Indian Journal of Pharmaceutical Education and Research | Association of Pharmaceutical Teachers of India

Enhancing Solubility and Dissolution of Celecoxib by Spray Drying using Pluronic F 127

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ABSTRACT

Submitted: 6-12-2010 Revised: 13-4-2011 Accepted: 29-5-2011

Celecoxib, a selective COX-2 inhibitor, exhibits poor water solubility, dissolution and flow properties. Thus, the aim of the present study was to improve the solubility and dissolution rate of celecoxib by preparing microspheres by spray drying technique using pluronic F 127. Celecoxib Microspheres containing different ratios of pluronic F 127 were produced by spray drying using dichloromethane as solvent system to enhance solubility and dissolution rate. The prepared formulations containing different ratios of drug and pluronic F 127 were evaluated for solubility and in-vitro dissolution. The prepared formulations were characterized by differential scanning calorimeter (DSC), fourier transform infrared spectroscopy (FT-IR), x-ray diffraction (XRD) and scanning electron microscopy (SEM). Dissolution profile of the prepared spray dried microspheres was compared with its physical mixture and pure sample. Spray dried microspheres exhibited decreased crystallinity. The solubility and dissolution of the microspheres containing different ratios of drug and polymer were significantly improved compared with physical mixture and pure sample of celecoxib. The solubility of microspheres containing Celecoxib and pluronic F 127 (1:5w/w) exhibited five fold increases than the pure celecoxib and dissolution of same ratio microsphere showed 98 % release in 30 min. while same composition in physical mixture showed 88% release in 60 min. Consequently, from the above result it can be concluded that spray dried microspheres of celecoxib is a useful technique to improve the solubility and dissolution of poorly water soluble drug like celecoxib.

Keywords: Spray drying, microspheres, celecoxib, pluronic F 127, solubility, dissolution.

INTRODUCTION

Celecoxib, 4-[5-(4-methylphenyl)-3-(trifluoromethyl) - 1*H*-pyrazol-1-yl] benzene sulphonamide, belongs to a novel class of agents that selectively inhibit cyclooxygenase- 2 (COX-2) enzymes. The introduction of this first selective COX-2 inhibitor (375-fold selectivity)[1,2] in the pharmaceutical market revolutionized 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 [3,4,5]. US FDA has approved its use in OA, RA, and dysmenorrheal with dose strengths of 100–200 mg once/twice daily. According to the biopharmaceutical classification system (BCS), celecoxib is an extreme example of a class II compound meaning that its oral bioavailability is determined by its dissolution rate in the GI tract [6-8]. Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of very poorly soluble compounds might be improved to minimize the limitations to their oral availability. There have been numerous efforts to improve drug dissolution rates. These include (a) reducing the particle size to increase the surface area; (b) using water-soluble carriers to form inclusion complexes; (c) solubilization in surfactant systems; (d) using pro-drugs and drug derivatization; and (e) manipulation of the solid state of drug substances to improve the drug dissolution i.e. by reducing the crystallinity of drug substances through formation of solid dispersions. However, there are practical limitations to these techniques [9]. Although particle size reduction is commonly used to increase the dissolution rate, there is a practical limit to the size reduction that can be achieved by such commonly used methods as controlled crystallization and grinding. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability. Salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs which are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants

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and co solvents leads to liquid formation that is usually undesirable from the viewpoints of patient acceptability and marketing [10]. Solid dispersions have been widely used to enhance the solubility, dissolution rate, and bioavailability of poorly soluble drugs[11-14]. There are different types solid dispersion systems categorized according to the physical states of the drug and the carrier in the systems. It may be a molecular solid solution, a dispersion of amorphous or crystalline drug particles in an amorphous carrier matrix, or a combination of a solution and dispersion of solids.

The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wettability, and drug precipitation as a metastable crystalline form or a decrease in substance crystallinity. The type of solid dispersion formed depends on both the carrier-drug combination and the method of manufacture. Spray drying is one of the such technique of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size [15,16,17]. The large surface area of the resulting particle should result in an enhanced solubility and dissolution rate, consequently, improved bioavailability. Pluronic F 127 is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene copolymers in a concentration ranging from 20- 30%. In general, pluronic F 127 are composed of white, waxy, free-flowing granules that are practically odorless and tasteless. The aim of the present study was to improve the solubility and dissolution rate of celecoxib by spray drying technique using different ratio of pluronic F 127.

METHOD AND MATERIAL

Materials

Celecoxib and pluronic F 127 were obtained as a gift sample from Ipca Pharmaceutical, Mumbai, India. All chemicals and buffers used were of analytical grade.

Preparation of microspheres

The microspheres were prepared by spray-drying technique. The spray drying was performed by Mini Spray Dryer LSD - 48; (Jay instrument & systems Pvt. Ltd. Mumbai). The different drug–polymer ratios used for various microsphere formulations were prepared described in Table 1. The polymer solution was prepared by adding given quantity of polymer to the dichloromethane as solvent. The given quantity of celecoxib was added to the polymer solution and the resulting mixture was spray-dried. The spray drying parameters are described in Table 2.

Table 1: Spray-Dried microspheres formulation

No.	Formulation Code	Different ratio of polymer and drug
Spray drying formulations		
1	SD 1	1:1
2	SD 2	1:3
3	SD 3	1:5
Physical mixture formulations		
1	PM 1	1:1
2	PM 2	1:3
3	PM 3	1:5

Table 2: Spray-Drying Parameters

Inlet temperature(°C)	Feed pump speed%	Vacuum (mm Wc)	Aspirator level (kg/cm^2)
43	15	-70	2

Preparation of physical mixtures

The different drug–polymer ratios used for various physical mixtures formulations were prepared as described in Table 1 and were prepared by mixing different ratio of celecoxib and pluronic F 127 in the mortar for 5 min and then sieving.

Evaluation of microspheres

Determination of percentage yield and drug content

The percentage yield of each formulation was determined according to the total recoverable final weight of microspheres and the total original weight of celecoxib and pluronic F 127.

Microspheres (50 mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml. After suitable dilution, samples were measured at 251 nm. Drug content was determined from standard plot.

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 spectroscopy (FTIR)

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). Samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-ray diffraction analysis (XRD)

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.The process parameters used were set as scan step size of 0.0170 (2).

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 surface topography of the crystals.

Mechanical properties

Tensile strength of microspheres was determined by compressing 500 mg of crystals using hydraulic press at different ton/cm^2 for 1 min. The compacts were stored in desiccator 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 (ó) of the compact (ton/cm^2) was calculated using following equation.

$$ó = 2F/ð Dt$$

where, F, D and t are hardness (ton), compact diameter (cm) and thickness (cm), respectively.

Determination of solubility

Drug solubility was determined by adding excess amounts of pure celecoxib, their physical mixture and microspheres to water and pH 7.4 phosphate buffer at 37 ± 0.5°C, respectively. The solution formed were equilibrated under continuous agitation for 24 h and passed through a 0.8 µm membrane filter to obtain a clear solution. The absorbance of the samples was measured using UV spectrophotometer method (UV 1601 A Shimadzu, Japan) at 251 nm and the concentrations in µg/ml were determined. Each sample was determined in triplicate.

Dissolution studies of microspheres

The dissolution of pure celecoxib, their physical mixture and microspheres was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml of pH 7.4 phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometer method (UV 1601 A Shimadzu, Japan) at 251 nm. Each sample was determined in triplicate.

RESULT AND DISCUSSION

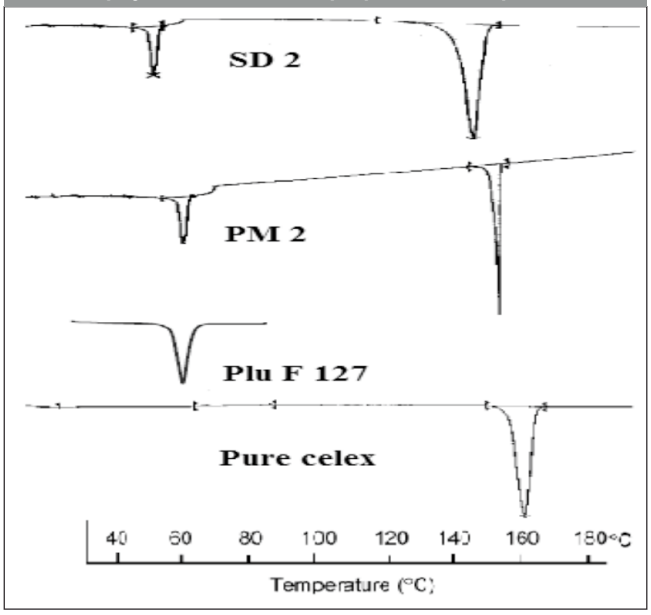
The glass transition temperature (Tg) is the second-order phase change temperature at which a solid glass is transformed to a liquid-like rubber. As the temperature increases above, Tg various changes, such as increase of free volume, decrease of viscosity, increase of specific heat, and increase of thermal expansion, are noticed. During spray drying, if the drying temperature exceeds the Tg of the polymer, the powder becomes soft or sticky while still warm. This cause sticking of the powder to the side walls of drying chamber. The Tg of Pluronic F 127 as provided by the manufacturer is 56°C, so dichloromethane was selected as solvent with boiling point 36°C, which is., lower than the Tg of Pluronic F 127.

The spray dried microspheres formulations were collected and were found to be free-flowing and white in color. The percentage yield of spray dried microspheres of different ratios of pluronic F 127 and celecoxib was found to be in the range of 59-77 %. This small yield could be increased by addition of solid substance or in large scale production. Drug content for the spray dried microspheres of different ratio of pluronic F 127 and celecoxib formulation was found to be in the range of 79-98 %±0.013.

DSC curves obtained for pure material, physical mixtures and microspheres are showed Fig.1. In DSC curve, pure celecoxib had a sharp endothermic peak at 160°C that corresponded to the melting point of celecoxib. In the thermogram of pluronic F 127, a sharp peak (56.1°C) was observed, which was associated with the endothermic melting of pluronic F 127. In DSC spectra of physical mixture and different ratios of microspheres were showed two peaks at 157 to 160 °C and 55 to 56.5 °C for celecoxib and pluronic F 127 respectively. The two melting transitions in the system made up of celecoxib and pluronic F 127 indicated that both materials formed a separate phase. It was found that celecoxib was in a crystalline state in the microspheres. In case of sample of microspheres (1:5 w/w), the endothermic peak of celecoxib was observed at 157.8°C indicating the decreased in crystallinity. This could be because of celecoxib was molecularly or amorphously dispersed in the phases and the melting endotherm was shorten on the DSC thermogram of microsphere then the physical mixture and pure sample of celecoxib, suggesting absence or reducing crystallinity and presence of amorphous state of drug[18]. On the other hand the physical mixtures of celecoxib and pluronic F 127 showed an apparent endothermic peak of celecoxib and pluronic F 127 at 159.88°C and 56.1°C respectively.

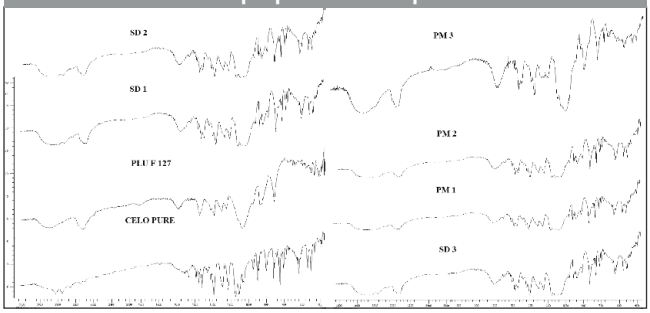
The FTIR spectra of pure celecoxib, pluronic F 127, their physical mixture and microspheres of different ratios are shown in Fig 2. FTIR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing and hydrogen bonding arrangements for different solid-state forms of an organic compound. Spectral variations originate due to alteration in bonds that exhibit characteristic vibrational frequencies,

Fig. 1: DSC Thermograms of pure celecoxib, pluronic F 127, its physical mixture and prepared microspheres.



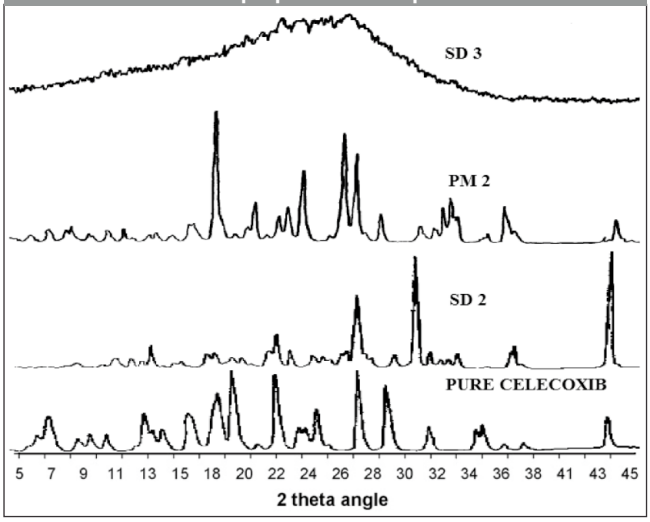
leading to frequency shifts and splitting in absorption peaks. The FTIR spectra of celecoxib **(Fig. 2)** showed a characteristic S=O symmetric and asymmetric stretching at 1164 and 1347 cm^{-1}, respectively. Medium intensity bands at 3338 and 3232 cm^{-1} were seen as a doublet, which are attributed to the N–H stretching vibration of $–SO_2NH_2$ group. The C–N stretching band observed at 1397 and 1388 cm^{-1} for prepared microspheres **(Fig. 2),** but in case of physical mixture these same bonds were shifted to lower frequencies at 1374 and 1379 cm^{-1} respectively. The shifts in frequencies indicate the possibility hydrogen bonding between the –C=O group of solvents and $–NH_2$ group of sulfonamide moiety present in celecoxib. This hydrogen bonding leads to increase in negative charge over oxygen atom caused by shift of electrons of –C=O group, resulting in the weakening of its double bond character. Hydrogen bonding alters the force constant of C=O as well as C–N, thus altering the frequency of stretching and bending vibrations. The bands corresponding to N–H stretching of $–NH_2$ group became diffused and broadened in case of microspheres and also a shift to lower frequency (1339 cm^{-1}) was observed in asymmetric stretching of $–SO_2$ group. This clearly indicates the participation of $–NH_2$ and $–SO_2$ groups in intermolecular hydrogen bonding between celecoxib molecules. The spatial arrangement of celecoxib molecules in crystal lattice does not allow intermolecular hydrogen bonding which starts to occur once the orderliness of crystalline lattice is disturbed by formation of amorphous form. Hence above result revealed that there was no significant change in IR spectra of celecoxib samples.

Fig. 2: FT-IR spectra of celecoxib, pluronic F 127, celecoxib & pluronic F 127 physical mixture and different ratio of prepared microspheres.



X-Ray diffraction was carried out to analyze potential changes in the inner structure of celecoxib nanocrystal during the formulation. The extent of such changes depends on the chemical nature and physical hardness of the active ingredient. The powder X-ray diffraction patterns of the unprocessed celecoxib and pluronic F 127, their physical mixture (1:5 w/w) and microspheres (1:5 w/w) formed by spray drying are showed in Fig. 3. The characteristic peak of the celecoxib appeared in the 2θ range of $10–30^{0,}$ indicating that the unprocessed celecoxib was a crystalline material. In x-ray diffractograms of pure celecoxib powder, pluronic F 127, their physical mixture and prepared microspheres showed that crystallanity of celecoxib in the formulations was not affected significantly. But in the XRD diffraction pattern of microsphere (1:5 w/w) of drug showed absence, broadening and reduction of major celecoxib diffraction peak indicating that mostly an amorphous form (disordered state) existed in the microspheres this could explain the observed enhancement of solubility and dissolution of celecoxib in microspheres[18].

Fig. 3: XRD patterns of celecoxib, pluronic F 127, celecoxib & pluronic F 127 physical mixture and different ratio of prepared microspheres.



The SEM image of the celecoxib, pluronic F 127, their physical mixture and microspheres are shown in Fig. 4. The celecoxib particles in the physical mixture were broken into much smaller ones and irregular size (19-37 µm) and the shape of prepared microspheres are uniform and spherical in shape with small in size (6-11 µm).The spherical shape of microspheres does not lead to cake formation during storage because of less point of contact thereby increasing the stability of the microsphere formulation, Which is an advantage over other shapes.

Microspheres exhibited superior compressibility characteristics compared to physical mixture and pure sample of celecoxib drug crystals (Fig. 5). It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals[19]. Surface freshly prepared by fracture enhanced the plastic inter particle bonding, resulting in a lower compression force required for compressing the microspheres under plastic deformation compared to that of single crystal[19]. Tensile strength of the same ratio of microspheres and physical mixture (5:5 w/w) showed that tenstile strength of microspheres higher than physical mixture as well as pure sample. But tensile strength of microspheres containing celecoxib and pluronic F 127 (1:5w/w) of show much higher than physical mixture (1:5w/w) and pure sample this may be due to the increasing in the plastic inter particle bonding of microspheres.

The solubility result of pure celecoxib, their physical mixture and prepared microspheres in water and in pH 7.4 phosphate buffer is shown in Table 3. The solubility of pure celecoxib in water and pH 7.4 at 37°C was found to be 7.10µg/ml and 13.35µg/ml respectively. The results show that the solubility of celecoxib increased on increasing the concentration of pluronic F 127. The solubility of celecoxib from the microspheres was significantly higher than that from it is physical mixture and pure celecoxib, when the microspheres and physical mixture contained the same weight ratio of

Fig. 4: SEM of celecoxib, pluronic F 127, celecoxib & pluronic F 127 physical mixture and different ratio of prepared microspheres.

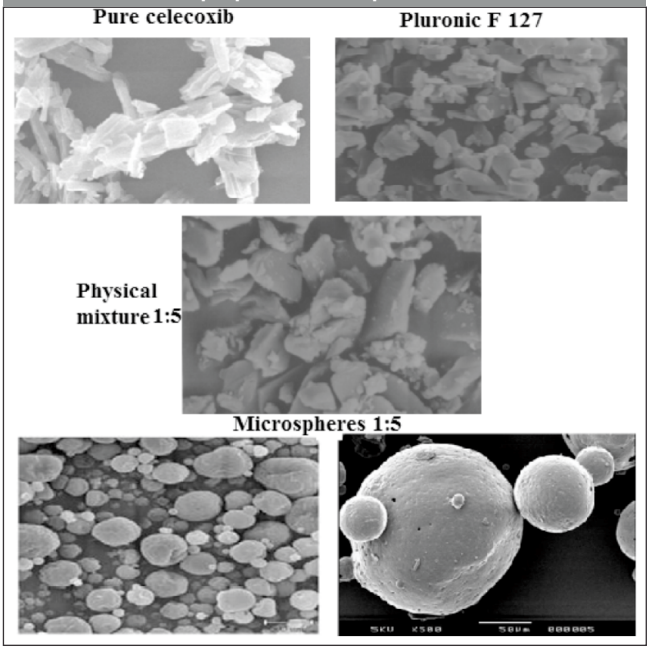


Fig. 5: Tenstile strength of different samples of celecoxib

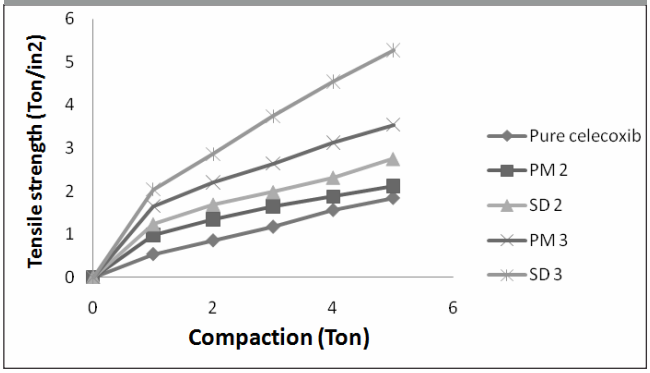
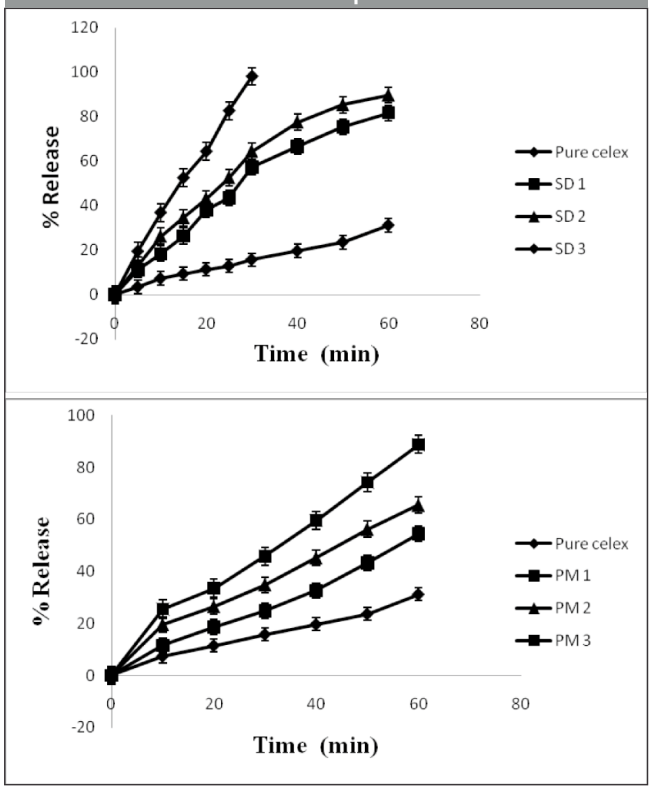


Table 3: Solubility of celecoxib microspheres and physical mixture in water and pH 7.4 phosphate buffer .

Different formulations containing polymer: Drug ratio(w/w)	Concentration of celecoxib in water (µg/ml) ± SD	Concentration of celecoxib in pH 7.4 µg/ml ± SD
Pure drug	7.10±0.02	13.35 ±0.02
SD 1	13.826±0.03	26.038±0.01
SD 2	23.983±0.03	46.286±0.01
SD 3	35.103±0.01	63.826±0.02
PM 1	9.873±0.025	16.148±0.04
PM 2	14.131±0.023	27.324±0.03
PM 3	19.695 ±0.031	38.760±0.01

Fig. 6: Dissolution profiles of different samples of pure celecoxib, its Physical mixture and different ratio of spray dried microspheres.



celecoxib and pluronic F 127 (1:5 w/w). It was found that the solubility of celecoxib from the microspheres almost double folds than compared to its physical mixture in water and pH 7.4 respectively. The higher solubility of celecoxib from microspheres may be due to the increased in surface area, wetbility of microspheres and solubilizing effect of the pluronic F 127 as carrier to microspheres[20].

The dissolution of pure celecoxib, physical mixture and prepared microspheres in pH 7.4 phosphate buffer shown in Fig. 6. The dissolution profiles were plotted as the % release from the different microspheres, physical mixture and pure celecoxib versus time in minute. The rate of dissolution of pure celecoxib was slow compared with celecoxib from its physical mixtures and different microspheres formulation in 60 min. The % release from ratio of (1:5 w/w) drug and pluronic F 127 showed more release compared to other ratios. In case of microspheres containing (1:5 w/w) showed 98% release in 30 min and at the same ratio of physical mixture showed 88% release in 60 min. There was a significant difference in the drug release between the microspheres and physical mixture. The increase in dissolution from the microspheres and physical mixtures was probably due to the wetting and solubilizing effect of the pluronic F 127, which could reduce the interfacial tension between the celecoxib and the dissolution medium, thus leading to a higher dissolution rate then pure celecoxib. The large surface area of the resulting microspheres should result in an enhanced dissolution rate and thereby improve the bioavailability.

CONCLUSION

In this present study, an increased solubility and dissolution rate of celecoxib were achieved by preparing microspheres by spray drying technique using different ratio of pluronic F 127. DSC, FT-IR and XRD studies showed that there is no change in the crystal structure of celecoxib during the spray drying process and showed that spray dried microspheres exhibited decreased crystallinity. The solubility and dissolution of the spray dried microspheres was improved significantly compared with its physical mixture and pure sample of celecoxib. The celecoxib microspheres containing (1:5) w/w (celecoxib: pluronic F127) showed highest % of drug release and solubility compare to other ratio, physical mixture and pure sample of celecoxib. Hence this spray drying technique can be used for formulation of tablets of celecoxib by direct compression without further process like (mixing, granulation) with directly compressible tablet excipients. Formulation SD3 containing celecoxib and pluronic F127 (1:5 w/w) can further be studied for its bioavailability study, stability study and pharmokinetics parameters as this ratio exhibited increased dissolution.

ACKNOWLEDGEMENTS

The authors are thankful to Ipca labs, Mumbai, India for the gift sample of Celecoxib and pluronic F 127, and Principal, J.S.S.College of Pharmacy, Mysore for providing facilities to carry out this work.

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