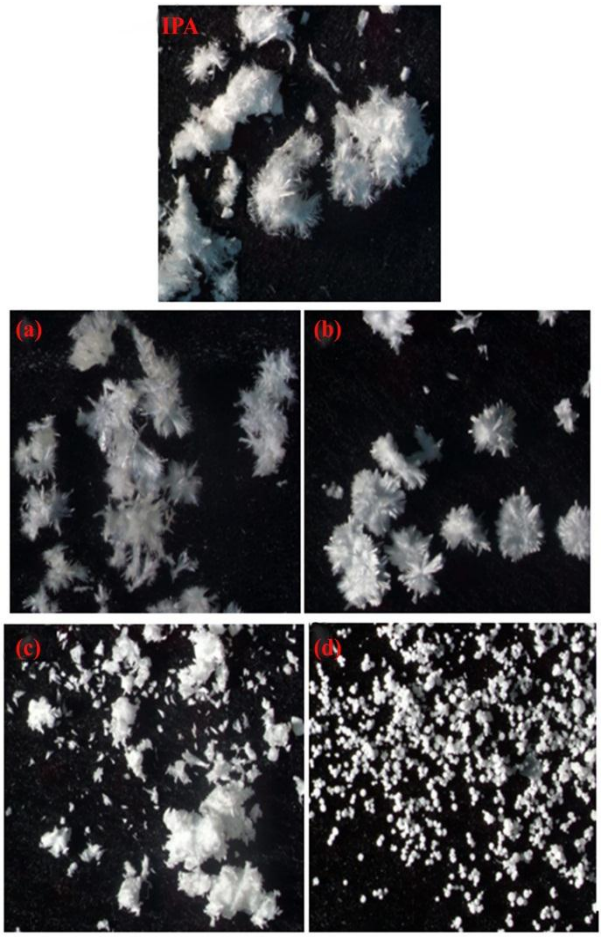

Figure 1. Optical microscopic image of agglomerates made of IPA, a: SLS, b: tween, c: PVP, d: HPMC.

Comparing the results of surfactants, SLS and tween 80, showed that when tween (non-ionic surfactant) was used as a stabilizer, larger agglomerates were formed regardless of solvent type compared to SLS (anionic surfactant). Surfactants have a hydrophobic and hydrophilic part of the molecule which are shown in Figure 2. This Figure shows the presence of polyethylene glycol tail (PEG) as hydrophilic domains and hydrocarbon chain (R groups) as hydrophobic region for tween 80 molecule. In case of SLS, the hydrophilic part of this anionic surfactant (sulphate group) has high hydrophilicity positioned in a small area. In contrast to SLS structure, polysorbate 80 with a PEG chain have a long hydrophilic chain where the hydrophilicity is not positioned in small area. It has been demonstrated that aggregation of surfactants and consequently their efficiency as stabilizer is controlled by a balanced molecular geometry.[28] A critical packing parameter, P_c as the ratio of volume to surface area is defined (equation (2))

$$P_c = \frac{v}{(a_o \times l_c)} \qquad \text{Eq. 2}$$

Where a_o is the minimum interfacial area occupied by the hydrophilic group, v is the volume of the hydrophobic tail and l_c is the maximum extended chain length of the tail in the micelle core.

In the case of tween, large interfacial area (a_o) due to large head group ethylene oxide chain leads to low the value of the packing parameter (P_c) which may contribute to low efficiency of this surfactant. Furthermore, higher efficiency of SLS may also be attributed to its smaller molecule (MW: 288) than tween 80 (MW: 1310). The small size of SLS may be expected to result in faster diffusion to the droplet surface and more rapid adsorption kinetics at the surface, to inhibit the otherwise coalescence of droplets.[29] However, since tween has higher molecular weight, it will take longer to diffuse and adsorb onto the droplets surfaces. Similar results have been reported by others where different stabilizers have been used to stabilize drug crystals and prevent their crystal growth. In these studies, it has been demonstrated that the small size of stabilizer allows it to diffuse more quickly to the surface of drug crystal and, therefore, may help stabilize it before crystallization sets in.[30,31]

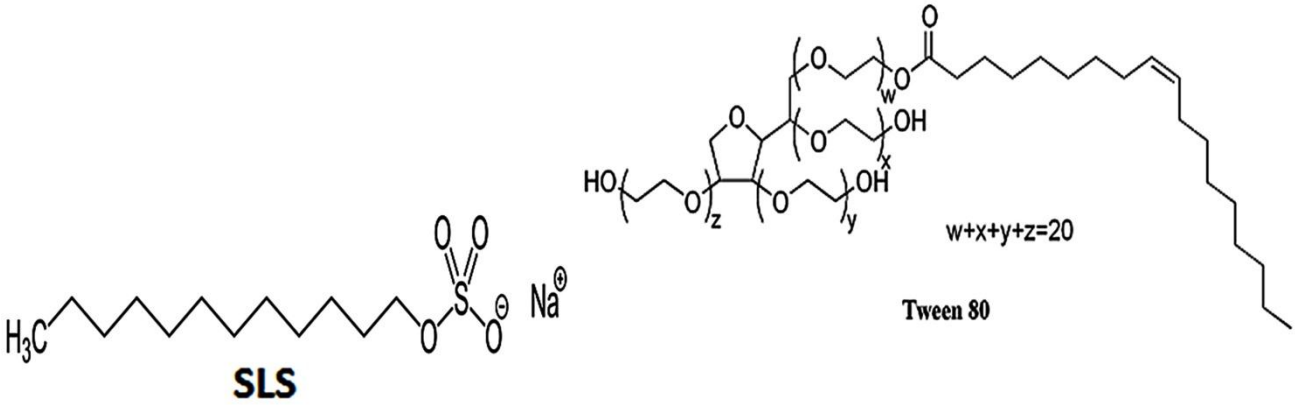

Figure 2. Structure of SLS and tween 80.

For all solvents, it was obvious that the effect of the stabilizer on the size of the agglomerates was dependent on the type of solvent. The differences between solvents could be attributed to their hydrophobicity: IPA has longest hydrocarbon chain and thus highest hydrophobicity; whereas MA with shortest hydrocarbon chain is least hydrophobic. EA takes an intermediate position in terms of hydrophobicity. On the other hand, HLB value of the stabilizers can be ranked as SLS>PVP>tween>HPMC.[31,32]

The use of SLS, PVP and tween produced moderate effects on the particle size of the agglomerates when MA and EA were employed, but in case of IPA poor effects was observed. In fact, in the case of IPA, very similar particle sizes were observed in relation to pure water if SLS, PVP and tween (Figure 1) were applied. For all solvents examined, the use of HPMC produced finer particles than those obtained using other stabilizers. However, the agglomerates made in the presence of this stabilizer became smaller and relatively more homogenous in size by increasing the hydrophobicity of the solvent and consequently, the highest efficiency of HPMC was found in the IPA solvent (Figure 3). Therefore, the efficiency of stabilizer was assumed to be influenced by the degree of hydrophoicity of the solvent.

Yield

Drug crystallized in the absence of stabilizer formed the agglomerates with a percentage yield of 89-92% (w/w), whereas all other crystallized drug – stabilizer products generated a lower yield ranging between 62 and 88 % (w/w) (Table.1). The observed changes in the shape of the agglomerates (Figure 1), and reduction in the yield are indicative that stabilizers had a marked effect on the crystallization of CLX. The effects of additives on the shape and yield of crystals have been demonstrated in many other studies. For example, in the crystallization of phenytoin in the presence of three different ester homologues of diphenylhydantoin, it has been shown that changes in

crystal habit and remarkable fall in crystal yield was due to the adsorption of additive onto the crystal faces of phenytoin.[33-35] In another study, it has been shown that the crystallization of paracetamol from water in the presence of gelatin or PVP, changed the crystal habit of paracetamol and caused a decrease in crystal yield.[36,37] The reduction in the yield of the agglomerates made in the presence of stabilizer could be due to the influence of stabilizer on drug solubility. Greater drug solubility in the presence of stabilizer (Table 2), may result in incomplete solvate of the initial crystals, leading to a reduction in the yield for agglomerates. As expected, the lowest yield of the agglomerates was found in the presence of tween, stabilizer with highest improving effect on the solubility of the drug. In the case of polymers, PVP and HPMC, the formation of viscose gel around particles by polymers and consequently generation of sticky agglomerates may also contribute to lower yield. During the process, the sticky particles adhered to the impeller and also to the crystallizer wall which these led to a reduction in the production yield.[38]

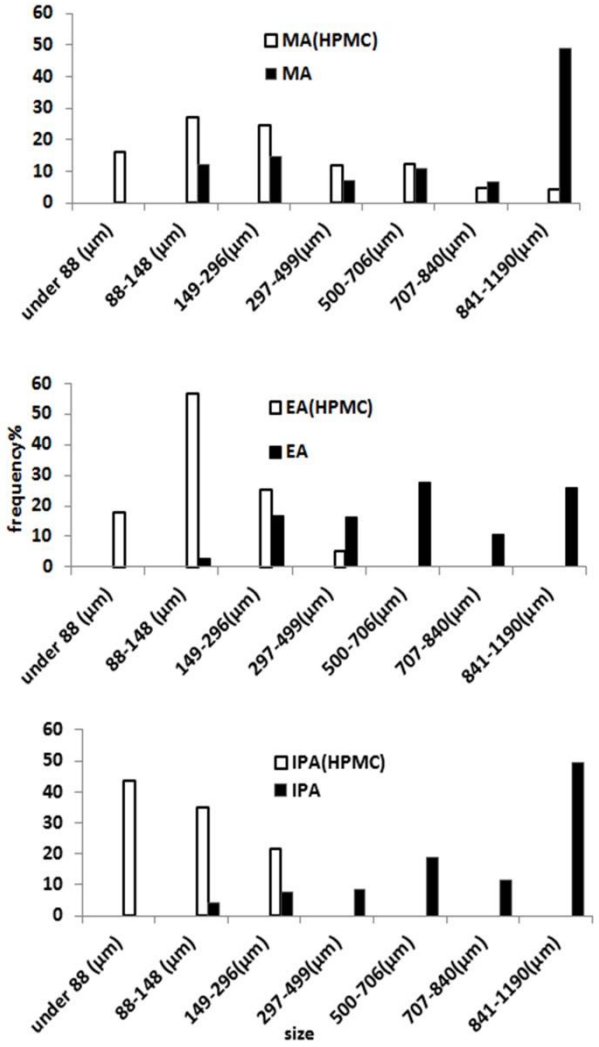

Figure 3. Particle size distribution of the agglomerates prepared in presence of HPMC.

Table 2. Solubility of drug in water containing stablizer

Stabilizers	Solubility of drug in Water containing 0.1% stablizer (µg/ml)
PVP	14.5±1.2
HPMC	15.9±2.0
SLS	18.1±2.0
Tween 80	23.5±2.2
Without stablizer	5.6±3.0

Dissolution

The dissolution behavior of the agglomerates performed in the dissolution medium containing 0.25% (w/v) SLS were shown in Figure 4. To assess the influence of stabilizers on the dissolution of the drug, the amount of drug dissolved within 90 minutes was analyzed statistically. Dissolution results indicated that stabilizers had no strong effect on the dissolution rate of CLX from the agglomerates which could be explained as follows. The most important effect of stabilizers influencing the dissolution profile of crystals is distribution behavior. Better wettability of crystals and consequently their easy dispersion in dissolution medium is the main cause of increasing dissolution rate of the drug in presence of stabilizers.[39] However, taking into account this fact that during dissolution tests the agglomerates did not break due to lack of disintegrant, the role of stabilizer in the distribution of crystals could be ruled out. Moreover, the dissolution happens from the agglomerated particle surfaces in direct contact with the dissolution medium as well as from diffusion through the water-filled pores of the agglomerates.[40] Consequently, it is supposable that different dissolution rate of drug from the agglomerates would be mainly attributed to the different porosity of the agglomerates. For example, in the case of EA, the agglomerates made in the presence of SLS dissolved a little faster than the control agglomerates which could be attributed to the moveable structure of the agglomerates (Figure 1). It is obvious that agglomerates with more pores allow faster penetration of water leading to quicker dissolution of drug from the agglomerates, as discussed above.

FT-IR

The molecular states of CLX are studied by means of FT-IR spectroscopy, according to the information on vibration in the powder composition. The FT-IR of the untreated drug was shown in Figure 5. For comparison, the FT-IR spectra of prepared agglomerates made of IPA was also shown in this Figure. In the spectrum of the CLX agglomerates made in the presence of tween, SLS and PVP, peaks relative to CLX were present without any change (data not shown), however, the shift of band of CLX at 1150 cm^{-1} to 1132 cm^{-1} was detected in the FT-IR spectrum of the agglomerates prepared in the present of HPMC. The FT-IR spectrum of celecoxib showed diagnostic bands at 1345 and 1150 cm^{-1} (S=O

asymmetric and symmetric stretching) and at 1227 cm^{-1} (C-F stretching). Furthermore, medium intensity bands at 3334 and 3227 cm^{-1} (N-H stretching vibration of SO_2NH_2 group) were seen as a doublet.[41,42] Good match between the spectrum of the agglomerates prepared in absence of stabilizer and untreated drug revealed that the crystallization process does not affect the chemistry composition of the drug. In the spectrum of the CLX agglomerates made in presence of tween, SLS and PVP, peaks relative to CLX were present demonstrating no interactions between the drug and the stabilizers (data not shown). However, the negative shift of symmetric S=O group of CLX from 1150 cm^{-1} to 1132 cm^{-1} was observed in the FT-IR spectrum of the agglomerates prepared in the present of HPMC. Concerning the molecular structure of the celocoxib and HPMC the formation of hydrogen bonding is possible. The hydrogen bonding could be formed between the S=O (proton acceptor) of CLX and OH (proton donor) group of HPMC. FT-IR spectrum of these agglomerates supports our assumption that HPMC to be the most efficient stabilizer.

Differential scanning calorimeter (DSC)

DSC analyses were performed to differentiate any changes in solid state of CLX in various formulations. Figure 6 shows the DSC thermograms of original celecoxib and different samples obtained by IPA in presence of different stabilizers. This Figure demonstrated the uniformity of crystalline structure in all samples. The results ruled out any significant difference between melting points of original CLX (160 °C) and the treated samples. All samples, irrespective of used stabilizer exhibited a distinctive sharp peak (melting point), which indicated that the CLX was unaffected by hydration or solvation during crystallization with different stabilizers.

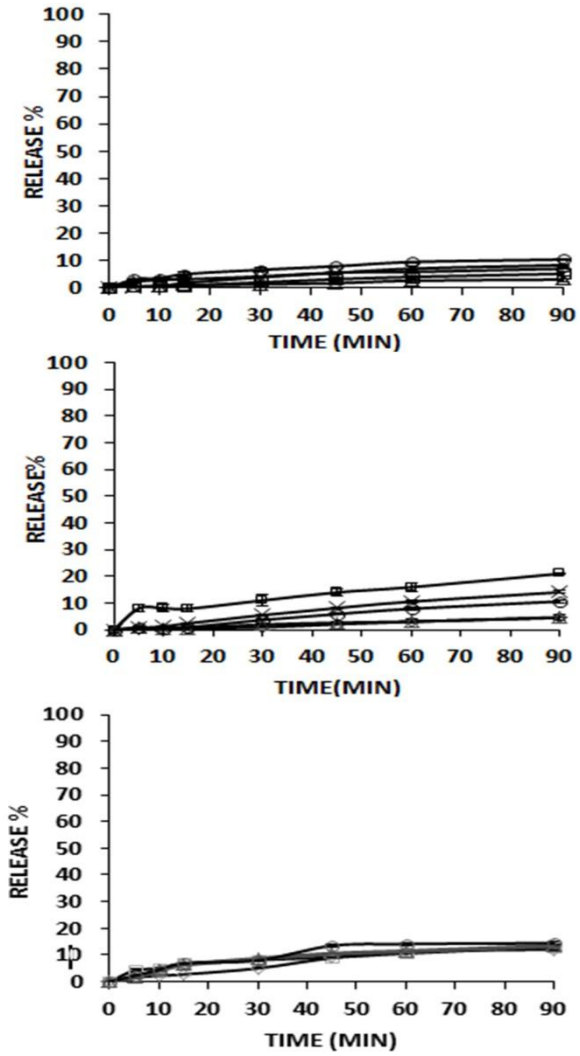

Figure 4. Dissolution profile of the agglomerates prepared with (from top) MA, EA and IPA; □: SLS, ◊: tween, Δ: PVP, ×: HPMC, ○: without stabilizer.

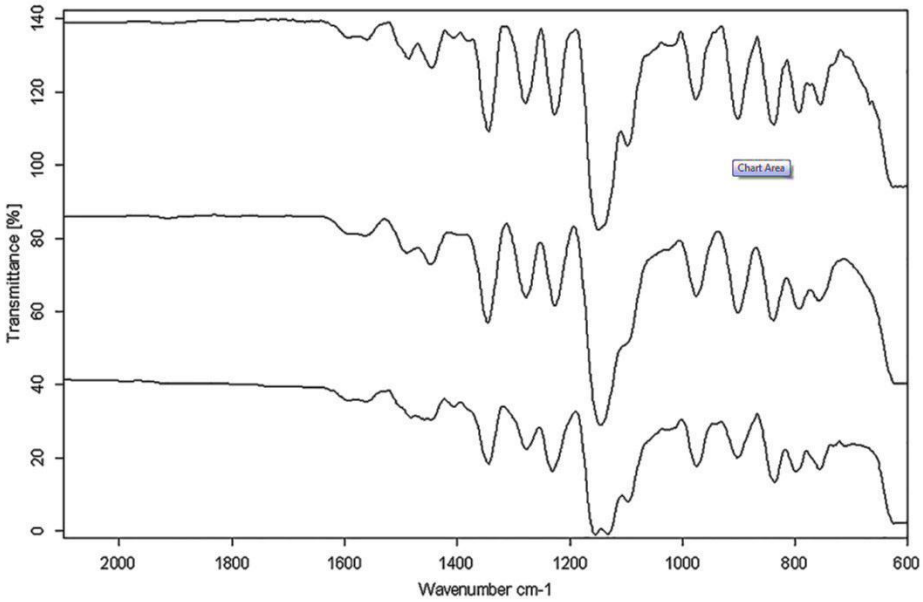

Figure 5. FT-IR spectrum of the samples from top; untreated CLX, agglomerates prepared with IPA without stabilizer and agglomerates prepared with IPA in presence of HPMC.

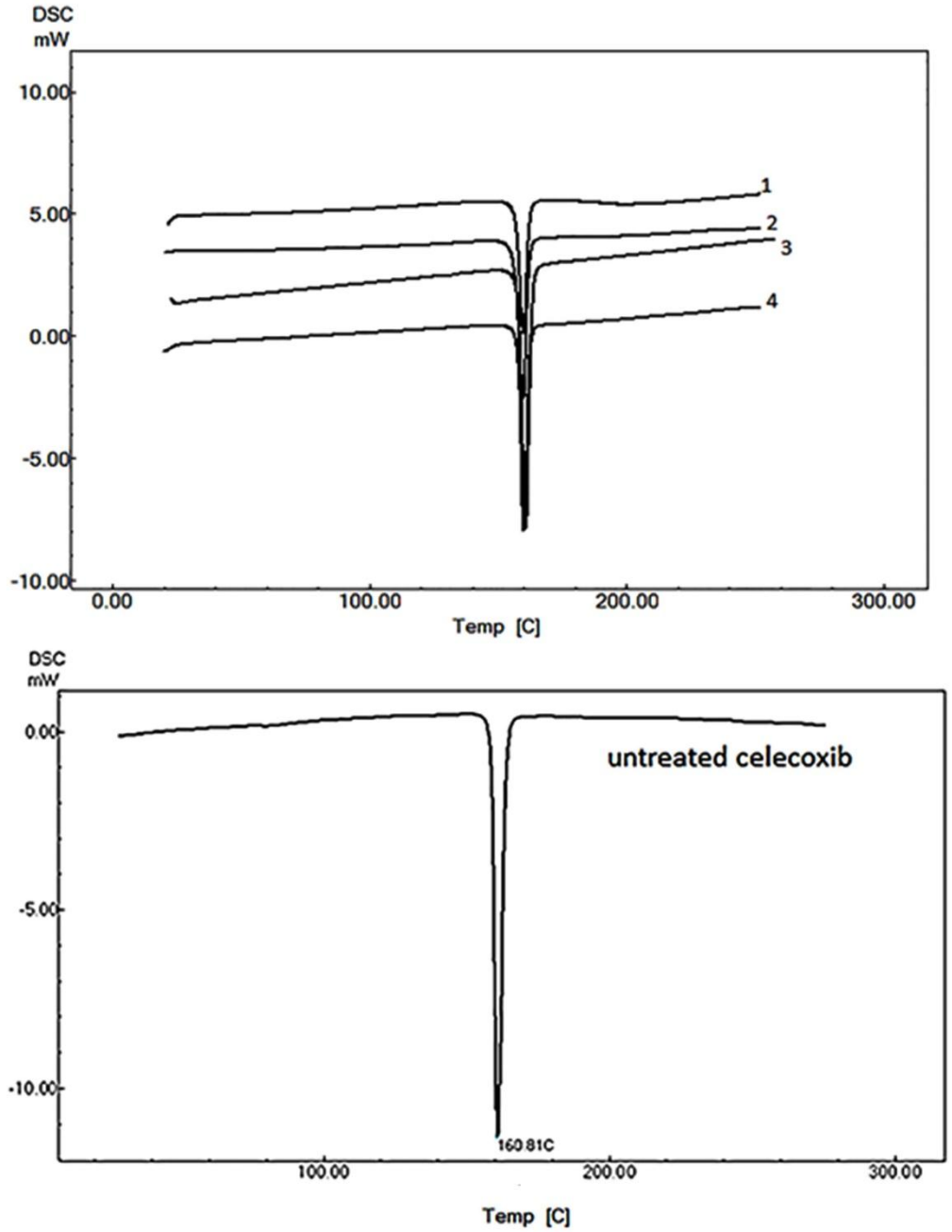

Figure 6. DSC scans of the agglomerates prepared with IPA in presence of; 1: SLS, 2: tween, 3: PVP, 4: HPMC and untreated celecoxib.

Conclusion

It can be concluded that, the type of stabilizer is pivotal to obtain CLX agglomerates via emulsification-diffusion method. In this study, the effect of various stabilizers in relation to different solvents on the stability of produced agglomerates of CLX was tested, as different stabilizers has different capacity to prevent coalescence of droplets and consequently the formation of smaller agglomerates with tight particle size distribution. The particle size of agglomerates prepared in presence of HPMC was significantly smaller than that stabilized with PVP, SLS or Tween, in all solvents. Moreover, a dispersion prepared with HPMC showed a tight particle size distribution. It should be mentioned that HPMC effectiveness increased with the solvent candidates with higher lipophilicity. It was shown that the useful stabilizers for hydrophobic organic solution in aqueous phase are those ones with a hydrophobic substituent and hydratable functional groups. The quasi-emulsion solvent diffusion method using judiciously selected type of stabilizer and solvent can be a potential approach for preparing agglomerates of drugs with promising pharmaceutical properties.

Ethical Issues

Not applicable.

Conflict of Interest

The authors declare no conflict of interests.

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