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Preparation of spherical agglomerates of tolfenamic acid

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ABSTRACT

The purpose of the study was to prepare spherical agglomerates (SA) of Tolfenamic acid (TA) by solvent change method. Crystallization medium used for spherical agglomerates of Tolfenamic acid consisted of *N,N*-dimethylformamide (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. Residual Solvents in SAs were found to be within the limit and exhibited decreased crystallinity as well solubility and dissolution of the spherical agglomerates was improved than commercial sample of Tolfenamic acid. In stability study, it was found that physical properties and release profile of the spherical agglomeration was unaffected for 6 months. Hence this technique can be used to obtain modified drug raw material for formulation of tablets of Tolfenamic acid by direct compression with directly compressible tablet excipients.

Introduction

Tolfenamic acid is a potent anti-inflammatory drug, resembling other fenamates in clinical use, namely mefenamic and Flufenamic acid[1]. Together with other drugs from the carboxylic acid family, it is used to treat inflammatory and pain-causing diseases of rheumatic and non-rheumatic origin. Tolfenamic acid has also been used extensively in both human and veterinary medicine for its analgesic and antipyretic properties[2].

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 tabletting 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 tabletting machine and sufficient mechanical strength of the compacted tablets[3].

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[4,5]. 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.[6,7].

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[8,9]. This technique can also be exploited to increase solubility, dissolution and hence bioavailability of poorly soluble drugs[10,11,12]. These modifications allow for the practice of more efficient manufacturing methods that could save time and also reduces economic costs. Tolfenamic acid exhibits poor flow, a high tendency of adhesion and shows poor dissolution properties[13]. 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 Tolfenamic acid by solvent change method and to evaluate them for solvent residuals and characterized by DSC, FT-IR, XRD, and SEM analysis. Solubility and dissolution release study of Tolfenamic acid spherical agglomerates and their physical stability at 25°C and 60% relative humidity (RH) for 6 months were also investigated.

Materials and methods

All chemicals and buffers used were of analytical grade.

Preparation of spherical agglomerates of Tolfenamic acid (SA)

Tolfenamic acid (3 g) was dissolved in 30 ml of DMF and heated at 30°C until a clear solution was obtained. The drug solution was quickly poured into 56 ml of water maintained at 20°C, under continuous stirring at 600 rpm with a propeller. When fine crystals of Tolfenamic acid began to precipitate (about after 5 min), 10 ml of chloroform was added. After 5 min stirring, 4 ml of chloroform was added again. After 40 min of stirring spherical agglomerates were formed and were separated from the solution by filtration. Spherical agglomerates were dried at room temperature for 12 hours. The spherical agglomerates were kept in a desiccator at room temperature until further experiment.

Recrystallization of Tolfenamic acid (RS)

Tolfenamic acid (3 g) was dissolved in 30 ml of DMF, heated at 30°C and 14 ml of chloroform was added. The drug solution was quickly poured into 56 ml of water maintained at 30°C with occasional stirring. The crystals of Tolfenamic acid were collected by filtration and were dried at room temperature for 12 hours.

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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 Tolfenamic acid 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 290 nm.

Dissolution studies of agglomerates

The dissolution of Tolfenamic acid 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 7.4 Phosphate buffer and 10 ml of dissolution medium was withdrawn at every 10 min interval for 1 h and replace with fresh media. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 290 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 40°C and 75% 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, 2, 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]

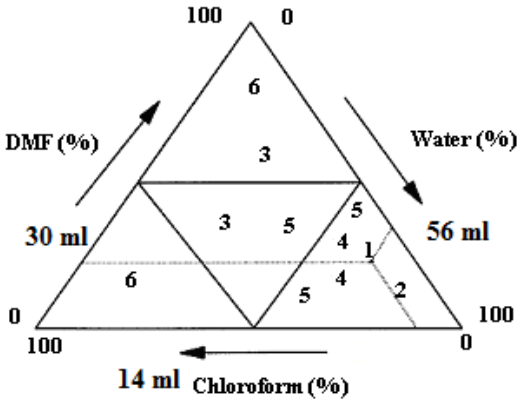


Fig 1. Ternary diagram

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

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

Recrystallization of Tolfenamic acid 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 Tolfenamic acid was carried out using same solvent composition as was used for spherical crystallization.[9, 10]

To optimize Tolfenamic acid 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 Tolfenamic acid

Parameter	Variables	Observation
Conc. of bridging liquid (Chloroform)	8% 14% 17%	No agglomeration Agglomeration No Agglomeration
Agitation speed	500±25 rpm 600±25 rpm 700±25 rpm	Spherical & large Spherical Irregular shape & small
Agitation time	30 min 40 min	Incomplete agglomerates Spherical agglomerates
Temperature	10 ± 2^0 20 ± 2^0 25 ± 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 Tolfenamic acid in DMF, high viscosity and crystal morphology, DMF was determined to be suitable as spherical agglomerates medium for Tolfenamic acid because of its high solubility in DMF (1 g/10 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.[15, 16]

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.[17] 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.[18]

The DSC thermograms showed a sharp endothermic peak for all the Tolfenamic acid crystals. This one step melt might be due to only one crystal form (Triclinic) of the Tolfenamic acid formed during the crystallization process, thus indicating that Tolfenamic acid did not undergo any crystal modification. The temperature range of the endothermic peak of all the Tolfenamic acid crystals lies in the range of 206°C to 214°C (Fig. 2). In DSC curve, commercial sample of Tolfenamic acid had a sharp endothermic peak at 214.8°C with enthalpy of 167.56 J/g that corresponded to the melting point of Tolfenamic acid .[18] Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endotherm for agglomerated Tolfenamic acid was 206.4°C with decreased enthalpy of (159.31 J/g) indicating decreased crystallinity of Tolfenamic acid in SA.

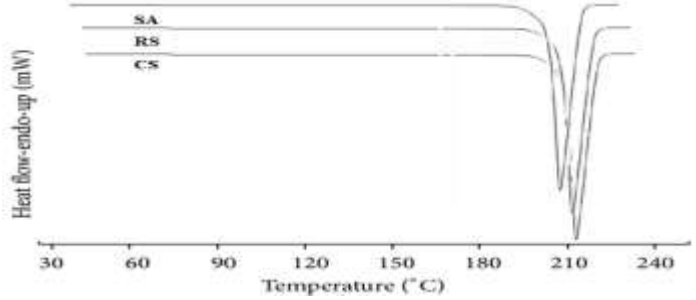


Fig 1. DSC thermograms of Tolfenamic acid Samples

Spectroscopic methods due to their nondestructive nature can be used along with other solid-state techniques for quantitative analysis of pharmaceutical solids. FTIR spectroscopy is considered as a valuable technique to study the degree of crystallinity based on the measurement of characteristic peak intensity for its particular polymorphic crystal state[19]. Infrared technique is also very useful to study the hydrogen bond formation of polymers with different drugs[20, 21, 22]. Therefore, FTIR spectroscopy was used in this study to identify the possible interaction between TA and solvent. It is envisaged that TA contain Peaks at 1661, 1590, 1575, 1500, 1270, and 749 cm^{-1} are the most intense, characteristic peaks of TA (Fig-3). The FTIR spectrum of pure TA shows NH-stretching vibrations at around 3342–3340 cm^{-1}. Since commercial TA and prepared crystals share the same spectral region to exhibit their characteristic peaks of NH-stretching vibrations, it was difficult to identify the changes taking place in the peak height of TA in the prepared crystals at the spectral region of 3350–3300 cm−1. However, the prepared SAs still show broadening of the peak in the same region that 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.

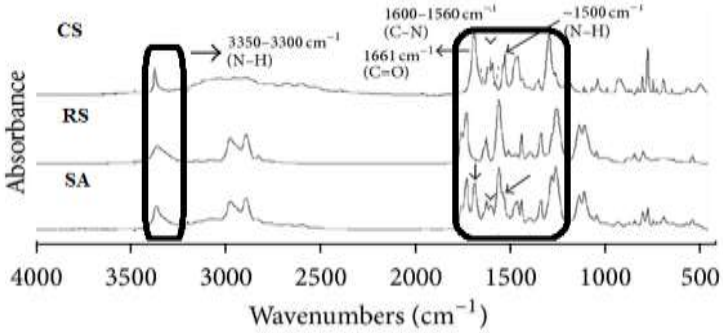


Fig 3. FT-IR spectra of Tolfenamic acid Samples

In order to confirm the changes in the physical properties of the crystalline TA and prepared SAs were studied using XRD technique. XRD is usually considered as the most definite method of detecting and quantifying the crystalline/amorphous nature of the sample. XRD shows strong characteristic diffraction peaks for crystalline solids whereas diffused and hallow diffraction patterns for amorphous powders[20]. The pure crystalline TA shows characteristic diffraction peaks at 2θ values of 5.21°, 11.58°, 15.72°, 18.70°, 19.77°, 24.90°, 25.32°, 25.90°, and 26.81°, respectively (Fig-4). In case of The X-ray diffraction of the RS and prepared SAs, both the samples showed same characteristic diffraction peaks although their intensity was lower than commercial drug may be due to the differences in crystal sizes. This could be due to the increasing the wettability of SA. These results could explain the observed enhancement of solubility and dissolution of Tolfenamic acid in spherical agglomeration.

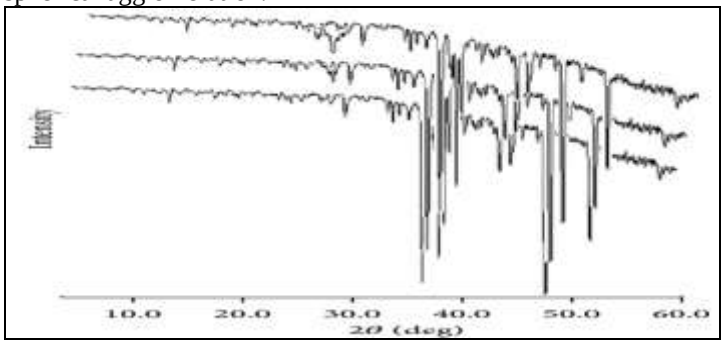


Fig 4. X-ray diffraction spectra of Tolfenamic acid Samples

SEM study showed that crystals of commercial sample are of the smallest size (11-16 µm) and irregular shape and size. Recrystallization leads to crystals with intermediate size (7-23 µm) which had 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.

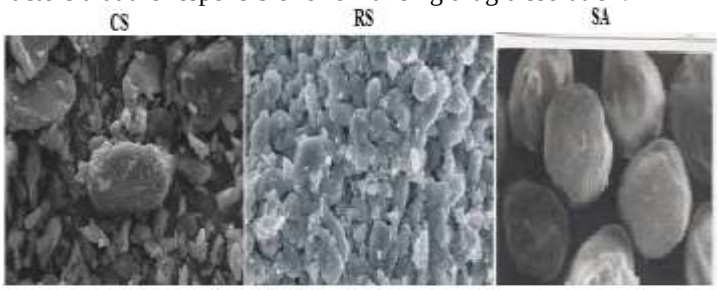
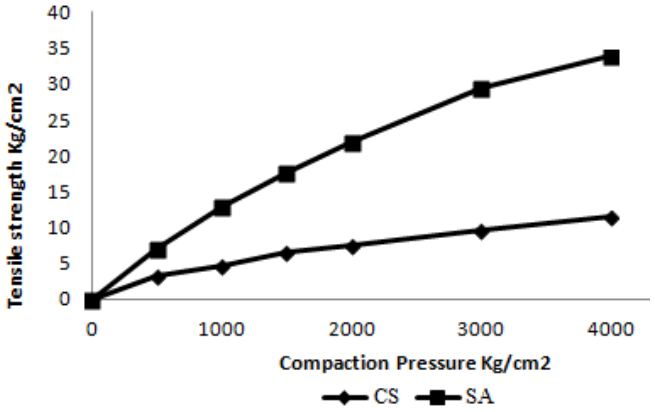


Fig 5. SEM of Different samples of Tolfenamic acid

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]



CS-Commercialized sample and SA- Spherical agglomerates

Fig 6. Tensile strength of spherical agglomerates and commercial sample as a function of compaction pressure

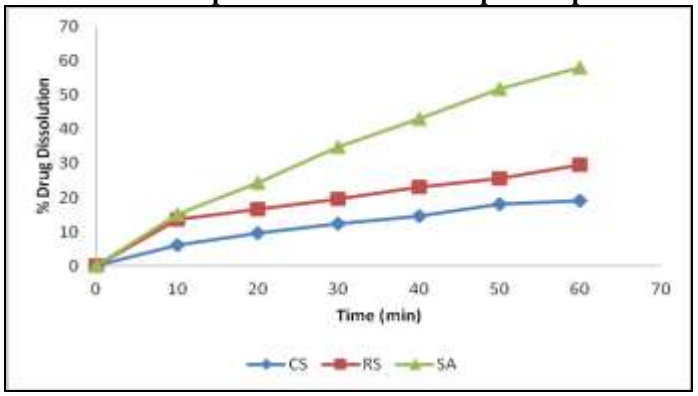


Fig 7. Dissolution profile of Tolfenamic acid samples

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

Spherical agglomerates showed increased solubility than the commercial sample in water and increased near fivefold higher (0.886 mg/ml) than commercial Tolfenamic acid (0.171 mg/ml). The higher solubility of Tolfenamic acid from SA may be due to the increased wettability of Tolfenamic acid in spherical agglomerates.[12, 13]

The dissolution profiles of Tolfenamic acid (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 Tolfenamic acid 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 Tolfenamic acid were stable for 6 month and complied with all the selected properties when compared to initial results of prepared SAs of Tolfenamic acid.

Conclusion

Spherical agglomerates of Tolfenamic acid 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 Tolfenamic acid during the crystallization process i.e., polymorphism has not occurred. The dissolution of the spherical agglomerates was improved compared with commercial sample of Tolfenamic acid. Stability showed that prepared Spherical agglomerates were stable for 6 month. Hence this technique could be used for formulation of tablets of Tolfenamic acid by direct compression with directly compressible tablet excipients.

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Conflict of interest

Conflict of interest declared none

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