Research Article

Preparation and Characterization of Spherical Agglomerates of Tenoxicam

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ABSTRACT

The purpose of the study was to prepare spherical agglomerates (SA) of Tenoxicam by solvent change method. Crystallization medium used for spherical agglomerates of Tenoxicam consisted of DMF: Water and chloroform. The presence of solvents residuals in SA was determined by Gas chromatography and particles were characterized by DSC, FT-IR, XRD and SEM. The respective solubility study and dissolution behavior studies were carried out. The samples were stored in stability chamber to investigate their physical stabilities. Solvents residuals in SA were found to be within the limit and exhibited decreased crystallinity than commercial sample of Tenoxicam. The solubility and dissolution of the spherical agglomerates was improved compared with Tenoxicam commercial sample and recrystallized sample. In stability test, the release profile of the spherical agglomeration was almost unchanged as compared with initial results of spherical agglomeration stored at 25°C and 60% relative humidity for 6 months. Hence this technique can be used to obtain modified drug raw material for formulation of tablets of Tenoxicam by direct compression with directly compressible tablet excipients.

Keywords: spherical agglomerates, Tenoxicam, crystallinity, dissolution, stability study.

INTRODUCTION

Tenoxicam is a derivative of the oxicam group of Non-steroidal anti-inflammatory drugs (NSAIDs). It is 4-hydroxy-2-methyl-N- (pyridine-2-yl) -2H-thieno [2, 3-e] 1, 2-thiazine -3-carboxamide 1, 1-dioxide, is a yellow, crystalline powder, practically insoluble in water.[1]

Formulation and manufacture of solid oral dosage forms, and tablets in particular, have undergone rapid change and development over the last several decades. One of the most revolutionary technologies is that of direct compression. Direct compression is economical, facilitates processing without the need of moisture or heat and involves small number of processing steps. In direct tableting method, it is necessary to increase flowability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tableting machine and sufficient mechanical strength of the compacted tablets.[2] In addition to increasing efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder. Spherical agglomeration is one among such techniques used to improve the micromeritic properties and dissolution of drug.

Spherical agglomeration process is a multiple unit process in which crystallization, agglomeration and spheronization can be carried out simultaneously in one step. The resultant crystals can be designated as spherical agglomerates.[3, 4] Due to the characteristic shape, the micromeritic properties such as flowability, packability and compressibility of the resultant crystals are dramatically improved, so that direct tableting or coating is possible without further processing (e.g. mixing, agglomeration, sieving, etc.).[5, 6]

Spherical agglomeration is a process of formation of aggregates of crystals held together by liquid bridges. The agglomerates are formed by agitating the crystals in a liquid suspension in presence of binding agent. The binding liquid should be immiscible in the suspending medium but capable of cementing the particles to be agglomerated. The properties of the particles so designed vary greatly as compared to the fine crystalline material. These agglomerates were found to have good flowability and compressibility.[7, 8] This technique can also be exploited to increase solubility, dissolution and hence bioavailability of poorly soluble drugs.[9-11] These modifications allow for the practice of more efficient manufacturing methods that could save time and also reduces economic costs. Tenoxicam exhibits poor flow, a high tendency of adhesion and shows poor dissolution properties.[12] Various methods were used to increase the flow properties of poorly water soluble drugs, e.g., coating, granulation etc.

The objective of the present study was to prepare spherical agglomerates of Tenoxicam by solvent change method and to evaluate them for solvent residuals. In similar way, DSC, FT-IR, XRD, and SEM analysis were performed to determine the physicochemical properties of the spherical agglomerates and to compare them with recrystallized sample and commercial sample. Solubility and dissolution characteristics of the Tenoxicam spherical agglomerates and their physical stability in a climate chamber at 25°C and 60% relative humidity (RH) for 6 months were also investigated.

MATERIALS AND METHODS

Tenoxicam was obtained as a gift sample from IPCA Lab. Mumbai., India. All chemicals and buffers used were of analytical grade.

Preparation of spherical agglomerates of Tenoxicam (SA)

Tenoxicam (3 g) was dissolved in 27 ml of *N,N*-dimethylformamide and heated at 45°C until a clear solution was obtained. The drug solution was quickly poured into 63 ml of water maintained at 30°C, under continuous stirring at 50 rpm with a propeller. When fine crystals of Tenoxicam began to precipitate (about after 2 min), 8 ml of chloroform was added. After 2 min stirring, 2 ml of chloroform was added again. After 20 min of stirring spherical agglomerates were formed and were separated from the solution by filtration. Spherical agglomerates were dried at 45°C for 12 hours. The spherical agglomerates were kept in a desiccator at room temperature until further experiment.

Recrystallization of Tenoxicam (RS)

Tenoxicam (3g) was dissolved in 27 ml of DMF, heated at 45°C and 10 ml of chloroform was added. The drug solution was quickly poured into 68 ml of water maintained at 30°C with occasional stirring. The crystals of Tenoxicam were collected by filtration and were dried at 45°C for 12 hours.

Determination of residual solvents in spherical agglomerates by gas chromatography

GC studies were carried out on SHIMADZU model 2014 (Shimadzu Technologies, Japan) coupled with a split/split less injector, operated in a split-mode and FID. The computer with GC solutions software has been used to control the gas chromatograph. Rtx-5 capillary column (cross bond 5% diphenyl/95% dimethyl polysiloxane) with a length of 30 meters and an internal diameter of 0.25 mm was used throughout the study.

Differential scanning calorimetry (DSC)

A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

Fourier transform infrared (FTIR) spectroscopy

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). About 2 mg of the commercial sample, recrystallized sample and spherical agglomerates were used separately. Commercial sample, spherical agglomerates and recrystallized samples were dispersed in KBr powder and the pellets were made by applying 6000 kg/cm^2 pressure.

X-ray analysis

X-Ray powder diffraction patterns were used to detect possible polymorphic transition during the crystallization process. X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffractometer, with Cu as anode material and graphite monochromator, operated at a voltage of 40 mA, 45 kV.

Scanning electron microscopy (SEM)

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm spherical nature and morphological characters of the crystals.

Mechanical Properties

Tensile strength of spherical agglomerates was determined by compressing 500 mg of crystals using hydraulic press at different kg/cm^2 for 1 min. The compacts were stored in a desiccator for overnight to allow elastic recovery. The thickness and diameter were measured for each compact. The hardness of each compact was then measured using Pfizer hardness tester. The tensile strength (σ) of the compact (kg/cm^2) was calculated using following equation.

$$\sigma = 2F/\pi Dt$$

Where, F, D and t are hardness (kg/cm^2), compact diameter (cm) and thickness (cm), respectively.

Solubility studies

The solubility of Tenoxicam spherical agglomerates in water was determined by taking excess quantity of spherical agglomerates and adding to screw- capped 50 ml glass vials filled with water. The vials were shaken for 24 hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and the drug concentration was determined spectrophotometrically at 375 nm.

Dissolution studies of agglomerates

The dissolution of Tenoxicam commercial sample, spherical agglomerates and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium (900 ml) consisted of pH 1.20.1N HCl and 10 ml of dissolution medium was withdrawn at every 10 min interval for 1 h. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 375 nm.

Determination of the physical stability

To determine the physical stability of spherical agglomerates, a long term and accelerated stability study of prepared spherical agglomerates was carried out at 25°C and 60% relative humidity for 6 months according to the ICH guidelines. The spherical agglomerates were packed in high density polyethylene (HDPE) container and placed in stability chamber. The samples were withdrawn at the interval of 0, 1, 3 and 6 months and evaluated for appearance, characterization by FT-IR and drug content and compared with initial results.

RESULTS AND DISCUSSION

A typical spherical crystallization system involved a good solvent (DMF), a poor solvent (water) for a drug and a bridging liquid (chloroform). The selection of these solvent depends on the miscibility of the solvents and solubility of the drug in individual solvents.[13, 14]

DMF is miscible in any proportion with water and chloroform. If the ternary diagram is envisaged, to select the solvent composition, chloroform and water are like an emulsion in a large area of the diagram (Fig. 1). The points on the vertex correspond to a pure liquid; those on the sides correspond to a mixture of only two liquids. Since the presence of three liquids is necessary (good solvent, bridging solvent and poor solvent) for spherical agglomeration, points on the sides of the triangle are excluded. 36 points remain for experiments. Each triangle in the ternary diagram was investigated for the crystallization. The optimal ratio for spherical agglomeration is found in zone (Fig. 1). These proportions of DMF/water/chloroform were finally chosen for the study.[11]

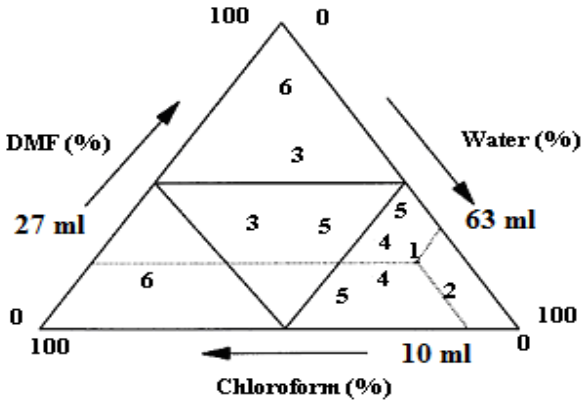


Figure 1: Ternary diagram.

1-Spherical crystals; 2-Flocs; 3-Suspension; 4-Irregular agglomerates; 5-Dense suspension with some agglomerates; 6-Limpid liquid

In this diagram results of different studies and the area for agglomerate formation are indicated.

Recrystallization of Tenoxicam was done to find out the changes in crystal lattice, being induced by solvents that can influence the physicochemical properties of the substance. Hence the mechanical, micromeritic and dissolution properties of spherical crystals were compared with commercial sample and recrystallized sample. Recrystallization of Tenoxicam was carried out using same solvent composition as was used for spherical crystallization.[9, 10]

To optimize Tenoxicam spherical agglomeration by DMF/water/chloroform system, other process parameters like amount and mode of addition of bridging liquid, stirring speed and time and temperature were considered (Table 1).

Table 1: Effect of variables on formulation of spherical agglomerates of Tenoxicam

Parameter	Variables	Observation
Conc. of bridging liquid (Chloroform)	6% 10% 12%	No agglomeration Agglomeration No Agglomeration
Agitation speed	400±25 rpm 500±25 rpm 600±25 rpm	Spherical & large Spherical Irregular shape & small
Agitation time	10 min 20 min	Incomplete agglomerates Spherical agglomerates
Temperature	5 ± 2^0 30 ± 2^0 45 ± 2^0	No agglomeration Spherical agglomerates Very large agglomerates
Mode of addition of bridging liquid	Whole at a time Drop wise	Crystals of irregular geometry Spherical agglomerates

Based upon high solubility of Tenoxicam in DMF, high viscosity and crystal morphology, DMF was determined to be suitable as spherical agglomerates medium for Tenoxicam because of its high solubility in DMF (1g/9 ml). The controlling of residual DMF was needed though. DMF is a toxic organic solvent based on their concentration and has little detriment to human body. Therefore, the low level of both DMF and chloroform in the spherical agglomerates should not be harmful to animals and human.[14, 15]

Gas chromatography results confirmed that they were below detection levels for both the solvents (DMF and chloroform) used in the spherical agglomerates against the ICH limits i.e. 880 and 60 ppm respectively.[16] The low level of both DMF and chloroform in the spherical agglomerates results from its ability to form high surface area crystals and from the fact that the intermolecular forces among both DMF and chloroform molecules are not as strong as those of water. This allows both DMF and chloroform to evaporate more completely and easily than water.[17]

The DSC thermograms showed a sharp endothermic peak for all the Tenoxicam crystals. This one step melt might be due to only one crystal form (Triclinic) of the Tenoxicam formed during the crystallization process, thus indicating that Tenoxicam did not undergo any crystal modification. The temperature range of the endothermic peak of all the Tenoxicam crystals lies in the range of 206°C to 214°C (Fig. 2). In DSC curve, commercial sample of Tenoxicam had a sharp endothermic peak at 214.8°C with enthalpy of 167.56 J/g that corresponded to the melting point of Tenoxicam.[18]

Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endotherm for agglomerated Tenoxicam was 206.4°C with decreased enthalpy of (159.31 J/g) indicating decreased crystallinity of Tenoxicam in SA.

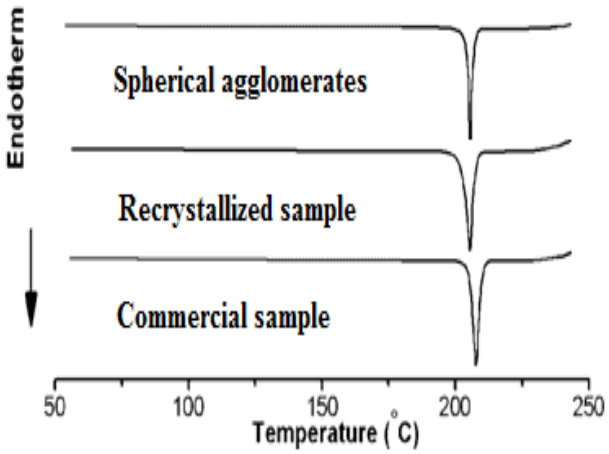


Figure 2: DSC thermograms of Tenoxicam Samples

Infrared spectra of commercial Tenoxicam, recrystallized sample, spherical agglomerates showed characteristic peaks at 3447 cm-1, which is assigned for the O-H stretching vibration and two bands at 3155 and 3090 cm-1, which are due to the N-H stretching and aromatic C-H vibrations. In addition, a strong band was observed at 1636 cm-1, which was attributed to the amide carbonyl stretching band (C=O) as showed in (Fig. 3).[1, 12] Specific changes in IR spectra are not very clear and could be due to variations in the resonance structure, rotation of a part of a molecule on certain bonds. Alteration could be due to minor distortion of bond angles, or even a result of the presence of solvents of crystallization.

X-Ray diffraction was used to analyze potential changes in the inner structure of Tenoxicam crystal during the formulation of SA. The characteristic peak of the Tenoxicam appeared in the 2θ range of 10–50°, indicating that the unprocessed Tenoxicam was a crystalline material. Further, the presence of numerous distinct peaks in the x-ray diffraction spectrum of Tenoxicam indicates that the drug is present as a crystalline material with characteristic diffraction peaks appearing at diffraction angles of 2θ at 12Å, 14.9 Å, 16.5 Å, 23.8 Å, 28.8 Å and 29.7 Å [12] (Fig. 5). However, all the samples showed similar peak positions (2θ) in X-ray diffraction that is formation of different polymorphs of Tenoxicam was ruled out. However relative intensities of XRD peaks were modified (Fig. 4).

The relative intensities of SA reduced nearly half time than commercial Tenoxicam. This could be attributed to the markedly different crystal habits of the samples. Therefore the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peak or may be due to differences in crystal sizes.[9, 12] The commercial sample exhibits its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity. The X-ray diffraction of the RS of drug showed the peak corresponding to the crystalline drug molecules present in the RS, although their intensity was lower than commercial drug due to the differences in crystal sizes.

The X-ray diffraction pattern of the SA showed that Tenoxicam peak intensity was much lower than the commercial sample and RS samples of Tenoxicam. This could be due to the increasing the wettability of SA. These results could explain the observed enhancement of solubility and dissolution of Tenoxicam in spherical agglomeration.

SEM study showed that crystals of commercial sample are of the smallest size (6-12 µm) and irregular shape and size. Recrystallization leads to crystals with intermediate size (4-19 µm) which had rod and irregular shapes.

The agglomerates were formed by coalescence of the microcrystalline precipitates, so the resultant agglomerates had a rough surface (Fig. 5). The spherical shapes of the agglomerates with might be one of the factors that are responsible for enhancing drug dissolution.

Spherical agglomerates exhibited superior compressibility characteristics compared to Recrystallized and commercial drug crystals (Fig. 6). It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals.

Surface freshly prepared by fracture enhanced the plastic inter particle bonding, resulting in a lower compression force required for compressing the agglomerates under plastic deformation compared to that of single crystal.[10, 11]

Spherical agglomerates showed increased solubility than the commercial sample in water and increased more than threefold higher (0.286 mg/ml) than commercial Tenoxicam (0.092 mg/ml). The higher solubility of Tenoxicam from SA may be due to the increased wettability of Tenoxicam in spherical agglomerates.[12, 13]

The dissolution profiles of Tenoxicam (Fig. 7) exhibited improved dissolution behavior for SAs than commercial sample. The reason for this faster dissolution could be linked to the better wettability of the SAs. The amount of drug dissolved in 60 min greatly varied for spherical agglomerates.

With respect to the influence of SAs on the physical stability of prepared SAs of Tenoxicam stored at 25°C and 60% relative humidity for 6. The influence of physical stability on the prepared SAs was investigated. Prepared spherical agglomerates of Tenoxicam were stable for 6 months and complied with all the properties when compared to initial results of prepared SAs of Tenoxicam.

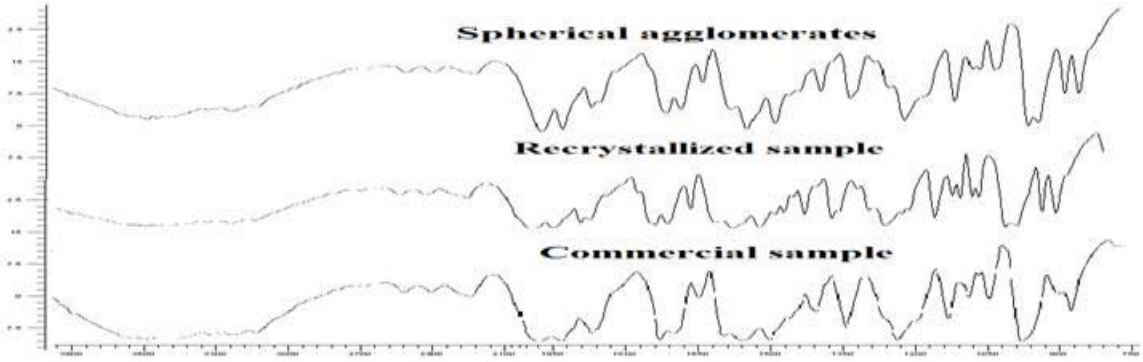


Figure 3: FT-IR spectra of Tenoxicam Samples

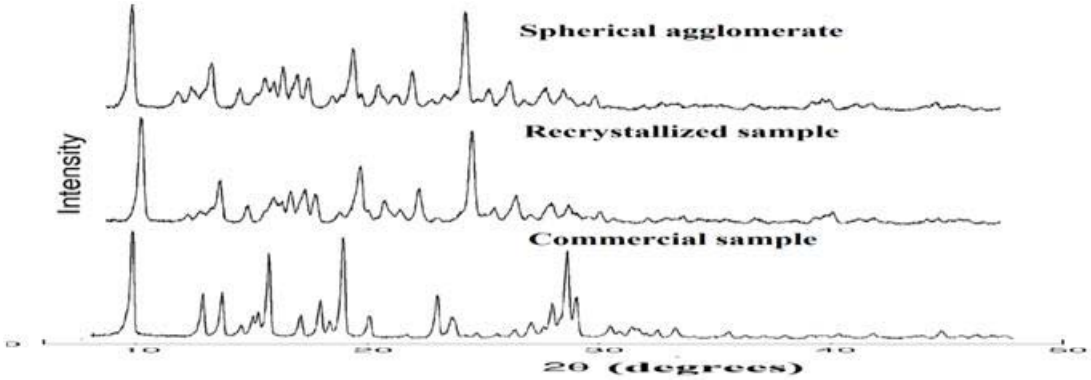


Figure 4: X-ray diffraction spectra of Tenoxicam Samples.

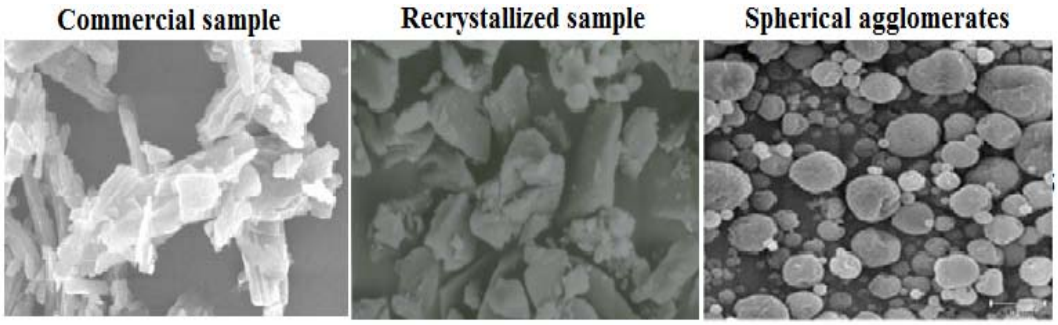
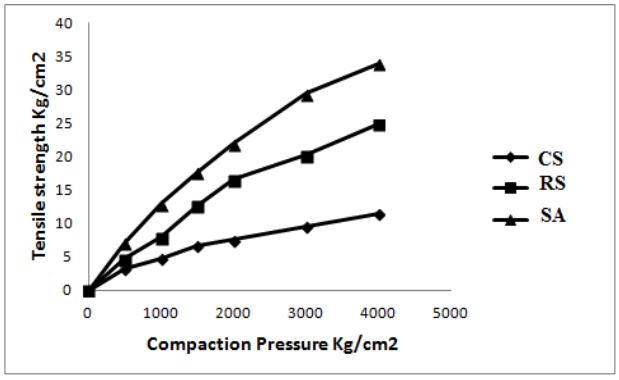
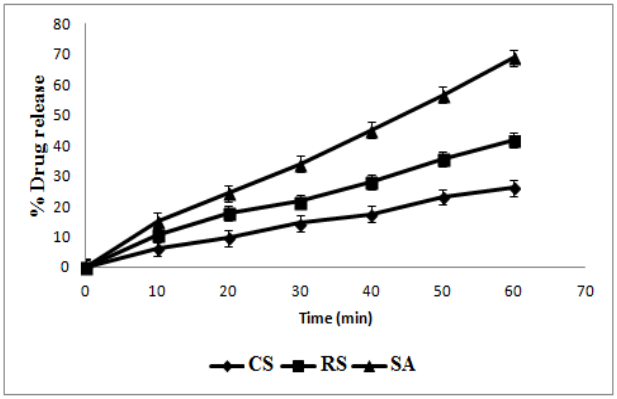


Figure 5: SEM of Different samples of Tenoxicam.



CS-Commercialized sample, RS-Recrystallized sample, S.A- Spherical agglomerates

Figure 6: Tensile strength of spherical agglomerates, Recrystallized sample and commercial sample as a function of compaction pressure.



CS-Commercial sample, RS.-Recrystallized sample, SA-Spherical agglomerates

Figure 7: Dissolution profile of Tenoxicam samples

CONCLUSION

Spherical agglomerates of Tenoxicam were prepared by solvent change technique. SA exhibited decreased crystallinity and improved mechanical properties. Amount of bridging liquid, speed of agitation and duration of agitation affects the mechanical and micromeritic properties of spherical crystals. DSC and XRD studies showed that there is no change in the crystal structure of Tenoxicam during the crystallization process i.e., polymorphism has not occurred. The dissolution of the spherical agglomerates was improved compared with commercial sample of Tenoxicam. Stability showed that prepared Spherical agglomerates were stable for 6 month. Hence this technique could be used for formulation of tablets of Tenoxicam by direct compression with directly compressible tablet excipients.

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