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Original Research Article

Pharmaceutical characterization and dissolution behavior of ibuprofen/Soluplus solvent cast films

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Abstract

Purpose: *To characterize the physicochemical and dissolution properties of Soluplus®/ibupofen solid dispersions prepared by solvent casting technique.*
Methods: *Soluplus® was used as a film-forming agent whereas ibuprofen served as a poorly soluble biopharmaceutics classification system (BCS) class II active pharmaceutical ingredient (API). The solution casting of ethanolic Soluplus®/ibuprofen was carried out on a release liner and dried under a vacuum. The crystallinity of crushed films was examined using powder x-ray diffraction (PXRD), while a USP Type II apparatus was used to determine their dissolution behaviour.*
Results: *Ibuprofen was uniformly distributed in an amorphous form into the cast films. The PXRD-based confirmation of crystalline peaks' absence revealed a significantly higher dissolution rate in alkaline and acid media when compared to the pure drug.*
Conclusion: *Soluplus® (polymeric dispersant)-based solvent casting is a simple and efficient technique to prepare highly water-soluble solid dispersions of ibuprofen. This film cast technique may be suitable for various applications where a film or powder form of a drug with enhanced solubility in different aqueous media is desired.*

Keywords: *Solid dispersions, Spray drying, Film-casting, Soluplus®, Ibuprofen*

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INTRODUCTION

The poor solubility of several active pharmaceutical ingredients (APIs) could lead to the failure of newly developed medicines, variable therapeutic outcomes, and decreased patient compliance [1-3]. Therefore, solubility is a key factor in the improvement of drug formulations and the development of better drug delivery systems [4]. Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is a classic example of an API with poor aqueous solubility (Figure 1A). Ibuprofen possessing a high

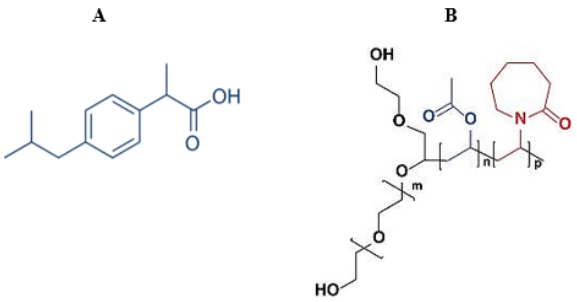

Figure 1: Chemical structure of (A) Ibuprofen (B) Soluplus®

membrane permeability is practically water-insoluble (21 mg/liter at 25 °C). Ibuprofen dissolution rate mainly limits its absorption, which necessitates high-dose administration to achieve desired therapeutic outcome [5,6].

Several methods including precursor design, salt generation, reduction of particle size, lipid formulation, complexation, and induction of solid dispersants have been tested for enhancing ibuprofen solubility and bioavailability [6-10]. Solid dispersion is a widely used cost-effective formulation technique to increase the dissolution rate, aqueous solubility, and permeability of poorly water-soluble drugs with limited bioavailability [11].

Active ingredient dispersal in an amorphous polymer matrix, mostly at the molecular level, is known as solid dispersion [12]. Sulfathiazole eutectic mixture with aqueous soluble excipients is a primary example of solid dispersion that was followed by several FDA-approved solid dispersions [13]. Factors such as excipients, drug/excipients ratio, and processing techniques are crucial for successfully generating solid dispersions [14-16]. Polymeric excipients with a high glass transition temperature (T_g) in a solid dispersion formulation could slow down the nucleation and subsequent growth of drug crystals [17,18].

Soluplus® (Figure 1B) is a copolymer of polyethylene glycol, polyvinyl acetate, and polyvinyl caprolactam. In recent years, it has been investigated as a potential polymeric aid to prepare solid dispersions. The unique solubility and chemical properties of Soluplus® have facilitated the development of solid solutions by hot extrusion and formulation of amorphous solid dispersions through film casting, spray drying, high shear dispersion, microwave radiation, electric rotation, and ball milling [17,18]. In this study, a simple solvent casting method was investigated to prepare Soluplus®/Ibuprofen dispersions. Solvent evaporation-based film casting of the drug/polymer blend is a classical approach for the preparation of solid dispersions [19-21].

EXPERIMENTAL

Materials

Ibuprofen and Soluplus® were provided by BASF (Ludwigshafen Germany). Ethyl alcohol was purchased from Pharmco AAPER (Brookfield, CT, USA). Scotchpak™ Release Liner (code number: 1022) and Scotchpak™ Backing Beige Polyester Film (code number: 1109) were provided by 3M (Oakdale, MN, USA).

Preparation of Soluplus®/ibuprofen solvent cast films

Solid dispersions were prepared by casting an ethanolic mixture of ibuprofen and Soluplus® onto open trays under controlled drying instead of using a rotovap. Briefly, 3 g of Soluplus® was dissolved in 5 mL ethanol in a clear glass flask using a homogenizer (Power Max 200, VWR International, Radnor, PA, USA) and a transparent solution was obtained. Then, ibuprofen was added to attain a final ibuprofen concentration of 20 % w/w (calculated as a ratio of ibuprofen to the dry Soluplus®/ibuprofen mixture). The ethanolic Soluplus®/Ibuprofen solution was mixed for 5 min and sonicated for about 10 min using an acoustic bath (5510RDTH Ultrasonic Corporation, Danbury, CT, USA) to remove the air bubbles. Soluplus® and ibuprofen solution was then molded with a film applicator (8-dimensional sizes) on a release liner (ScotchpakTM 1022) to a 0.5 mm thickness. After casting, the wet films were dried at room temperature for 2 h followed by vacuuming for 48 h to remove the residual solvent.

Powder x-ray diffraction (PXRD)

A Bruker multifunctional X-Ray diffractometer fitted with a Vantec 500 probe and monochromatic radiation from a Cu K x-ray tube (= 1.5 056) was used to capture PXRD forms of the Soluplus®/Ibuprofen cast films. Samples were scanned from 10° to 70° at 25 °C.

Quantification of drug content

A UV spectrophotometer (Unicam, Cambridge, UK) was used at a wavelength of 275 nm to quantify the amount of ibuprofen in a physical mixture with Soluplus®, and its content in the cast film.

In vitro dissolution study

The ibuprofen dissolution rate was measured using a USP Type II apparatus (VK 7000, Varian Incorporation, Cary, NC, USA). The crushed ibuprofen or Soluplus®/Ibuprofen cast films were placed in size 2.0 clear gelatin capsules (Qualicaps, Whitsett, NC, USA). These capsules were dropped in 900 mL of dissolution medium (distilled water, pH 6.8, and phosphate buffer solution of pH 1.2) using sinkers. The dissolution medium temperature was constantly maintained at 37.5 °C (VK750 heater, Varian Incorporation, Cary, NC, USA). The rotation speed of the agitator was adjusted at 100 rpm. Three milliliters samples were collected at different time intervals (0, 1, 5, 15, 30, 60, 90, and 120 min) using a sampling cannula fitted with a porous micrometer filter (10 µm), (Accessory Quality Laboratories LLC, Bridgewater, New Jersey, USA). A UV/visible spectrometer was used to quantify the amount of ibuprofen in the samples at an absorption wavelength of 275 nm.

RESULTS

Drug content

The ibuprofen uniform dispersion in the solid dispersions and cast films was confirmed by spectrophotometrically quantifying the drug amount in various samples. Ibuprofen concentration was found to be within 98 – 99 % of its theoretical amount.

Powder x-ray diffraction (PXRD)

The PXRD analysis revealed ibuprofen crystallinity in solid dispersion form with Soluplus® (Figure 2). Diffraction patterns of ibuprofen, Soluplus®, and their cast film were obtained. The individual spectra of ibuprofen and Soluplus® were similar to previous reports. Ibuprofen exhibited distinctive crystalline peaks. These peaks were absent in the ibuprofen/Soluplus® film, which exhibited amorphous characteristics as a consonance to the absence of stereo uniformity and the presence of a large lateral group in the Soluplus® carrier.

Dissolution studies

The dissolution profile of pure ibuprofen, its physical mixture with Soluplus®, cast films, and crushed Soluplus®/Ibuprofen films are presented in Figures 3, 4, 5, and 6, respectively. All samples contained 100 mg ibuprofen in water and phosphate buffer (pH 1.2 and pH 6.8). Ibuprofen is a relatively weak acid, therefore, its higher solubility was expected under alkaline conditions. Figure 3 depicts that approximately 30 % of neat ibuprofen was dissolved in alkaline media after two hours whereas a significantly lesser amount was dissolved in water and acidic media. The physical mixture of Soluplus® and ibuprofen also could not improve the drug dissolution despite the known emulsifying properties of the polymer (Figure 4). Solid dispersions (intact or crushed films) of ibuprofen were almost completely (100 %) dissolved in the media at pH 6.8 whereas 50 % of the drug was dissolved in acidic media (Figures 5, Figure 6, and Figure 7).

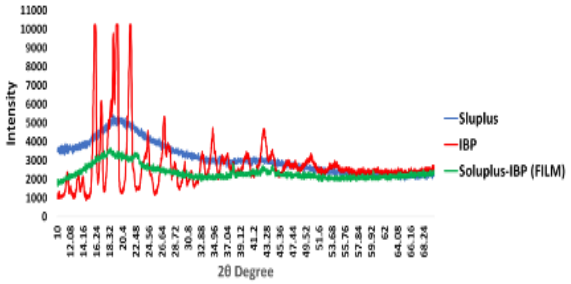

Figure 2: PXRD of pure ibuprofen, Soluplus®, and Soluplus®/Ibuprofen films

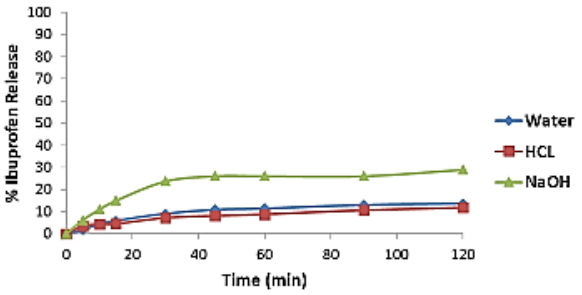

Figure 3: Release Profile of pure ibuprofen

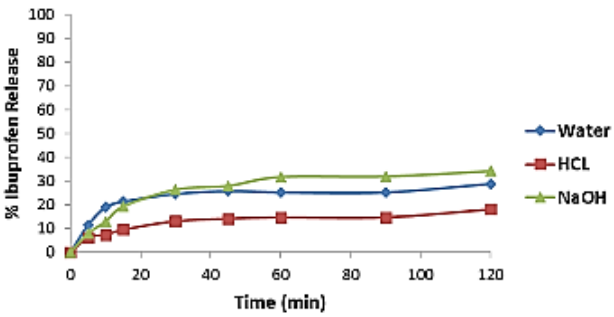

Figure 4: Release Profile of Soluplus®/Ibuprofen physical mixture

DISCUSSION

The PXRD was used to examine the crystallinity of the cast films. Ibuprofen in its pure form generated sharp and narrow peaks within 2θ

angles of 0 – 70 ° indicating its crystalline nature. Contrarily, Soluplus® is a non-crystalline polymer [18]. Therefore, Ibuprofen peaks were absent within the same 2θ range on casting films with Soluplus®. These results indicated the absence of crystallinity and the amorphous nature of the dispersion. The results further confirmed ibuprofen embedment within the Soluplus® matrix at the molecular level and the efficiency of the solvent casting technique [17].

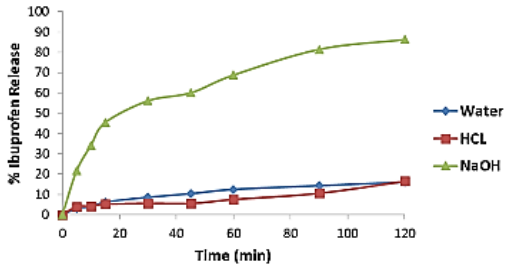

Figure 5: Release Profile of Soluplus®/Ibuprofen films

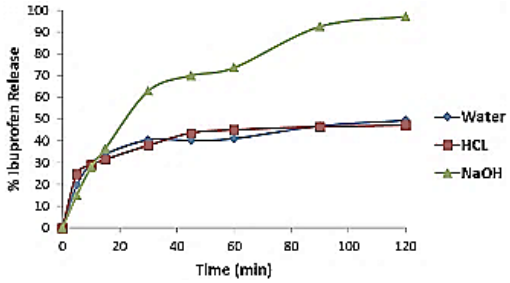

Figure 6: Release Profile of crushed Soluplus®/Ibuprofen films

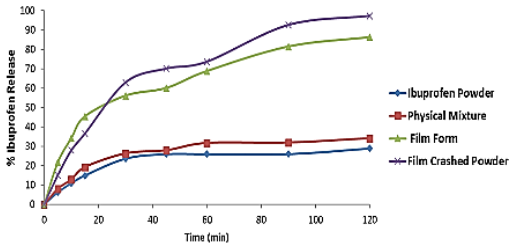

Figure 7: Ibuprofen release profile of pure ibuprofen, physical mixture, films, and crushed films of Soluplus®/Ibuprofen

Drying of the films under a vacuum did not negatively impact the formation of solid dispersion, stability, and drug homogeneity in the polymer. These findings were confirmed spectrophotometrically by quantifying ibuprofen through UV analysis. The distinct and well-defined ibuprofen absorption peak facilitated the quantification procedure. The amount of ibuprofen in each sample (physical mixture, cast/crushed films, or dissolution media) was noted to be within the expected theoretical range, which indicated its uniform distribution and retained chemical nature within Soluplus® matrix [17].

The amorphous nature of cast films significantly enhanced the ibuprofen solubility in acidic and alkaline media [3]. As expected, pure ibuprofen had poor solubility in water and acidic media whereas the solubility was slightly better in alkaline media. Surprisingly, ibuprofen dissolution was not improved in the physical mixture with Solupuls® despite its known emulsifying and solubilizing properties. However, a significantly enhanced ibuprofen dissolution was observed when formulated into amorphous solid dispersion and it completely dissolved (100 %) in alkaline media within two hours. Interestingly, intact film retarded the ibuprofen dissolution in water and acidic media but the crushing of films into fine powder significantly enhanced ibuprofen dissolution in water and acidic media [20]. Approximately 50 % of the drug-crushed films were dissolved in water and acidic media, which was significantly higher than the pure drug and physical mixture [21]. The retarded drug dissolution from intact films could be attributed to their smaller surface area and the time it takes for the dissolution media to penetrate an intact film [17]. Crushed films have a comparatively larger surface area that significantly increased drug dissolution in water and acidic media, and dissolution rate in alkaline media as compared to intact films [21]. The study further elaborated that cast films can be used either in intact form or as free-flowing crushed powder. The crushed powder could be potentially compressed into tablets.

CONCLUSION

Ibuprofen solid dispersions have been successfully formulated using Soluplus® as the dispersing and film-forming polymer using the solvent casting technique. This approach efficiently reduces ibuprofen crystallinity and enhanced its solubility in acidic and alkaline media when compared to pure drugs. Furthermore, the film casting technique may be suitable for various applications where a film or powder form of the drug with enhanced solubility in different aqueous media is desired.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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