Research Article

Microparticulate Formulations and Physicochemical Evaluation of Poorly Water Soluble Drugs by Using Spray Drying Technique

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ABSTRACT

Naproxen is a novel, second generation, selective COX-2 inhibitor, administered orally as a non-steroidal anti-inflammatory and analgesic drug. It has poor solubility and low bioavailability. Therefore, improvement in solubility and/ or dissolution rate of poorly water-soluble drug may be achieved through the formation of solid dispersions. In the present study, solvent evaporation method by spray drying technique was utilized to prepare solid dispersions of Naproxen with non-ionic surfactant as poloxamer 188. Spray-drying is a common technique used in pharmaceuticals to produce a dry powder from a liquid phase. This technique has also been employed as a microencapsulation method because it can be adapted to the development of different systems, microspheres or microcapsules, depending on the initial aqueous formulation, a solution, a suspension or an emulsion. We have developed a method to dry micro particulate aqueous suspensions by spray-drying in order to obtain dried particles formulations. Solid dispersions in the form of spray-dried powder and spray dried Naproxen were characterized initially in comparison with pure Naproxen, by drug content, saturation solubility, dissolution rate, Scanning electron microscopy (SEM), Thermal analysis, Radiograph powder diffraction (XRPD) and Infrared spectroscopy (FTIR).

Keywords: Spray-drying, Naproxen, Solid dispersion, Dissolution rate.

INTRODUCTION

In current era, various innovative chemical entities (NCEs) have been synthesized on the strength of structure of their target receptors by means of combinatorial chemistry, which consequences in the creation of very large molecules among superior degree of hydrophobicity. Their poor aqueous solubility may grounds reduced solublization in the gastrointestinal tract with little and changeable bioavailability.[1] It is recurrently documented that approximately 40% of NCEs revealed by the pharmaceutical researchers are poorly soluble or lipophilic in nature.[2] several studies have been performed to overcome the limited dissolution rate hurdle. The aim of all these attempts is to increase the dissolution rate and thus to enhance absorption and bioavailability. This can be achieved by reducing the particle size in the micro- or nano-scale according to the Noyes–Whitney equation. Therefore, for this particular purpose, several approaches are used such as jet-milling, high pressure homogenization, supercritical fluid technology and spraydrying.[4] Solid dispersion based spray drying technology is extensively applied in pharmaceutical industry because it is easy, financial and beneficial.[5]

In order to unfold the possible underlying causes of the dissolution inconsistency of SD in the current study the aspect of polymeric was focused on. Here hydrophilic polymers were used as a carrier in the preparation of spray dried solid dispersion.

Naproxen sodium, (NAP) [(+)-(S)–2-(6-methoxy naphthalen-2-yl) propanoic acid], a nonsteroidal anti-inflammatory drug (NSAID), has been indicated for various painful indications and proved as effective as other NSAIDs with lower indications of gastro-intestinal adverse effects and thus, resulted in a greater compliance with treatment. Naproxen sodium is practically insoluble. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. Therefore, improvement in solubility and/ or dissolution rate of poorly water-soluble drug may be achieved through the formation of solid dispersions. In the present study, solvent evaporation method by spray drying (SD) technique was utilized to prepare solid dispersions of Naproxen with poloxamer 188.

MATERIALS AND METHODS

Materials

Naproxen, Poloxamer 188, Lactose, Methanol, Distilled Water, Acetone , 0.1 N Hcl

Methods

Microparticles prepared by spray drying

Spray dried particles consisted of Naproxen /Poloxamer 188/lactose (1:1:1 ,1:2:1(w/w) ratio) were prepared by dissolving the drug or drug/polymer mixture in acetone/water (40:60 (v/v) ratio) solution. The solution was spray dried using Mini Spray Dryer B-290- (JISL) at a pump rate of 35%, an air flow rate of 600 L/h, aspirator level at 100%, Inlet temperature at 97 ±2°C and outlet temperature at 38 ±1°C. The formed microparticles were separated using cyclone separator, collected and stored in a desiccators at ambient

temperature until ready to be used naproxen/ Poloxamer 188 mixture.

Table 1: Various solid dispersion batches with different ratios prepared by spray drying

Type of formulation	Naproxen 500 (mg)	Poloxamer188 500(mg)	Lactose 250(mg)
Batch-A	1	1	1
Batch-B	1	2	1

Evaluation of micro particles

Determination of percent yields and drug contents

The percentage yield of each formulation was determined according to the total recoverable final weight of microparticles (prepared by spray drying) and the total original weight of Spray dried particles. Samples of each complexes were assayed by dissolving weighed amounts (100mg) of phosphate buffer PH 7.4. The solution is filtered, diluted and drug content was determined spectophotometrically at 238 nm.

Saturation Solubility Studies

Saturation solubility was determined by the shake-flask method[16]. Plain NAP and SDs in excess quantity were placed in separate glass-stoppered flasks containing 10 mL of distilled water. The samples were placed in an orbital shaker (CIS-24 Remi, India) at 37 °C and 100 rpm until equilibrium was achieved (24 h). The aliquots were filtered through Whatman No. 41 filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometrically at 238 nm.

***In vitro* dissolution studies**

The dissolution studies were performed using United State Pharmacopoeia type II dissolution test apparatus(Veego). Naproxen, particles equivalent to 100 mg of drug were placed in the dissolution vessel containing 900 mL of water maintained at 37°C ±0.5°C and stirred at 100 rpm. Naproxen, raw material was used as control. Filtered samples, using 0.45µm membrane filter, were collected periodically and replaced with a fresh dissolution medium. The concentration of Naproxen, released was determined spectrophotometrically at 238 nm on a UV/Vis spectrophotometer. The dissolution studies were conducted in triplicates for each formulation (spray dried naproxen, particles with Poloxamer 188 and control).

Scanning electron microscopy

Surface morphology of naproxen /Poloxamer188 spray dried and naproxen /Poloxamer 188 were examined using a scanning electron microscope (Hitachi S3000N Electron Microscope, Hitachi, UK). Naproxen particles were fixed on an aluminium stub with a conductive double sided carbon tape and sputter- coated with gold/palladium. The coating was done by exposing the samples to an Argon atmosphere at about 10 Pascals at 20mA for 5 minutes.

Fourier-transform Infrared spectroscopy (FT-IR)

FT-IR spectra of Naproxen and Naproxen Poloxamer 188 particles (spray dried) were obtained using IR spectrophotometer (PerkinElmer FT-IR System, Spectrum BX, Perkin- Elmer, UK). The samples were scanned over the wave number range from 4000 to 550 cm^{-1}.

Differential scanning calorimetry (DSC)

The changes, if any, in the thermal characteristics of naproxen in the prepared formulations were studied by differential scanning calorimeter (DSC Q1000, TA instrument, England). Approximately 3-6 mg samples of Naproxen, Poloxamer 188 and Naproxen /Poloxamer 188particles (prepared by spray drying) were hermatically sealed in aluminum pans and heated between 20 and 90°C with a heating rate of 5°C/min. The DSC instrument was calibrated with sapphire and indium before running the samples.

X-ray Diffraction

XRD was performed using X-ray fluorescence spectrophotometer with a line as the source of radiation. Standard runs were carried out using a voltage of 56 kv, a current of 182 mA and scanning rate of $2^{0}Min^{-1}$ over a 2 θ range of 5-90^{o}C

RESULT AND DISCUSSION

Determination of percent yields and drug contents

Percent yields

The spray drying conditions were optimized based on the process yield, which was 69- 71 % for Batch A, 62- 65 % for solid dispersions of naproxen with poloxamer-407 for batch B

Drug content

The drug content in spray dried Batch A and Batch B were found to be 99.05 ± 0.98 and 97.93 ± 0.76 % (n= 3) respectively. Thus, the spray drying technique was suitable for the preparation of solid dispersions with high content uniformity.

Saturation Solubility Studies

Saturation Solubility Studies, pH Solubility Profile

Figure 1 and 2 represents the saturation solubility of the Spray dried and pure Naproxen showed a solubility of 1.45 µg/mL in distilled water, 18.5 µg/mL in pH 1.2 buffer, and 27.7 µg/mL in pH 7.0 buffer. The saturation solubility increased with an increase in carriers. This might be due to better wetting ability associated with poloxamer and lactose solid dispersions by spray drying method. Carriers have very fine particle size and, hence, large surface area, so as the proportion of carrier increases, a larger surface is presented for adsorption of the drug crystals. Evaporation of solvent leads to an increase in interfacial area of contact between the drug particles and dissolution medium. The affinity between the hydrophilic inert carriers of the dissolution fluids facilitates rapid

penetration into the particles, further enhancing the dissolution process.

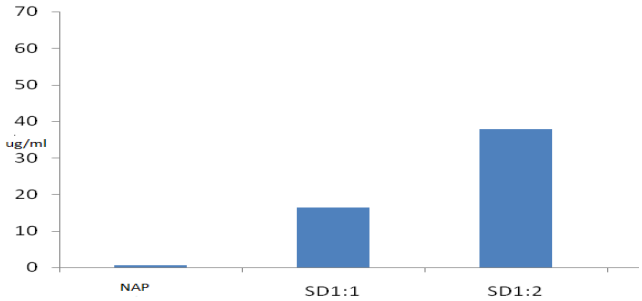

Figure 1: Saturation Solubility (µg/mL)

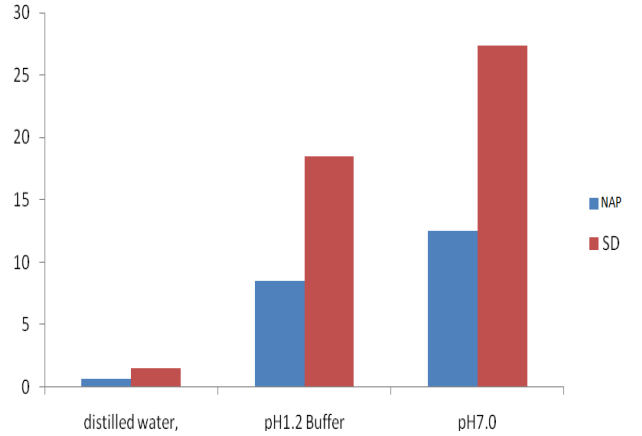

Figure 2: pH dependent Solubility in different media (µg/mL)

Dissolution rate

Naproxen showed saturation solubility 27.45% and 90-95 % drug release (Fig.3) within 60 minutes in the dissolution medium. Spray dried Naproxen showed a significant improvement in saturation solubility and dissolution rate (Fig. 3) over pure naproxen This could be attributed to the decreased crystallinity of naproxen (revealed by DSC and XRPD studies) and reduction in particle size i.e. increased surface area during spray drying (revealed by SEM images).

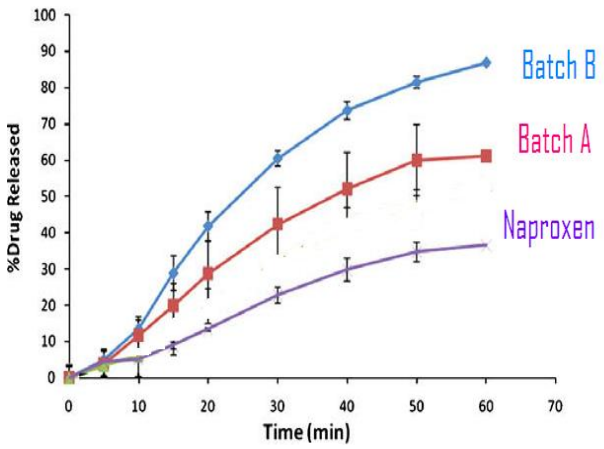

Figure 3: Dissolution pattern of Naproxen, Batch A, Batch B

Slightly better drug release profiles were observed for Batch A and Batch B of SDs than that of pure drug (Fig. 3). It was because of the inherent differences between two ratio in terms of dissolution rates, hydration, possible complexation of drugs with two ratio and hence degree of amorphization of drug achieved with two carriers. Among the two proportions batch B SDs, 1:2:1 proportion reported highest saturation solubility than batch A 1:1:1. For SDs, 1:2:1 proportion exhibited maximum drug release and saturation solubility over other proportions.

Scanning electron microscopy

The microphotographs of naproxen and solid dispersions are shown at different magnifications in Fig. A, B, pure drug respectively. Naproxen consisted of discrete, elongated flake– like crystal structures with rough edges. These structures were also covered on their surfaces by the fine particles.

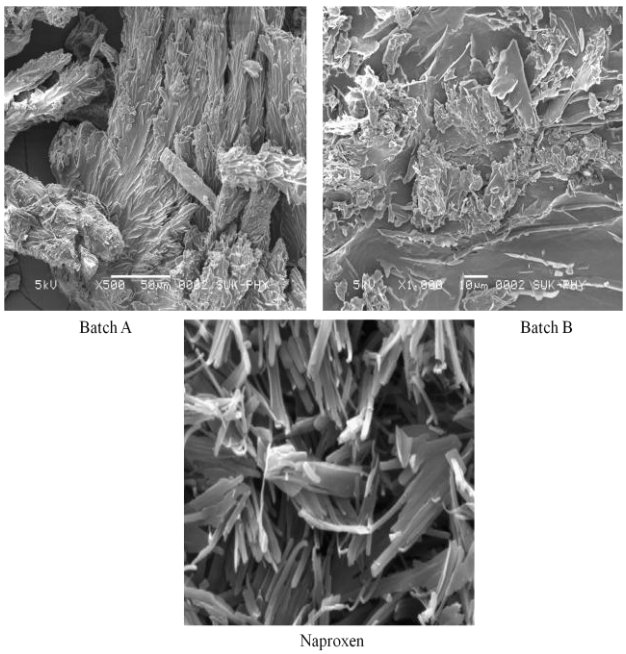

Figure 4: SEM of Naproxen and solid dispersions Batch A and Batch B

The SEM images of solid dispersions showed a distinct morphology after spray-drying. The photomicrographs revealed that the larger crystals of naproxen were transformed to less crystalline structures in their solid dispersions. Thus, the appearance of all the solid dispersions like matrix of spherical or near- spherical microparticles indicated physical transformation of naproxen in the solid dispersions, which was further confirmed by the DSC and XRPD studies. The surface morphology of Batch A SDs showed porous appearance, whereas Batch B showed the near- spherical shaped naproxen. Particles were coated with poloxamer and these small aggregates were found to grow as layers were built upon each other with increasing concentration of poloxamer[12, 13]. Such irregularities at the surface of particles have resulted in increased apparent surface area of particles, resulting in enhanced saturation solubility and dissolution rate of naproxen in the respective proportions of solid dispersions.

Fourier-transform Infrared spectroscopy (FT-IR)

FT-IR patterns of naproxen, naproxen/ poloxamer pure drug as well as the related nanoparticles are demonstrated in Fig 5. Matching up to FT-IR spectrum of naproxen with the physical mixtures in the ratios of 1:1:1 and 1:2:1 revealed no distinctive changes indicating that poloxamer188 was not involved in intermolecular interaction with naproxen in physical mixtures However, the intermolecular interaction between naproxen and can be plainly observed in the FT-IR spectrum of the related microparticles [14,15]. A reduction in the intensity of peak in 1265cm^{-1} as well as coming out of two jointed peaks in 2952cm^{-1} and 2987cm^{-1} might be attributed to the hydrogen bonding interaction between naproxen and poloxamer in the microparticles. Powders were subjected to FT-IR spectroscopic analysis, and their spectra at 800–1800 cm^{-1} are shown in (Fig 5).

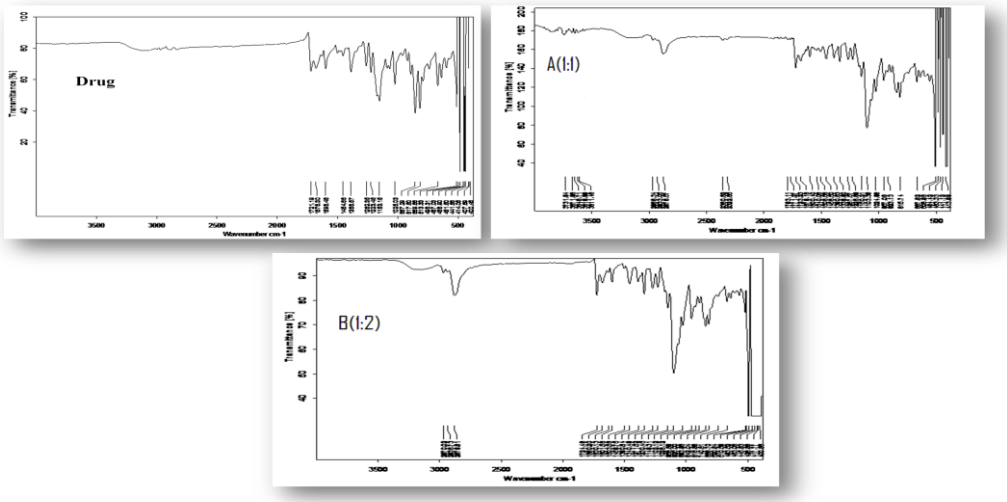

Figure 5: FTIR of Naproxen and solid dispersions Batch A and Batch B

The FT- IR spectra of the solid dispersions of naproxen showed a slight shift and broadening of –C-O-C- stretching vibration peak (at 956.6 cm^{-1}) and –C–H stretching vibration peak (at 2877.6 cm^{-1}) characteristic of poloxamer-407 and a free O–H stretching vibration peak (a broad band between 3650 cm to 3150 cm^{-1}) and S=O stretching vibrations (at 1145.6 cm^{-1}) characteristic of naproxen. These observations indicated possibility of intermolecular hydrogen bonding via S = O group of naproxen and –C-O-C- group of poloxamer-407 in their respective solid dispersions[16]. Thus, it can be concluded from the abovementioned observations that though the drug molecules are hydrogen bonded with the polymers to a greater or lesser extent through sulfonamide groups, the overall symmetry of the molecule is not significantly affected.

Differential scanning calorimetry (DSC)

DSC is one of the most general methods to find out the physicochemical interaction between drug and polymer in a formulation. DSC thermograms of intact naproxen, poloxamer188, microparticles are demonstrated in Fig 6. The prominent and sharp endothermic peak at 154 ◦C in the thermogram of naproxen represents its melting point. This sharp endothermic peak indicated that the intact naproxen was in crystalline anhydrous state.

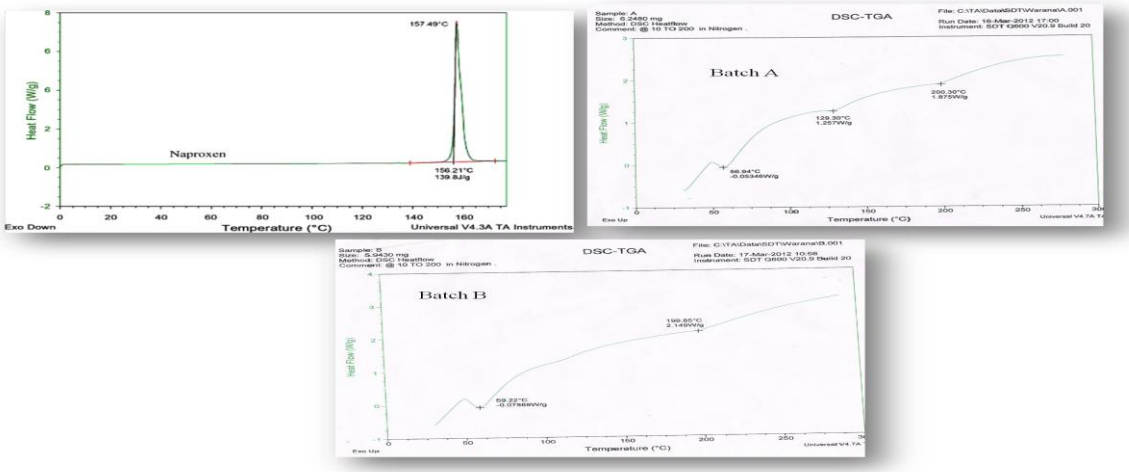

Figure 6: DSC of Naproxen and solid dispersions Batch A and Batch B

The intensity of endothermic melting peak was reduced in the DSC thermograms of drug/polymer physical mixtures which could be because of solubilization of naproxen into carrier and/or solid state interaction induced by heating as well as dilution effect of polymer [17,18]. The microformulations depicted no distinctive peak in the DSC profiles owing to the decreased crystallinity in the formulations and/or drug lavation in the amorphous carrier as well as solid state interaction induced by heating.

X-ray Diffraction

As indicated by X-ray examinations (Fig. 7), the intact Naproxen manifested the distinct peaks at 2°: 6.5°, 12.4°, 16.6°, 19°, 20°, 22.2°, 23.8° and 28.2°, although there was no clear peak in the X-ray diffractograms for the amorphous polymer.

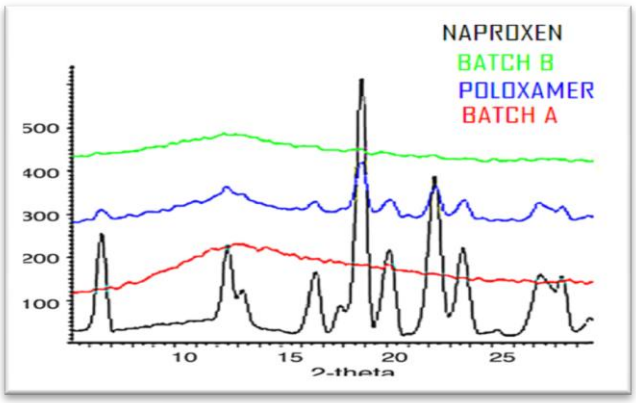

Figure 7: XRD of Naproxen and solid dispersions, Batch A and Batch B

The X-ray spectra of the pure drug exposed that the intensities of typical peaks for intact drug were lowered by increasing the poloxamer weight ratio due to the dilution effect without a qualitative disparity of drug diffractogram. Microparticles prepared with poloxamer 188 were characterized by the absence (or faint) of distinct diffraction peaks, signifying a drug amorphization or its 61lavation in the amorphous carrier.

CONCLUSION

Enhancement in the solubility and dissolution characteristics of poorly water- soluble drugs is important to achieve better bioavailability. Thus, the present study was aimed to enhance the solubility and dissolution rate of naproxen by solid dispersions with poloxamer-188 and prepared by spray drying technique. It can be concluded based on the observations of the study that the amorphous form of naproxen showed improved biopharmaceutical properties., solid dispersions of naproxen with poloxamer-188 enhanced solubility of drug and reported only an insignificant decrease in solubility properties during stability study, in comparison with pure naproxen and spray dried naproxen. The DSC and PXRD studies confirmed decrease of drug crystallinity in the microparticles. The intermolecular interaction between naproxen and poloxamer was detected in the FT-IR spectrum of the micro particles. It should be also evoked that all micro particles displayed a slowed release pattern with the reduced burst release in comparison with the intact drug powder and physical mixtures of drug and polymer.

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