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RESEARCH ARTICLE

MODIFICATION OF PHYSICOCHEMICAL AND MICROMERITIC PROPERTIES OF ACTIVE PHARMACEUTICAL INGREDIENT BY CRYSTALLIZATION TECHNIQUE

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ABSTRACT

The present work involves the study of effect of different additives on spherical crystalisation of celecoxib, to optimise the experimental conditions for obtaining spherical agglomerates, and to study the various properties of prepared agglomerates. The crystalline lattice of the celecoxib is of long needle shape, which is responsible for its cohesive property. This abundance of cohesive nature results in poor flow property of celecoxib. It is vital to get the directly compressible form of celecoxib so that it can be directly compressed in high doses. This drug is mentioned under BCS class II category with a pka of 11.1. Several studies have been done on preparation of directly compressible form of celecoxib by spherical crystallisation method, the agglomerates were prepared alongwith incorporation of different excipients during crystallisation procedure, to study their effects on prepared agglomerates. In the investigation, studies have been done to check the effect of surfactant and various methacrylate polymers on spherical agglomeration behaviour and compaction-consolidation properties of celecoxib.

1. INTRODUCTION

Celecoxib, is a 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide. It is a potent and selective inhibitor of cyclooxygenase-2 (Cox-2) enzyme. Celecoxib is prescribed mainly in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis in dose range of 50-100 mg once/twice daily. In certain conditions like familial adenomatous polyopsis it is prescribed in regimen of 800mg daily. The introduction of this first selective COX-2 inhibitor (375-fold selectivity) in the pharmaceutical market has significantly improved the treatment of osteoarthritis (OA), rheumatoid arthritis (RA), and management of pain. It is one of the top selling molecules (ranked 8th), with a worldwide sales of $2614 million in year 2000. US FDA has approved its use in OA, RA, and dysmenorrheal with dose strengths of 100–200 mg once/twice daily. The crystalline lattice of the celecoxib is of long needle shape, which is responsible for its cohesive property. This abundance of cohesive nature results in poor flow property of celecoxib. It is vital to get the directly compressible form of celecoxib so that it can be directly compressed in high doses. This drug is mentioned under BCS class II category with a pka of 11.1. Several studies have been done on preparation of directly compressible form of celecoxib by spherical crystallisation method, the agglomerates were prepared alongwith incorporation of different excipients during crystallisation procedure, to study their effects on prepared agglomerates. But the compaction and consolidation properties of celecoxib agglomerates have not been investigated. In the further investigation, studies have been done to check the effect of surfactant and various methacrylate polymers on spherical agglomeration behaviour and compaction-consolidation properties of celecoxib. The present work involves the study of effect of different additives on spherical crystalisation of celecoxib, to optimise the experimental conditions for obtaining spherical agglomerates, and to study the various properties of prepared agglomerates.

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2. MATERIALS AND METHODS

2.1 Materials

Celecoxib, Polaxamer 188, Eudragit S100 & L100 were gifted by Lupin Pharma, Pune, India. Acetone, ethanol, hydrochloric acid, sodium dihydrogen phosphate, sodium hydroxide were all of analytical grade and purchased from loba chemie, Mumbai, India.

2.2 Methods

2.2.1 Preparation of spherical agglomerates

2.2.1.1 Preparation of agglomerates of celecoxib

1g of celecoxib was dissolved in 3 ml of acetone. This solution was sonicated on lab sonicator for 15 min, and then was added

to 60 ml of water, with stirring at 1600 rpm. The stirrer used was having three pitched blades with blunt edges (REMI 124-Q). The process was carried out at 25-26°c for 15 min. The formed agglomerates were filtered through whatmann filter paper no.45 and dried at room temperature for 12 hr.

2.2.1.2 Preparation of agglomerates of celecoxib with Polaxamer 188

1g of celecoxib was dissolved in 2 ml of acetone. This solution was added into 60 ml water containing 1.5, 3 or 6g of Polaxamer 188 dissolved in it, a small quantity of finely triturated drug nearly 90 mg was added into the resulting solution to improve the rate of crystallisation, under stirring at 1000 rpm to get agglomerates of celecoxib containing three different concentration of Polaxamer 188. The agglomerates were filtered through whatmann filter paper no.45 and dried at room temperature for 12 hr.

2.2.1.3 Preparation of agglomerates of celecoxib with Eudragit S100 & L100

1g of celecoxib was dissolved in 2ml of acetone. To this solution Eudragit S100 or L100 was added in quantity of 80, 90 and 100mg. The resultant solution was then added into120ml of 0.1N HCL, under stirring at 2500 rpm to get agglomerates of celecoxib containing three different concentration of Eudragit S100 or L100. The agglomerates formed were then filtered through whatmann filter paper no.45 and dried at room temperature for 12 hr.

2.2.2 Determination of Drug Content of formed agglomerates

Drug content was determined by dissolving 10mg of formed agglomerates in 100ml of ethanol. The solution was then filtered through whatmaan paper no 41, and absorbance was measured at 254.12nm using double beam spectrophotometer (Shimadzu 1800, Japan)

2.2.3 Differential scanning calorimetric analysis

Thermogram of celecoxib and its polymeric agglomerates were obtained on a Mettler DSC 30S (Mettler Toledo Pvt. Ltd. Switzerland). The samples were placed in aluminium pan and the process was carried out in nitrogen atmosphere (flow rate 40 ml/min) at scanning rate of 10°c/min in the range of 25-250°c.

2.2.4 X-Ray Powder Diffraction studies

XRPD analysis was carried on a Philips analytic X-Ray-PW 3710(Philips, Almelo, The Netherlands) over the interval of 5-60 2θ range. At generator tension of 40kv and generator current of 25 Ma

2.2.5 Fourier Transform Infrared Spectroscopy

FTIR spectra were obtained using Shimadzu FTIR spectrometer (IR Affinity 1model, Japan) by the conventional pellet method. The pellets were prepared in KBr press using mixture of celecoxib and KBr in 1:100 ratio.

2.2.6 Scanning electron Microscopy

The surface morphology of agglomerated crystals and untreated powder was analysed using scanning electron microscope (SEM-Jeol Instrument, JSM-6360, Japan) after sputter coating with platinum.

2.2.7 Pressure- Relative Density Relationship

The samples (500 ±10mg) were compressed at pressure of 20-100 Kg/cm^2 for 1min with the help of hydraulic press. The relation between applied pressure (P) and relative density (D) was analysed using heckel equation.

$$LN\ (1/1-D) = KP + A \quad \ldots\ldots\ldots\ldots (1)$$

Where, K is the slope of straight line portion of heckel plot; $K=1/3\sigma_0$, where σ_0 is yield strength and mean yield pressure Py is equal to $3\sigma_0$

2.2.8 Pressure-Tensile Strength Relationship

The effect of applied pressure on tensile strength of compacts was analysed. This was done by determining the force required to break the compacts used in study of applied pressure-relative density relationship. The tensile strength was determined by using equation.

$$\sigma t = 2F/\Pi\ d\ T \quad \ldots\ldots\ldots (2)$$

Where σt is tensile strength, F is the force required to break the compacts, d is diameter of compacts and T is thickness of the compacts.

2.2.9 Micromeritic analysis

The micromeritic analysis was carried out for agglomerates. The angle of repose was determined by fixed funnel method. The tapped and bulk density was determined by tapping method. Further Carr's index and Hausner's ratio was determined.

2.2.10 Dissolution studies

The dissolution study was carried out using paddle method. The dissolution test apparatus used was of Disso 2000 Tablet Dissolution Test Apparatus, Lab India, India. The dissolution medium used was 900 ml of Phosphate buffer pH-7.4 at 50 rpm maintained at 37±0.5°c. Amount containing 100mg of pure drug was added into dissolution medium and the samples were withdrawn at 10, 20, 30, 40, 60 minutes. The solution was filtered through whatmann paper no-41 and then was analysed using UV spectrophotometer at a wavelength of 253.24nm

3. RESULTS AND DISCUSSION

3.1 Preparation of Spherical Agglomerates

The method used for preparation of spherical agglomerates was solvent diffusion method. The continuous phase was water in which drug is insoluble, acetone served as good solvent for the

dissolved drug. The crystallisation of drug takes place inside the droplets due to counter diffusion of acetone through droplets. The average size of the agglomerates increased with increasing the volume of acetone. This resulted into increased squeezing out of good solvent, through newly formed surfaces causing more wetting of surface by acetone leading to enhanced agglomeration of crystals (Kawashima *et al*., 1995). During spherical crystallisation of celecoxib with polaxamer it was observed that, seeding increased the rate of crystallisation of drug (Kawashima *et al*., 1995) as the added seed acted as nuclei for the crystal growth. This factor contributed along with a low stirring speed for size enlargement of drug agglomerates with polxamer. In case of Eudragits the high stirring speed and absence of seeding caused less increase in partical size. This decreased partical size may be attributed to its more solubility in dissolution medium.

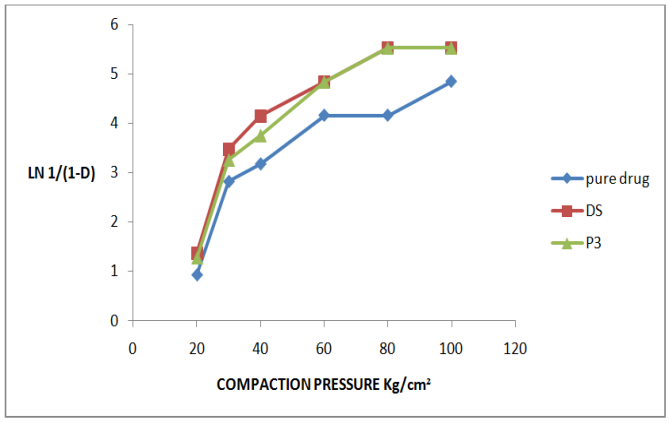


Fig.1. Heckel plot analysis

3.2 DSC studies

The DSC analysis of pure drug showed endothermic event at 163.60°c due to melting of celecoxib, which is in agreement with the reported value (Garima *et al*., 2003, Garekani *et al*., 2000). The results of analysis of L3 and S3 also showed endotherm at 161.21°c for both formulations, which is attributed to the melting of celecoxib. There was shifting in the endothermic peak to lower temperature, also peaks got broadened which is attributed to increase in solubility of these formulations. The DSC analysis of P3 showed shifting of endotherm to 162.10°C along with a diffused endotherm at 89.5°c this second endotherm was attributed to melting of Polaxamer 188 this shows that there is no interaction between Polaxamer 188 and celecoxib. The DSC analysis also showed the absence of desolvation endotherm in DSC spectra's of various formulations. Thus the possibility of formation of solvates with acetone and hydrates with water is excluded (Garima *et al*., 2003).

3.3 X-Ray Powder Diffraction studies

The XRPD studies (Figure 2) showed presence of distinct peaks in spectra of both pure drug and agglomerates at 14.77, 17.82, and 19.61 2θ values. The agglomerates showed crystalline pattern but the peak intensities got decreased. The relative degree of crystallinity was calculated and was found between the range of 0.146-0.660 which indicates a significant change in crystallinity of formed agglomerates. Also the agglomerates prepared with methacrylates showed lower peak intensities than the agglomerates prepared with polxamer. This will be attributed to formation of more amorphous form of celecoxib in agglomerates containing methacrylates which may result in the enhancement of solubility of formed agglomerates (Varsoshaz *et al*., 2011).

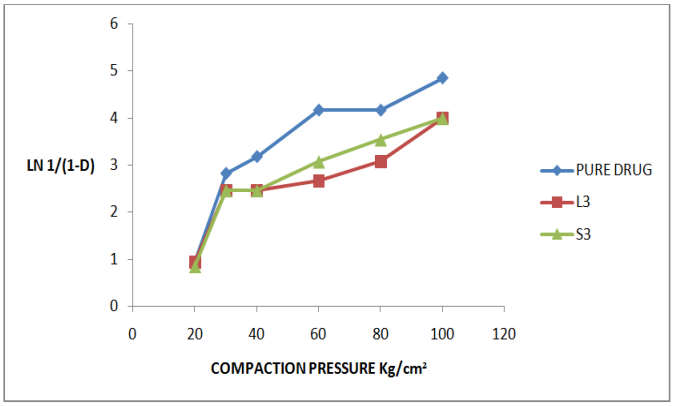


Fig. 2. Heckel plot analysis

3.4 Fourier Transform Infrared Spectroscopy

The Figure 3 shows the spectra obtained of celecoxib and its agglomerates, these spectra showed similar peaks: 1161cm^{-1} (-CF_3 group stretching), 1163 and 1348 (S=O symmetric and asymmetric stretching), 3235 and 3339 cm^{-1} (a doublet due to N-H stretching vibration). This indicates the chemical stability of drug during the process of spherical agglomeration (Rawat *et al*., 2004, dixit *et al*., 2011).

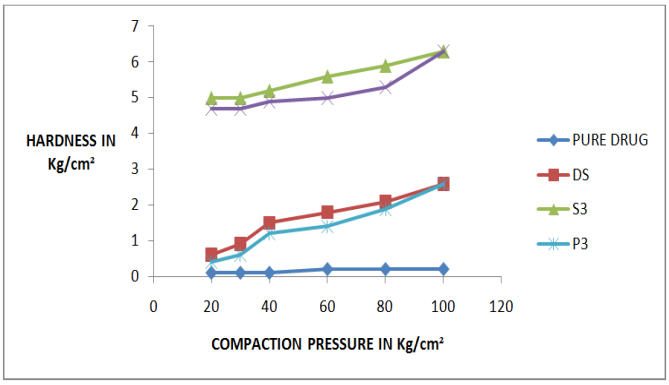
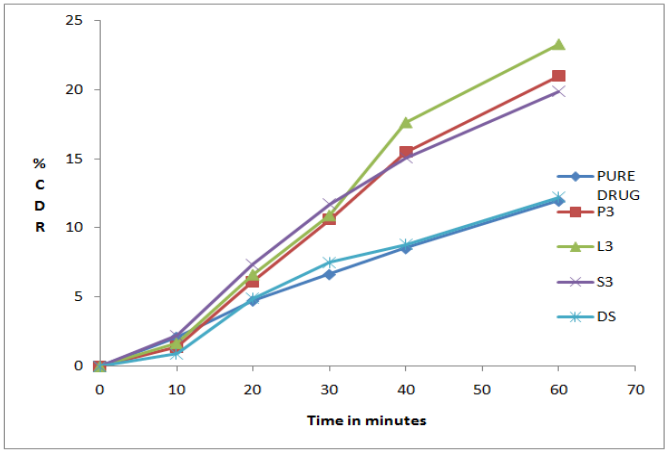


Fig.3. Heckel plot analysis

3.5 Scanning Electron Microscopy

Figure 4 shows the photomicrograph of pure drug and various agglomerates. The image of pure drug shows neddle shape and elongated form of morphology. The images of various polymeric agglomerates show spherical morphology, also the magnified images show slight alteration in the morphology of drug entrapped. This can be attributed to formation of amorphous form of celecoxib. The image DS shows the complete densification of formed agglomerates, this is attributed to complete and rapid diffusion of acetone through

formed emulsion droplets. The agglomerates prepared from Eudragits were smaller than the agglomerates of Polaxamer, which is attributed to the high stirring speed during agglomeration process of drug with Eudragits. Also the seeding done during preparation of agglomerates with Polaxamer resulted in rapid recrystallization of drug, leading to formation of agglomerates with larger particle size.



3.6 Pressure-Relative Density Relationship

The compression behaviour of agglomerates is expressed as the mean yield pressure value (MYP) derived from Heckel equation (Pawar *et al*,Sonnergard *et al*.). The low MYP values suggest plastic deformation as the predominant mechanism of consolidation. This type of mechanism is seen in comparatively softer material (Pawar *et al*.). The high value of MYP indicates fragmentation as the major mechanism, which is observed in brittle materials. The fragmentation leads to formation of new surfaces which on further compression come into closer contact of each other leading to strong bonding (Kachrimanis *et al*., 1998). This gives rise to a thicker compact. The table mentioned below shows various parameters of heckel analysis. It was found that the agglomerates prepared with Polaxamer 188 showed low MYP value indicating plastic deformation as major mechanism of consolidation. Also the crushing strength of these agglomerates was lower than the agglomerates prepared with Eudragits. This may be attributed to the entrapment of Polaxamer 188 in the agglomerates at the point of contacts, which results into weak bonding. The agglomerates prepared with Eudragits showed high crushing strength, this is attributed to their high brittle fracture index which is near to 1.20 (Kachrimanis *et al*., 1998). Thus the increase in fragmentation behaviour of these agglomerates resulted in high MYP values.

3.7 Pressure-tensile strength relationship

The tensile strength of agglomerates was calculated at120 Kg/cm^2. The relative increase in tensile strength of agglomerates compared to pure drug was calculated (Jadhav *et al*., 2007) this showed considerably higher values for agglomerates prepared by Eudragits, than the agglomerates prepared with Polaxamer 188. The high tensile strength of agglomerates containing Eudragit is due to complete and rapid diffusion of acetone due to high stirring speed. This resulted into increased wetting of surface by acetone giving rise to dense agglomerates (Yadav *et al*., 2009). Also the incorporated Eudragits have brittle fracture index comparatively higher than Polaxamer which resulted in high tensile strength of these agglomerates due to fragmentation. In case of Polaxamer 188 agglomerates the acetone: water ratio was high, the stirring speed was low also incorporation of Polaxamer in water increased viscosity of water, this all factors together contributed to decrease in diffusion of acetone through the system (Kawashima *et al*., 1995). The evaporation continued during filtration of agglomerates giving rise to irregular surface. And the entrapment of Polaxamer in agglomerates caused decrease in bonding within formed agglomerates.

3.8 Micromeritic analysis

The data in the table – shows the value of the values of angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. The value of bulk density is lowest for the pure drug which indicates a high intergranular space. The values of angle of repose, Carr's index and Hausner's ratio of all agglomerates are within desired range which indicates good flowability of all the spherical agglomerates. This is attributed to the increased sphericity, regular and large size of the crystals. Among all the agglomerates, the agglomerates P2 showed excellent flow properties.

4. Conclusion

The spherical agglomerates of celecoxib were prepared in presence of polaxamer 188 and Eudragits (S100, L100) in acetone water system. The physicochemical and micromeritic properties of agglomerates were considerably affected by this process.

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