Co-milling of oxcarbazepine with Soluplus for the enhancement of solubility and dissolution rate

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Background and objective
Poor solubility and dissolution rates affect the bioavailability of drugs. The aim of this study was to improve the solubility and dissolution rate of a poorly soluble drug, oxcarbazepine by its mechanochemical activation via the co-milling technique.
Materials and methods
The drug and Soluplus (in two different ratios) were co-milled in a planetary ball bill. The bulk properties, solubility, and dissolution rate were determined and differential scanning calorimetry, powder X-ray diffraction, Fourier-transform infrared spectroscopy (FTIR), and laser diffraction (for particle size determination) techniques were used to characterize drug and co-milled formulations.
Results and discussion
The results have shown good compressibility and excellent flow of co-milled mixtures as compared with the drug. The solubility of the drug (0.448±2 mg/ml) was increased by 2–3-fold in co-milled mixtures while the dissolution rate of oxcarbazepine was increased up to 2.5–3 times. Both differential scanning calorimetry and powder X-ray diffraction results have shown a reduction of crystallinity while the Fourier-transform infrared spectroscopy spectra indicated no interaction. Laser diffraction studies have shown ~5 times reduction in mean particle size.
Conclusion
The study concludes that co-milling is effective in enhancing solubility and dissolution of poor soluble drugs.

Keywords:
ball mill, crystallinity, mechanochemical activation, particle size

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Introduction

The compounds having limited aqueous solubility show low absorption and bioavailabilityof oral drugs and pose many manufacturing challenges that result into increased developmental cost, time, and burden transferred to the patient [1]. Poorly soluble drugs particularly of BCS class II have a poor dissolution rate and hence exhibit low oral bioavailability [2]. Therefore, solubility of the drug is an important parameter to get the desired concentration of drug in systemic circulation and to make it available for intended pharmacological effect. Among the newly developed chemical formulations, more than 40% are insoluble in water and thus formulation development has become a very serious problem [3].

Oxcarbazepine (OXC), an antiepileptic drug, belongs to BCS class II and therefore has poor solubility, which ultimately acts as a limiting factor for dissolution and bioavailability. To overcome the problem of poor solubility several techniques have been used in the literature, including solid dispersion [4], milling and co-milling [5], crystal engineering [6], and fusion method [7]. These methodologies cause changes like particle size reduction and increase in surface area, reduction in crystallinity, solubilization, and increase in hydrogen bonding [8]. These changes together increase the solubility and/or dissolution rate of poorly soluble drugs.

Co-milling is a mechanochemical activation approach that utilizes the mechanical energy to increase the chemical reactivity of the system without altering its chemical composition [9]. This technique collectively brings all those changes of size reduction, crystallinity, and solubilization; and therefore, has a great potential in increasing the solubility and/or dissolution rate of poorly soluble drugs. The process of co-milling involves the milling drug in the presence of some excipients [10]. During these processes, defects are produced in the drugs by mechanical activation, which is followed by specific interactions between the drug and the polymer that may lead to

stabilization of the amorphous phase. Therefore, one can achieve the benefit of stabilized amorphous phase as it has low enthalpy of fusion and thus high solubility and faster dissolution rates [4]. Other benefits include: first, simple processing techniques that can be scaled up; second, methods evade the use of organic solvents; third, quality manufacturing without a break; fourth, bitter taste can be masked; and fifth, high shear mixing provides better drug and polymer interaction [11].

The present study is based on reducing the particle size and mechanochemical activation of OXC by using the co-milling technique. An amphiphilic copolymer Soluplus was used as a co-excipient [12]. The aim of this study was to enhance the solubility and dissolution rate of a BCS class II drug, OXC through co-milling. The co-milled mixtures were studied for their physicochemical changes using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier-transform infrared spectroscopy (FTIR), and laser diffraction studies.

Materials and methods

Oxcarbazepine (abbreviated as OXC, a carboxamide derivative, that occurs as a white to slightly orange crystalline powder) was received as a gift sample from Shrooq Pharmaceuticals Pvt Ltd (Lahore, Pakistan). The Soluplus (a graft copolymer of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol; BASF, Ludwigshafen, UK) and Silica (Daejung Chemicals, Shiheung, South Korea) were obtained from a local supplier. The reagents (potassium dihydrogen phosphate monobasic, sodium hydroxide, hydrochloric acid) were purchased from Sigma Aldrich (Missouri, USA) and all were of analytical grade.

Methods

Co-milling of OXC

Physical mixture (PM) of the drug and Soluplus was also prepared by simply mixing in mortar and pestle the components in a 1 : 1 ratio. Co-milling of OXC and Soluplus in weight ratios of 1 : 1 and 1 : 2, CM1 and CM2, respectively was carried out in a planetary ball mill (NQM 0.4, Yangzhou Nuyo Machinery Co. Ltd., Jiangsu, China) as used in the literature [13]. PM of each ratio (~6 g) was added in each milling jar of the mill that was already charged SS balls of two sizes (10.5 and 6.2 mm diameter) in a ball to powder ratio of 30 : 1. The mill was operated at 24 Hz for 4 h at room temperature (25±2°C) and relative humidity of ~45% humidity. The co-milled samples were collected in glass vials and stored in a desiccator until used for subsequent studies.

Characterization of prepared solid dispersions

Bulk characterization

The bulk density (mass per unit volume, represented as ρb) of OXC and its co-milled formulations was determined from the mass and unsettled volume of each material added to a volumetric cylinder. The tapped density (ρt) was determined from the tapped volume of material until it becomes constant. From the values of bulk and tapped density, the Hausner ratio (HR) and Carr's indices (CI) of the drug and its co-milled mixtures were calculated using the following equations:(1)

$$\mathrm{HR} = \frac{\rho t}{\rho b}$$

(2)

$$\mathrm{CI} = 100 \times \left[\frac{\rho t - \rho b}{\rho t}\right]$$

The flowability of OXC powder and its co-milled mixtures was determined from the angle of repose calculated from the ratio of height of powder heap to its diameter on horizontal surface applying the equation (3):(3)

$$\varnothing = \tan^{-1}\frac{h}{r}$$

Solubility studies

Aqueous solubility of OXC and its co-milled formulations was determined using the well-known shake-flask method [4]. For this purpose, an excess quantity of OXC (~100 mg) was added in 50 ml of distilled water using 100 ml of conical flasks. The flasks were capped and shaken using an Orbital shaker (Heidolph, Instrument, Schwabach, Germany) at room temperature (25±2 °C). Samples were withdrawn after equilibrium is achieved (i.e. in 24 h), filtered through 0.45 µ syringe filters, and diluted appropriately. The soluble amount was determined by UV spectrophotometer (2550; Shimadzu, Japan) at a maximum wavelength (λ_{max}) of 256 nm using the calibration curve.

Dissolution studies

In-vitro dissolution studies of OXC from the prepared SDs was determined in USP type ?? basket test apparatus (Galvano Scientific, Lahore, Pakistan). Samples equivalent to 150 mg of OXC were placed in dissolution flasks containing 900 ml of 0.1 N HCl (pH 1.2) as the dissolution medium. The temperature of media was maintained at 37±0.5°C and the baskets were rotated at a speed of 50 rpm. Aliquots of 5 ml were withdrawn at different time intervals and replaced

every time with fresh dissolution medium in order to maintain sink conditions. The samples were filtered and assayed for OXC content using a UV spectrophotometer.

Differential scanning calorimetry

DSC thermograms of OXC and its co-milled mixtures were recorded on a TA, Q 2000 machine (TA Instruments, New Castle DE, USA), precalibrated using indium standard at 156.5°C. The samples (~10 mg) were scanned (against blank aluminum pans) in hermetically sealed *T*-zero aluminum pans over a temperature range of 25–350 °C at a heating rate of 10°C/min under nitrogen purge of 50 ml/min.

Powder X-ray diffraction studies

PXRD patterns for OXC, its co-milled mixture with Soluplus, were collected on a PanAnalytical diffractometer XPERT-PRO (Bruker, Karlsruhe, Germany) operating at 40 kV, 40 mA, using Cu-K radiation (k¼1.5418 Å) with a position-sensitive detector. All samples were measured in the 2θ angle range between 10 and 34° with a scan rate of 0.5 s per step and a step size of 0.2°.

FTIR spectroscopy

FTIR spectra of OXC and its co-milled mixtures were recorded using Carry-630 FTIR spectrometer (Agilent Technologies, California, USA). Powder samples were placed on the crystal surface and kept in place with the help of a clutch lever. Spectra were collected at a spectral resolution of 4 cm^{-1} and a zero-filling factor to give a spectral data point spacing of 2 cm^{-1} [14] and the wavenumber range was 5000-600 cm^{-1}.

Particle size analysis

Particle size distribution (PSD) of unmilled OXC and its co-milled mixtures was determined using a laser diffraction analyzer (Horiba LA-960; Kyoto, Japan). The size distribution was expressed by equivalent volume diameters at 10% (d10) and 90% (d90) cumulative volume.

Results

Bulk characteristics

The values of bulk (ρb) and tapped densities (ρt), Hausner ratio and Carr's index and angle of repose (θ) for OXC and its co-milled mixtures are given in Table 1.

Table 1 Bulk properties of oxcarbazepine, physical mixture, and its co-milled mixtures

Formulation	ρt (g/ml)	ρb (g/ml)	θ (°)	HR	CI (%)
OXC	0.81	0.58	41.7 ±2.1	1.40 ±0.08	28.4 ±4.2
PM	0.78	0.57	34.6 ±3.2	1.37 ±0.08	26.9 ±2.5
CM1	0.68	0.58	29.2 ±1.6	1.17 ±0.04	14.7 ±1.4
CM2	0.66	0.57	28.7 ±2.9	1.16 ±0.05	13.6 ±1.6

CI, Carr's indices; HR, Hausner ratio; OXC, oxcarbazepine; PM, physical mixture.

Solubility studies

Aqueous solubility of OXC was 0.448±0.038 mg/ml which is very close to the value as described in the literature [15]. The PM with Soluplus (1 : 1 ratio) has almost similar solubility, that is, 0.509±0.05 mg/ml. The solubility of the co-milled formulations CM1 and CM2 was 0.708±0.043 and 1.071±0.025 mg/ml, respectively [16].

Dissolution studies of oxcarbazepine and its co-milled mixtures

OXC showed only ~20% release in first 15 min followed by ~30% and 40% at 30 and 60 min, respectively (Fig. 1). PM of OXC with Soluplus showed a relatively quicker dissolution of the drug with ~45% release in the first 15 min, followed by 65% and 75% dissolution at 30 and 60 min time intervals. Co-milled mixtures on the other hand exhibited 60–70% drug dissolution in the first 15 min that reached to more than 80% in 30 min (see Fig. 1).

Differential scanning calorimetry

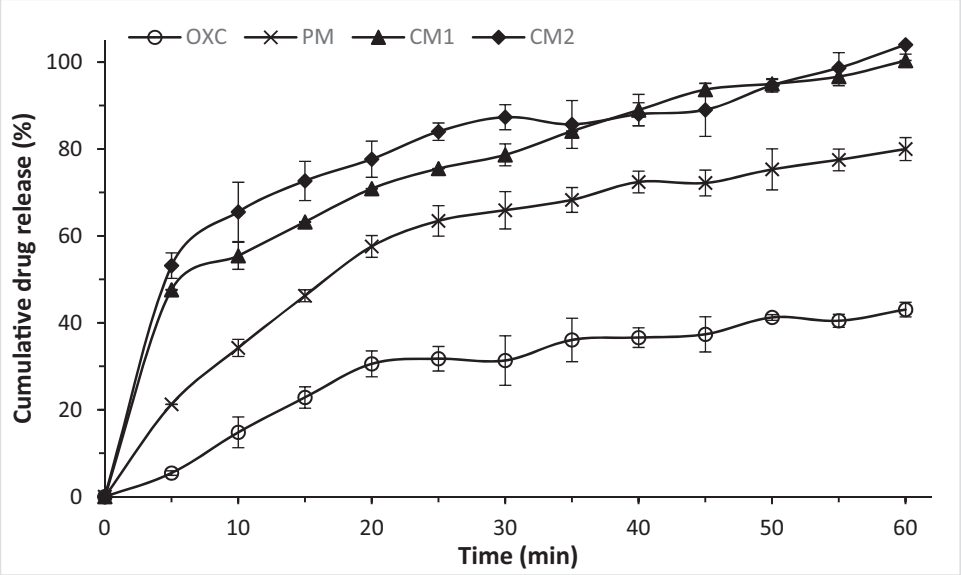
The DSC curve of OXC was distinctive of a pure crystalline substance, showing a sharp endothermic peak close to its melting point, with an onset temperature of 221.3°C and peak at 228.8°C with an enthalpy (ΔH) of 68.32 J/g (Fig. 2). This melting temperature was in accordance with that described in the literature, that is, 219–221°C [17]. There was no prominent degradation even till 350°C, which indicated the thermal stability of this drug.

In case of co-milled sample (CM1), a shallow endothermic peak was observed at 212.3°C with ΔH of 1.612 J/g. This shifting of the melting peak to lower temperatures along with a reduction in ΔH of fusion indicated a high degree of disorder by mechanochemical activation [18] This was the main reason for higher solubility and/or faster dissolution rate of the drug from these co-milled mixtures.

Powder X-ray diffraction

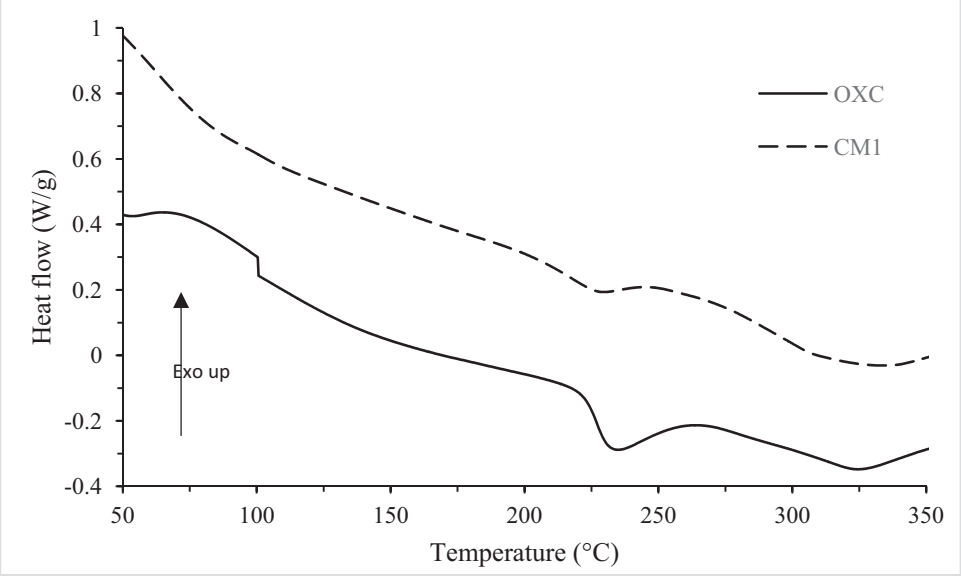
The X-ray diffraction patterns of OXC showed characteristic sharp peaks at 10.1, 11.8, 14.2, 18.9, 22.9, 23.5, 25.01, and 26.09 (Fig. 3), which are almost

Figure 1



Dissolution of oxcarbazepine from co-milled mixtures in 0.1 N HCL.

Figure 2



Differential scanning calorimetry curves of oxcarbazepine and its co-milled mixture (CM1).

similar to the peaks as reported by Chavan *et al*. [19]. The diffraction patterns of the co-milled formulation (CM1) showed almost same peaks with a much reduced intensity indicating a decrease in the crystallinity of OXC [20]. This showed that the crystalline structure of the drug OXC was almost same after co-milling while the crystallinity is considerably reduced.

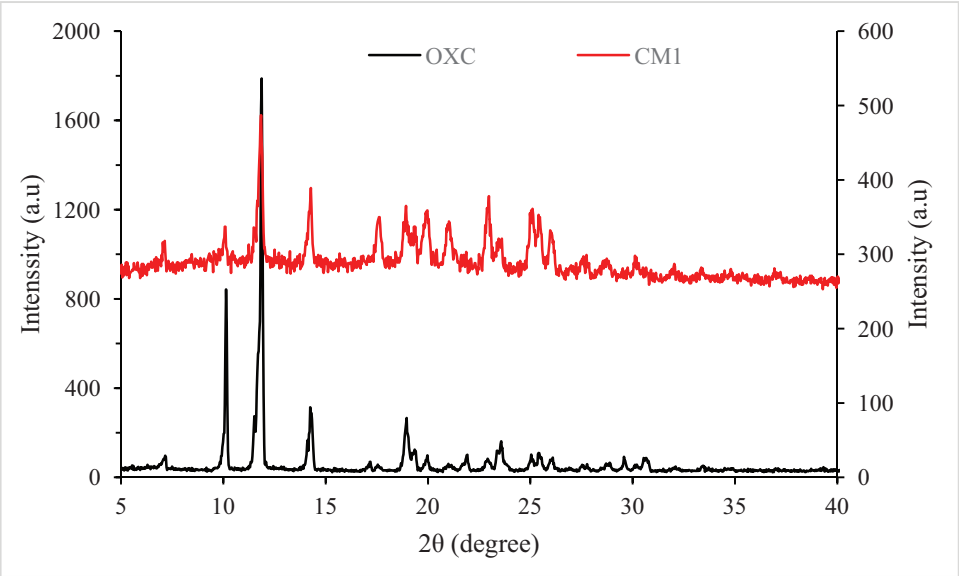
FTIR spectroscopy

The IR spectrum of OXC showed a strong absorption band near 3350 cm^{-1}, which is due to the stretching of amines (-NH- group). The carbonyl-stretching mode appears near 1600 cm^{-1}. This spectrum was exactly the same as shown in the literature [21]. The spectrum of co-milled samples of OXC with Soluplus was almost similar indicating the absence of any chemical changes caused during co-milling.

Particle size analysis

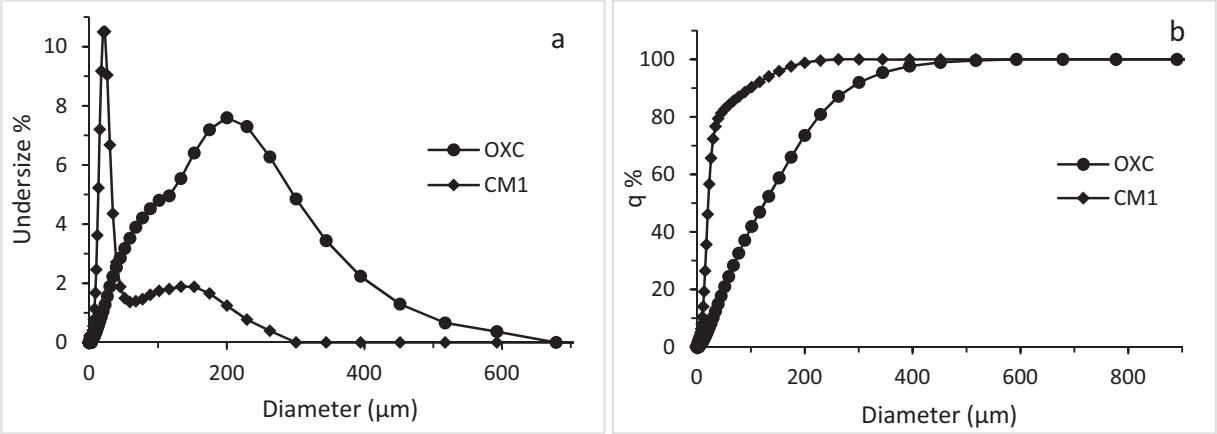
The PSD of unmilled OXC and co-milled mixture CM1 are presented as cumulative and density distribution plots (Fig. 4a and b). The PSD in the cumulative plot of unmilled OXC has shown wide

Figure 3



Diffraction pattern of oxcarbazepine and its co-milled mixture (CM1).

Figure 4



Particle size distribution plots of unmilled oxcarbazepine and co-milled mixture showing cumulative distribution (a) and density distribution (b).

Guassian assemblies of two sizes and centered around ~200 µm while it spreads over a range less than 300 µm in density distribution plot. PSD for the co-milled sample seems to shift toward the left side (smaller size window) with a larger peak at ~20 µm and a smaller peak at 130 µm in the cumulative distribution plot while density distribution has shown more than 80% particle of less than 40 µm.

The parameters of PSD including D10, D90, D50, and mean size are summarized in Table 2. The values of mean and median size of OXC was 143.9 and 125.5 µm, respectively, that was reduced to 36.63 and 20.9 µm in co-milled samples. This showed that the particle size has significantly decreased by using the co-milling technique.

Table 2 Particle size distribution of unmilled OXC and C_1

Parameters	OXC	CM1
D10	29.60	9.8
D90	284.2	98.6
Median size (D50)	125.5	20.9
Mean size	143.9	36.6

OXC, oxcarbazepine.

Discussion

The results of bulk characterization have indicated poor flow of drug and PM with Soluplus (i.e. angle of repose >35, HR >1.3 and CI >25) [22]. However, co-milled mixtures have shown efficient flow, as the values of angle of repose were between 25 and 30, HR less than 1.15 and CI less than 15. The solubility results

showed that the mechanical activation via co-milling have shown ~2.5-fold higher solubility of OXC as compared with the untreated drug. There was a linear increasing trend of solubility with increasing polymer concentration.

The co-milled mixtures with Soluplus have shown higher dissolution rate of OXC as compared with untreated OXC and its PM. These changes in solubility and dissolution rates were due to the solubilizing action of Soluplus and the mechanochemical activation of drug during co-milling in the presence of a copolymer. Furthermore, the reduction in particle size (laser diffraction results) and crystallinity as indicated by PXRD and DSC results have contributed to faster dissolution rates of OXC.

Conclusion

The study concludes that co-milling of poorly soluble drugs like OXC caused its mechanochemical activation that leads to size reduction, loss in crystallinity, and increase in H-bonding. These changes altogether are beneficial in enhancing the solubility and dissolution rate of such drugs.

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The manuscript has been read and approved by all the authors, and each author believes that the manuscript represents honest work.

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Conflicts of interest

There are no conflicts of interest.

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