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Communication

Understanding Role of Interfacial Interactions in Dissolution Behavior of an Encapsulated Amorphous Solid Dispersion

Vibha Puri [1], Ajay K. Dantuluri [1] and Arvind Bansal [1,*]

[1] Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Sector 67, SAS Nagar, Punjab 160062, India.

E-Mails: puri.vibhaa@gmail.com (V.P.); ajaykraju@yahoomail.com (A.K.D.); akbansal@niper.ac.in (A.K.B.)

* Author to whom correspondence should be addressed; Tel. +91-172-2214682-86. Fax: +91-172-2214692.

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Abstract: Amorphous solid dispersions (ASDs) offer a means to enhance oral bioavailability of poorly water soluble drugs. However, poor dissolution performance is one of the major challenges encountered in design of ASD based drug products. The present study emphasizes on understanding interfacial interactions occurring during dissolution, to aid rationalized design of ASD based drug products. Capsule dissolution of a molecularly interacting amorphous celecoxib solid dispersion (ACSD), comprising of amorphous celecoxib (A-CLB), polyvinylpyrrolidone (PVP) and meglumine (7:2:1 w/w), displayed non-dispersible plug formation, resulting in fall in the dissolution advantage. The solid dispersion displayed suppressed drug recrystallization during dissolution, studied using XRPD and DSC, and hence was not the major contributor to this phenomenon. Also, evaluation of physical mixture of ACSD components (PM-ACSD) negated the role of binder properties of PVP. Further, FTIR analysis of wet samples revealed that PVP in ACSD exhibited lesser interaction with water (shift of PVP carbonyl stretch from 1658 to 1654 cm^{-1}) as compared to that shown by PM-ACSD (shift from 1658 to 1646 cm^{-1}). This indicated formation of water-PVP-A-CLB hydrogen bonds during ACSD dissolution. Measurement of crushing strength for dry and hydrated compacts, showed 7-fold increase in ACSD compact strength as compared to 3-fold for PM-ACSD compact. The findings suggested a significant impact of intermolecular interactions of the solid dispersion on its dosage form drug release, which caused hydrophobhization of PVP and promoted interparticle cohesion via water mediated hydrogen bonds.

Keywords: Amorphous solid dispersion, interfacial interactions, dissolution, celecoxib

1. Introduction

Amorphous form of solids, due to their excess thermodynamic properties, can yield a higher apparent solubility and dissolution rate as compared to their crystalline counterpart and thus enhance oral bioavailability of poorly water soluble drugs[1]. Formulating them into amorphous solid dispersions (ASDs) is a preferred means to enhance their physical stability during shelf-life storage and in aqueous environment. However, the drug release behavior of an ASD is influenced by multiple parameters such as the type of additive, drug load, interaction strength of drug/additive complex, aqueous solubility of components, drug miscibility in additive and drug recrystallization tendency. Reported case studies indicate issues of poor dissolution performance of ASDs based drug products.[2,3] Accordingly, a better understanding of the processes occurring during dissolution would facilitate formulation development of ASD based drug products.

The present study aimed to understand the impact of solid-liquid interactions occurring during dissolution of an encapsulated ASD on drug release performance. Molecularly interacting amorphous celecoxib solid dispersion[4,5] (ACSD) comprising of amorphous celecoxib (A-CLB), polyvinylpyrrolidone (PVP) and meglumine in 7:2:1 weight ratio was taken as a model ASD. Its drug release was evaluated in powder and encapsulated state. In aqueous environment encapsulated ACSD formed a non-dispersible plug and displayed poor drug release. Thus, the physical and compositional changes occurring in aqueous media were investigated, to understand the underlying reasons.[6]

2. Results and Discussion

2.1. Drug release profiles of amorphous CLB solid dispersion

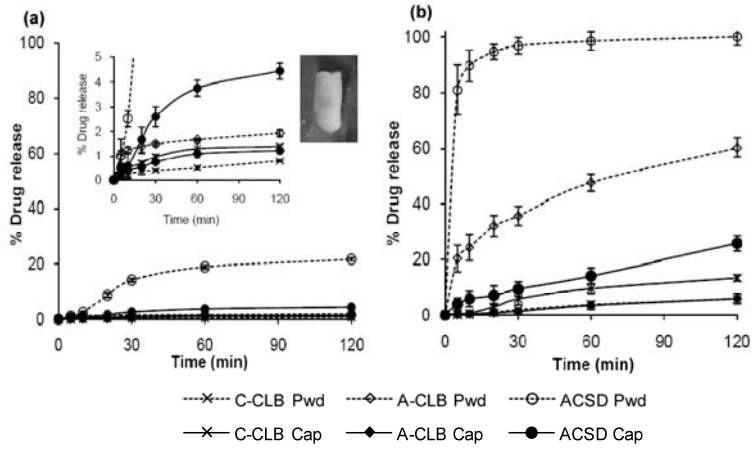
Fig. 1 presents the drug release patterns obtained in water (non-sink condition) and pH 12 phosphate buffer (sink condition). ACSD powder achieved dissolution efficiency at 60 min (DE_{60}) of 11.3% and 90.5% in water and pH 12 buffer, respectively. Conversely, ACSD filled capsules showed a significantly lower DE_{60} of 1.5 % and 9.0 % in water and pH 12, respectively. Visually, the capsules gelatin shell dissolved in about first ten minutes, however the fill material formed a plug and remained undispersed throughout the time period of study. In comparison, encapsulated crystalline CLB (C-CLB) showed no such phenomena. Thus, ACSD capsules displayed only a 2-fold (in water & pH 12) dissolution enhancement, as compared to the 28-fold (in water) and 50-fold (in pH 12) enhancement from its powder form.

2.2. Factors influencing dissolution of encapsulated amorphous CLB solid dispersion

2.2.1. Dissolution of control samples

A-CLB and physical mixture of ACSD components (PM-ACSD) were evaluated as a control samples, in the two media. A-CLB capsules showed similar plug formation (Fig. 1) with rapid crystallization of surface layer that formed a rigid non-eroding crust. However, PM-ACSD showed a faster erosion pattern and higher drug release as compared to ACSD capsules (data not shown). These observations suggested that presence of hydrophilic excipients, i.e., PVP and meglumine, facilitated the dissolution of A-CLB, and that the interactions between the solid dispersion components impacted the erosion pattern.

Figure 1. Powder and capsule dissolution profiles in **(a)** distilled water and **(b)** pH 12 buffer of C-CLB, A-CLB and ACSD (mean±SD, n=3). Inset shows photograph of ACSD solid mass withdrawn from capsule dissolution in water at 60 min. (Copyright© 2011 Wiley-Liss, Inc. and the American Pharmacists Association, reproduced from reference 6).



2.2.2. Compositional changes and solid state transformations

The composition of undissolved solid mass was periodically quantified during ACSD capsule dissolution in water, by HPLC method. Meglumine showed rapid leaching and was completely released from ACSD in the first 30 minutes. Beyond which (t= 30 to 120 min), the drug and polymer ratio remained almost constant at 75:25 w/w in the wet mass. This indicating sustained intermolecular interaction between A-CLB and PVP. Parallel X-ray powder diffraction (XRPD) and conventional DSC (cDSC) analysis of dissolution samples indicated no significant crystallization. Modulated DSC (MDSC) profiles showed glass transition temperature (T_g) shift to 80.9 and 75.9 ^{0}C for surface and core samples, respectively, as compared to the initial T_g value of 66.1 ^{0}C.

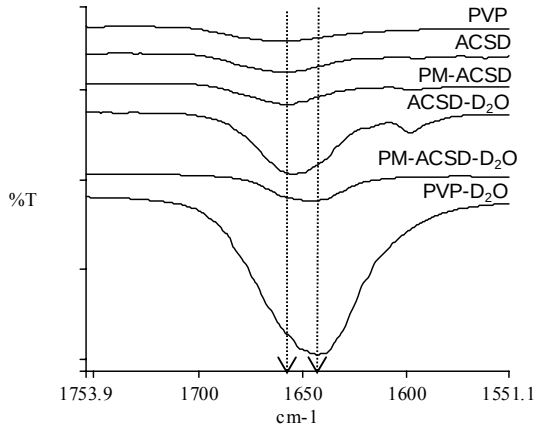
2.2.3. Intermolecular interaction of amorphous solid dispersion with water

PVP polymer chains hydrogen bond with water through its carbonyl group. FTIR analysis showed shift in PVP carbonyl stretching peak from 1660 cm^{-1} to 1644 cm^{-1} when hydrated with deuterated water (D_2O) (Fig. 2). Initial samples of ACSD and PM-ACSD powder showed PVP carbonyl peak at 1658 cm^{-1}, which after wetting with D_2O shifted to 1654 and 1646 cm^{-1} region, respectively. A lower shift observed in case of ACSD, suggested that the PVP hydrophilic sites were less accessible to water and it was interacting with both A-CLB and water molecules.

2.2.4. Interparticle interaction in aqueous media

The influence of intermolecular interaction in presence of water on interparticle interaction was studied by crushing strength analysis of dry and hydrated compacts. ACSD compacts immersed in water (t=15 min), showed swelling and about 7-fold increase in crushing strength. On the other hand, PM-ACSD compacts displayed lower hydration and less than 3-fold increase in compact strength. This indicated that in ACSD capsules water mediated hydrogen bonds promoted interparticle cohesion.

Figure 2. (a) FTIR spectra of PVP carbonyl stretching vibration in powder samples. (Copyright© 2011 Wiley-Liss, Inc. and the American Pharmacists Association, figure reproduced with modifications from reference 6).



3. Experimental Section

3.1. Materials

Celecoxib (CLB) was received as a gift sample from Zydus Cadila Healthcare Ltd. (Ahmedabad, India). PVP (K 29/32) was obtained from ISP Technologies (New Jersey, USA). Meglumine and deuterium oxide (D_2O, >99.990 atom % D) were purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany).

3.2. Generation of spray dried amorphous samples

Isopropyl alcohol/water solution (80:20 v/v) of CLB, PVP and meglumine (7:2:1 w/w) at 3% w/v was spray dried (laboratory scale spray dryer U228 Model, Labultima Ltd., Mumbai, India) to obtain ACSD. PM-ACSD was prepared in weight ratio of 7:2:1 by geometric mixing and sifting through sieve BSS no. 150.

3.3. In vitro dissolution studies

Dissolution was performed for powder samples and powder manually filled in hard gelatin capsules (size '0') for amount equivalent to 100 mg of the drug. Dissolution experiments (1000 ml medium; 37±0.5 °C; USP dissolution apparatus II (paddle); 50 rpm) were carried out in distilled water and pH 12 (0.04 M tribasic sodium phosphate) buffer and analyzed for drug concentration using HPLC method. DE_{60} was calculated from area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. In separate dissolution experiments of ACSD capsules in water, the undissolved solid mass were withdrawn at periodic intervals and assayed for the three components.

3.4. Crushing strength measurement

Compacts (100 mg) of samples were prepared at similar porosity on rotary tablet press (Mini II, Rimek, Ahmedabad, India). XRPD analysis confirmed that no solid-state transition occurred during compaction. The compacts were dipped in 30 ml water (37 °C) for 15 min. Force-displacement-time profiles associated with penetration of a 2 mm round-tipped steel probe into the dry and hydrated

compacts were recorded using a Texture Analyzer (TA-XT 2i, Stable Microsystems, UK) operating on Texture expert® software.

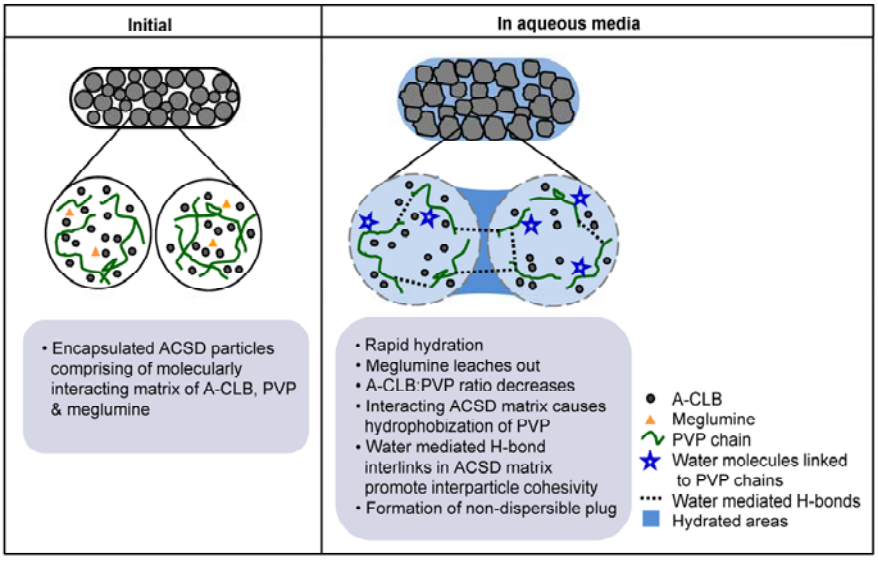
3.5. Solid-state characterization

XRPD were recorded using Bruker D8 Advance(Karlsruhe, West Germany) over range of 3° and 40° 2θ at a step size of 0.02° and scan rate of 1 s/step. DSC analysis was conducted using a Q2000 DSC (TA Instruments, DA, USA), under 50 ml/min nitrogen purge. Wet dissolution samples were first subjected to isothermal DSC scan at 40 °C for 20 min, in open aluminum pans, and then followed by cDSC scan at a heating rate of 10 °C/min or MDSC scan at a heating rate of 5 °C/min, amplitude of 0.5 °C and period of 60 s. FTIR spectra were recorded on a Perkin-Elmer spectrometer (Spectrum One, Perkin-Elmer, Buckinghamshire, U.K.), equipped with diamond/zinc selenide crystal attenuated total reflectance (ATR) accessory and spectrum v3.02 software. Each sample was scanned 64 times at a resolution of 4 cm^{-1}.

4. Conclusions

The underlying physical processes occurring during dissolution of encapsulated molecularly interacting ACSD are summarized in Fig. 3. ACSD displayed optimal wettability and suppressed drug recrystallization in aqueous media, however, in encapsulated state, the solid dispersion exhibited significant loss in 'dissolution advantage'. The was attributed to the intermolecular interactions in the solid dispersion matrix which reduced the diffusivity of PVP and increased interparticle cohesion by water mediated hydrogen bonds, leading to solid mass agglomeration. Thus, the study highlights the impact of amorphous solid-liquid interfacial cohesive interactions in dosage form performance.

Figure 3. Schematic representation of the phenomena occurring during dissolution of encapsulated ACSD. (Copyright© 2011 Wiley-Liss, Inc. and the American Pharmacists Association, figure reproduced with modifications from reference 6).



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