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Original research paper

Improvement of physicomechanical properties of carbamazepine by recrystallization at different pH values

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The morphology of crystals has an appreciable impact role on the physicochemical properties of drugs. Drug properties such as flowability, dissolution, hardness and bioavailability may be affected by crystallinity behaviours of drugs. The objective of this study was to achieve an improved physicomechanical property of carbamazepine powder through recrystallization from aqueous solutions at different pH values. For this purpose, carbamazapine was recrystallized from aqueous solutions at different pH values (1, 7, 11). The morphology of crystals was investigated using scanning electron microscopy; X-ray powder diffraction (XRPD) was used to identify polymorphism; thermodynamic properties were analyzed using differential scanning calorimetery (DSC). Dissolution rate was determined using USP dissolution apparatus. Mechanical behavior of recrystallized carbamazepine powders was investigated by making tablets under different compaction pressure and measuring their hardness. SEM studies showed that the carbamazepine crystallization in different media affected the morphology and size of carbamazepine crystals. The shape of carbamazepine crystals changed from flaky or thin plate-like to needle shape. XRPD and DSC results ruled out any crystallinity changes occurring due to the temperature during recrystallization procedure or pH of crystallization media. The crushing strength of tablets indicated that all of the recrystallized carbamazepine samples had better compactiblity than the original carbamazepine powder. *In vitro* dissolution studies of carbamazepine samples showed a higher dissolution rate for carbamazepine crystals obtained from media with pH 11 and 1. Carbamazepine particles recrystallized from aqueous solutions of different pH values (all media) appeared to have superior mechanical properties to those of the original carbamazepine sample.

Keywords: carbamazepine, crystalization, pH, polymorphism

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Solid-state forms exhibit variable physicochemical and physicomechanical (related to mechanical behavior) properties that affect their processing and product performance. These properties can be classified as fundamental and derived properties. The shape affects the flow and packing properties of a powder, having some influence on the surface area as well. The surface area per mass unit or volume is an important characteristic of a powder when undertaking surface adsorption and dissolution rate studies. According to the classic dissolution equation of Noyes and Whitney (1), the dissolution rate of a drug is directly proportional to its surface area available for dissolution. This fact could be used to enhance the dissolution rate of water-insoluble drugs. Many substances have the ability to crystallize in more than one crystalline form. Although they are chemically identical, there can be significant differences in their physicochemical properties. Tableting characteristics, flow dissolution profile as well as physicochemical stability of the drug during storage could be affected by different crystalline forms of the drug. Also the morphology of crystals has a considerable effect on the physicochemical properties of drugs. The crystallization technique can change the habit-crystal form and particle size. The nature and extent of these changes depend on the crystallization conditions such as type of crystallization medium (2).

Carbamazepine, a drug used routinely in the treatment of epilepsy and trigeminal neuralgia, exists in four polymorphic forms and as a hydrate (2–4). Physical stresses applied during manufacturing, like milling, affect transition of one crystalline form to another. One of the most common causes of habit modification is the presence of impurities in the crystallization solution. The presence of small amounts of an effective additive in the crystallization medium can dramatically change the crystal size and shape. There are several reports of changing the crystal habit or polymorphism in the presence of impurities during crystallization of carbamazepine (2). The objective of this study was to achieve improved physicomechanical properties of carbamazepine powder through recrystallization from aqueous solutions at different pH values.

EXPERIMENTAL

Materials

Carbamazepine was provided by Arastoo Co. (Tehran, Iran). All the chemicals were of analytical grade (Merck, Germany).

Spectrophotometric analysis

The spectrophotometeric analysis of carbamazepine samples in phosphate buffer (pH = 7.4) was performed at 285.8 nm (UV/visible spectrophotometer, Shimadzu-120, Japan). Standard curves were constructed by serially diluting an aqueous stock solution of the drug to obtain concentrations in the range of 0.8–40 μg mL^{-1} using phosphate buffer as the diluent. Each sample was analyzed in triplicate.

Buffer preparation

KCl and HCl were used for preparation of medium with pH = 1. Buffer pH = 7 was prepared from K_2HPO_4 and NaOH. Boric acid, KCl and NaOH were used for pH = 11 buffer.

Crystallization procedure

Carbamazapine was recrystallized from aqueous solutions at different pH values (1, 7 and 11). Saturated solutions of carbamazepine in water of different pH values were prepared by dissolving 3 g carbamazepine in 90 mL of appropriate medium at 80 °C. Saturated solutions were filtered through Milipore filter with pore size less than 0.45 μm and the filtrates were kept in a fridge at 8 °C for a period of 48 h. The precipitated crystals were filtered off and collected after 48 h using a sintered glass funnel under vacuum. The crystals were spread out on a Petri dish, air-dried overnight and further dried over phosphorous pentoxide in a vacuum oven, at room temperature (25 ± 2 °C) for 2 days. The crystals were stored in a desiccator at room temperature before use.

Flowability test

Flow properties of the powders were evaluated by determining the angle of repose. Static angle of repose was measured according to the fixed funnel and freestanding cone method. A funnel with the end of the stem cut perpendicularly to the axis of symmetry was secured with its tip 10 cm high, *H*, above graph paper placed on a flat horizontal surface. The crystals (about 50 g) were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. The mean diameter 2*R*, of *H*, the base of the crystal cone, was determined and the tangent of the angle of repose was given by:

$$\tan \alpha = H/R$$

where α is the repose angle. Data obtained were the mean and standard deviations of at least 10 determinations.

Scanning electron microscopy (SEM)

The morphology of crystals was examined with a scanning electron microscope (Leica Cambridge S360, UK) operating at 15 kV. The samples were mounted on a metal stub with double adhesive tape and coated under vacuum with gold in an argon atmosphere prior to analysis.

X-ray powder diffraction (XRPD)

The cavity of the metal sample holder of an X-ray diffractometer was filled with ground sample powder and then smoothed with a spatula. X-ray diffraction patterns of carbamazepine samples were obtained using the X-ray diffractometer (Siemens, D5000,

Germany) at 40 kV, 30 mA and a scanning rate of 0.06° min^{-1} over the range 5–50 2θ, using CuKα1 radiation of wavelength 1.5405×10^{-10} m.

Differential scanning calorimetery (DSC)

After calibration with indium and lead standards, samples of carbamazepine crystals were heated (range 25–200 °C) at 10 °C min^{-1} in crimped aluminium pans using a DSC instrument (Shimadzu DSC 60, Japan) under a nitrogen atmosphere.

Preparation of compacts of carbamazepine crystals

Crystals were ground using a mortar and pestle to achieve similar particle size distribution (90–250 μm) for each batch. Compacts were prepared directly from the ground crystals using 8-mm flat-faced punches on a hydraulic press (Riken, Japan). The material for each tablet was weighed, introduced into the die and compacted under various compression pressures. Compaction surfaces were lubricated with 1 % (*m*/*m*) magnesium stearate in acetone before compaction. The compacts were held under load for 30 s, ejected and stored in screw-capped bottles for 24 h before use to allow for possible hardening and elastic recovery.

Tablet crushing strength

The force required to fracture the compacts on a motorized tablet hardness tester (Erweka, Germany) was measured to determine the tablet crushing strength. The results are the mean and standard deviations of minimum six determinations.

Dissolution studies

A USP dissolution test apparatus No. 2 (Erweka DPT6R, Germany) (2) was used to monitor the dissolution profiles of carbamazepine powder. The dissolution medium was 900 mL phosphate buffer (pH = 7.4) equilibrated to 37 °C. The paddles were rotated at 50 rpm. From the dissolution flask 5-mL samples were withdrawn at selected time intervals and the concentration of carbamazepine in the samples was determined at 285.8 nm. At least three determinations per sample were carried out. As the dissolution rate could be affected by particle size, the mean particle size of 350 μm (250–450 μm) obtained by the sieving technique was chosen for dissolution studies of samples.

The *in vitro* release profiles of different carbamazepine formulations were compared using similarity factors, f_2, as defined by the following equation (5):

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_1) \right]^{-0.5} \times 100 \right\}$$

where n is the number of time points at which percent of dissolved drug was determined, R_t is the % dissolved from the formulation at a given time point and T_t is the % dissolved from the formulation for comparison at the same time point. The similarity factor

fits the result between 0 and 100. It is 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity increases. An f_2 above 50 indicates that the two profiles are similar.

Statistical analysis

All the data were statistically analyzed by the analysis of variance or Tukey's multiple comparison test.

RESULTS AND DISCUSSION

Fig. 1 shows the scanning electron micrographs (SEM) of untreated (starting carbamazepine obtained from supplier) and treated carbamazepine crystals obtained from water with different pHs. It is clear from the figure that carbamazepine crystallization in different media affected the morphology and size of carbamazepine crystals. According to SEM, the shape of carbamazepine crystals changed from cubic or thin plate-like to needle-shaped in all recrystallized samples. The crystallization medium pH had no significant effect on the crystal shape. Changes in the morphology of carbamazepine crystals could be due to pH alteration or the presence of some additives in the medium. The figures also show a clear difference in size of the treated crystals in comparison with untreated material. It can be concluded that crystallization of carbamazepine from distilled water at different pH values resulted in larger crystals than that of untreated samples.

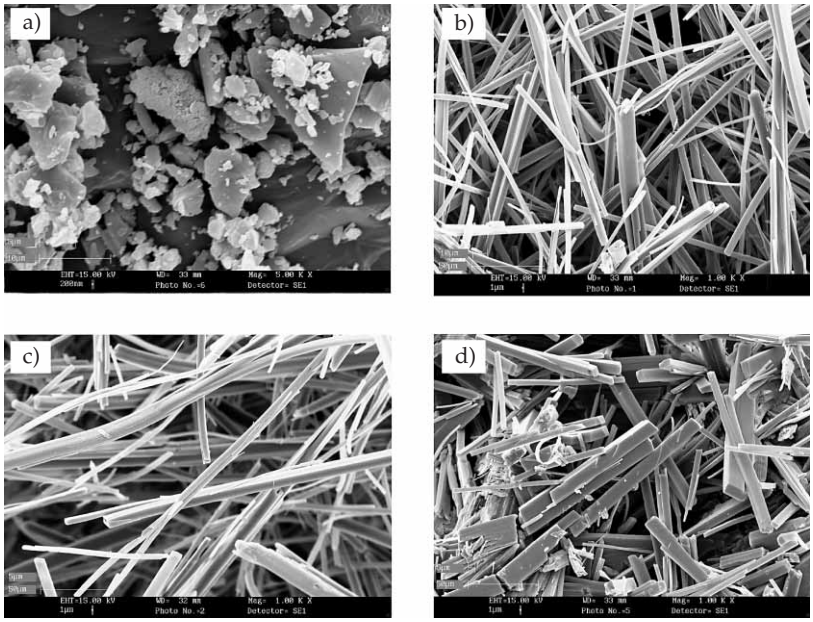

Fig. 1. SEM of carbamazepine: a) untreated and grown in media with pH: b) 1, c) 7 and d) 11.

XRDP patterns of treated and untreated samples for diffraction angles are shown in Fig. 2. Carbamazepine has four polymorphic forms and an anhydrous form (6). Form I has diagnostic peaks at 2θ of 7.92, 9.37, 12.28 and 19.99° and form II has diagnostic peaks at 2θ of 8.68, 13.26, 18.56 and 24.54°. The indicative peaks for form III occur at 2θ of 15.36, 19.56, 25 and 27.47°. Form IV has characteristic peaks at 2θ of 14.11, 17.89, 21.79 and 33.11°. The XRPD of commercial carbamazepine (untreated sample) was identical to that of form III reference standard and to that reported by the International Centre for Diffraction Data. The most providing piece of evidence for the existence of form III in the untreated sample is the absence of peaks between 2θ of 2–10° (2, 6). The XRPD spectra of the untreated material and recrystallized samples obtained from water at different pH showed similar patterns to that of the untreated sample, suggesting that particles crystallized from water at different pHs did not undergo structural modifications. However, the presence of very tiny peaks at 2θ = 6.1° (form I) and 14.1° (form II) indicates that these samples contain small amounts of form I and II. This is in agreement with the results published for forms I and II by Kala *et al*. (7) and Krahn and Mielck (8). Differences in relative intensities of the peaks of treated samples may be attributed to the differences in crystal sizes and habits of the samples, which may be attributed to the different solubility of the drug in crystallization media. Davey (9) reported that changes in solubility would imply differences in the growth rate of the crystals. It can be concluded that recrystallization of carbamazepine from media with different pH values caused minor polymorphic changes.

DSC thermograms of the carbamazepine polymorph form I show no transformation and melts between 189 and 193 °C (10). Form II does not melt but, instead, a transformation occurs between 135 and 170 °C and the new phase then melts between 188 and 192 °C. The large transformational interval is due, in part, to higher initiation temperatures for crystals with fewer defects, as determined by observing populations of crystals during heating. Form III melts and crystallizes to a new form almost simultaneously between 162 and 175 °C. The new form subsequently melts between 189 and 193 °C. Form IV shows melting and partial crystallization to a new form between 178 and 187 °C, significantly higher than the transition temperatures of forms II or III. This is followed by further crystallization to produce a material that then melts between 190 and 192 °C. Based on the measured melting point, it appeared that the untreated carbamazepine is form III and

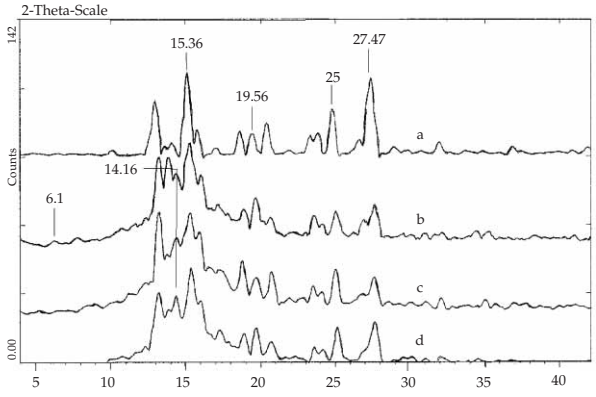

Fig. 2. XRDP patterns of carbamazepine crystals: a) untreated carbamazepine and that grown in media with pH: b) 1, c) 7 or d) 11.

the recrystallized samples can be mixtures of forms I and II. These findings support the results obtained by XRPD. It can be concluded that the pH might change the type of polymorph during crystallization. More studies should be carried out on these samples, using DSC or other available techniques, to quantify the amount of different polymorphs in carbamazepine samples, which was out of the scope of the present study.

The flowability results shown in Table I for carbamazepine crystals were obtained by measuring the angle of repose. According to the repose angle method, values for angles of repose ≤ 30° usually indicate a free-flowing material and angles ≥ 40° suggest a poorly flowing material (11). According to Table I, untreated carbamazepine showed better flow properties compared to recrystallized materials. The flow properties of a material result from a number of forces. Solid particles attract one another and forces acting between particles when they are in contact are predominately surface forces. There are many types of forces that can act between solid particles: (i) frictional forces, (ii) surface tension forces, (iii) mechanical forces caused by interlocking of particles of irregular shape, (iv) electrostatic forces, (v) cohesive or van der Waals forces. All of these forces can affect the flow properties of a solid. In case of fine particles (≤ 150 μm), the magnitude of frictional and van der Waals forces usually predominate. For larger particles (≥ 150 μm), frictional forces normally predominate over van der Waals forces. Also, as particles increase

Table I. Repose angles of untreated and recrytallized carbamazepine

Medium	Angle of repose (mean ± SD) (°)[a]
Untreated	16.74 ± 2.42
pH = 1	30.88 ± 1.14
pH = 7	30.76 ± 1.88
pH = 11	30.75 ± 2.05

[a] n = 10

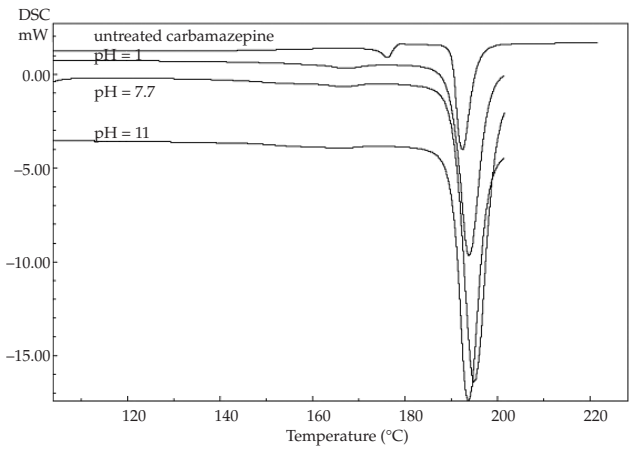

Fig. 3. Thermograms of different carbamazepine crystals.

in size, mechanical or physical properties of particles and their packing become important. As evident from the Table I, there are no significant differences between recrystallized materials in different media, but a lower value is obtained in untreated carbamazepine and there is a significant difference compared to other materials ($p < 0.05$), indicating better flowability. This is due to differences in their shapes and sizes. Cubic powders usually show a better flow rate than needle-shaped ones (12).

Fig. 4 shows the crushing strengths of tablets compressed under different pressures. Compression of untreated carbamazepine crystals at all compaction pressures produced weak compacts of low crushing strength. Needle-shaped carbamazepine crystals showed considerable improvement in compactibility of carbamazepine crystals. The results show that when the compression pressure increased from 1 to 2 MPa, the crushing strength of carbamazepine tablets recrystallized at different pHs decreased. It has been shown that the shape of a crystal is a complex characteristic, and its importance with regard to powder properties is therefore difficult to assess (13). It has been previously shown that various carbamazepine crystals undergo fragmentation during compression. Compaction of powders into tablets showed that the particle shape affected compact strength in materials which fragmented to a limited degree during compression. For example, more irregular particles improved the compactibility (14). However, for materials which fragmented markedly during compression, the shape of the particles before compaction did not affect compact strength. Hence, the effect of particle shape on the compact bonding characteristics is dependent on the volume reduction properties of the materials. For materials which fragment to a large extent, the physical structure of the formed compact is to a limited extent affected by variations in particle shape before compaction. It stands to reason that with increased particle irregularity the number of possible interparticulate attraction zones in a compact, and consequently the compact strength, will increase. It is also possible that during the compression process, the particles can undergo an increased degree of deformation due to increased particle irregularity at the edges and corners of the crystals. Increased local particle deformation will lead to an increased bonding force of the attraction zones between compact particles. These are the reasons for the increase in the crushing strength of compacts made from carbamazepine recrystallized

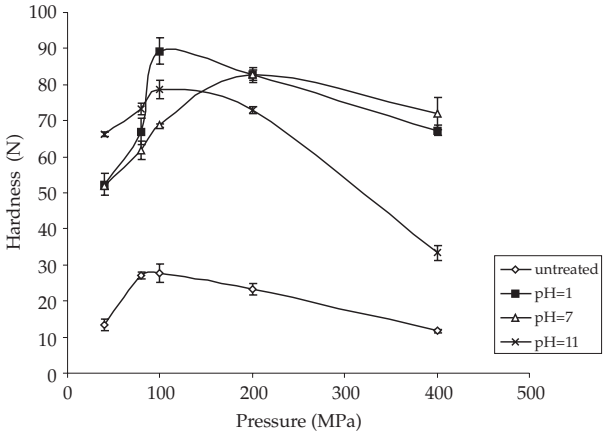

Fig. 4. The hardness-pressure profile of different carbamazepine crystals (SD bars, $n = 6$).

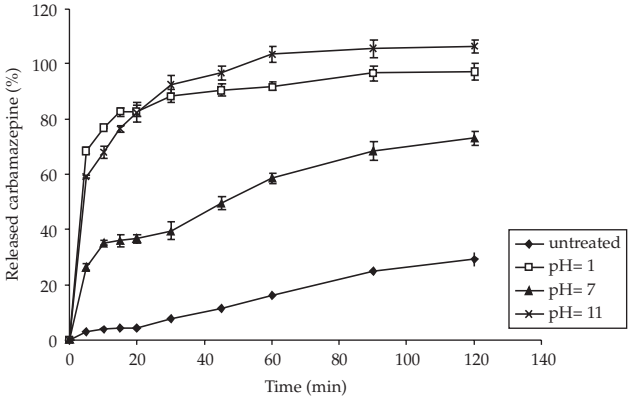

Fig. 5. The dissolution profile of different carbamazepine crystals (SD bars, n = 3).

material. It has been shown that there is generally an increase in tablet strength with a decrease in particle size (14). It was also observed that tablet strength is more or less independent of particle size in case of compacts of aggregated materials (highly fragmented particles).

Dissolution profiles of untreated and recrystallized carbamazepine are shown in Fig. 5. As it is clear from the figure, the amount of carbamazepine dissolved from treated samples was significantly ($f2 < 50$) higher than untreated carbamazepine. The highest dissolution rate was observed for the crystals recrystallized in media with pH 1 and 11 and the lowest dissolution rate was observed for untreated carbamazepine. Dissolution rate of materials could be affected by several factors, including morphology changes, particle size and adsorption of additives (such as Na^+, K^+ or PO_4^{3-}) on the crystal surface. It was shown (3) that form III of carbamazepine exhibited a rapid increase in dissolution rate at the initial stage, then the concentration gradually decreased with precipitation of dehydrated crystals. Also, it was shown that form I starts to dehydrate after 4 h. Crystal habit and closely related properties, such as particle size, anisotropy, defects and hydrodynamic conditions during dissolution are known to influence the dissolution profiles of crystals. The observed effects have been attributed to the different intrinsic dissolution rates of different crystal faces whose relative areas differ from habit to habit and also to their interaction with the solvent involved. It is possible that the presence of some additives in the crystal growth medium may block the growth of the higher energy sites of crystal surface, making them less available for active dissolution (2).

CONCLUSIONS

Carbamazepine particles recrystallized from aqueous solutions with different pH values appear to have superior mechanical properties to the original carbamazepine sample. This might be due to different morphological structures of carbamazepine samples. The pH of crystallization medium had a significant effect on the dissolution rate of carbamazepine powders and samples obtained at pH 11 and 1 showed a higher dissolu-

tion rate compared to samples (recrystallized at pH 7) and the original carbamazepine sample.

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S A Ž E T A K

Poboljšanje fizičko-mehaničkih svojstava karbamazepina prekristalizacijom pri različitim pH

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Morfologija kristala ima važnu ulogu na fizičko-mehanička svojstva lijekova. Kristaliničnost može utjecati na tečnost, oslobađanje, tvrdoću i bioraspoloživost lijekova. Cilj ovog rada bio je poboljšati fizičko-mehanička svojstva praha karbamazepina prekristalizacijom iz vodenih otopina pri različitim pH vrijednostima (1, 7 i 11). Fizičko-mehanička svojstva prekristaliziranog karbamazepina određivana su na sljedeći način: morfologija kristala ispitivana je pretražnom elektronskom mikroskopijom, polimorfi su identificirani rendgenskom difrakcijom praha (XRPD), a termodinamička svojstva analizirana su diferencijalnom pretražnom kalorimetrijom (DSC). Topljivost je određena pomoću aparata po USP. Mehanička svojstva prekristaliziranog karbamazepina ispitivana su tijekom tabletiranja pri različitim tlakovima i mjerenjem tvrdoće nastalih tableta. SEM ispitivanja pokazala su da kristalizacija karbamazepina iz različitih medija utječe na morfologiju i veličinu kristala. Oblik kristala mijenjao se od pahuljastog ili pločastog do igličastog. XRPD i DSC metodom mogle su se pratiti promjene u kristaliničnosti nastale zbog promjene temperature i pH. Mjerenje lomljivosti tableta ukazuje da su svi prekristalizirani uzorci karbamazepina kompaktniji od polaznog praškastog uzorka. Ispitivanja topljivosti *in vitro* pokazala su da su kristali dobiveni iz otopine pH 11 i 1 topljiviji. Uzorci karbamazepina dobiveni prekristalizacijom iz vodenih otopina različite pH vrijednosti imali su bolja mehanička svojstva od originalnog uzorka karbamazepina.

Ključne riječi: karbamazepin, kristalizacija, pH, polimorfizam

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