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*Communication*

# Barrier Coated Drug Layered Particles for Formulation Design of an Amorphous Solid Dispersion

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**Abstract:** The present study employed surface modification for formulation design of amorphous solid dispersion (ASD) based dosage form. Amorphous celecoxib solid dispersion (ACSD) comprising of amorphous celecoxib (A-CLB), polyvinylpyrrolidone (PVP) and meglumine (MEG) at 7:2:1 weight ratio was selected as a model ASD. In aqueous media, ACSD capsules displayed solid mass agglomeration which resulted in poor dissolution performance. Additionally, ACSD was predisposed to devitrification under environmental stress. Thus, barrier coated-ACSD layered particles (ADLP) were prepared by Wurster process and polyvinyl alcohol (PVA), inulin and polyvinyl alcohol phthalate (PVAP) were evaluated as coating excipients. In aqueous media, barrier coated-ADLP filled capsules achieved rapid dispersibility and high drug release, in comparison to uncoated ADLP capsules. Physical stability under 25 °C/75% RH and 40 °C/75% RH open conditions indicated crystallization inhibition by 2 to 10-fold (cf. uncoated ADLP) with barrier efficiency in the order of inulin<PVA≈PVAP.

**Keywords:** Amorphous, solid dispersion, surface modification, coating, physical stability, dissolution, celecoxib

## 1. Introduction

The high energy amorphous form of active pharmaceutical ingredients (APIs) can be kinetically stabilized by formulating them into amorphous solid dispersions (ASDs).[1] Further, physical instability during processing and shelf life, and poor drug release are two common issues associated with dosage form design of ASDs.[2] Both of these phenomena can be significantly influenced by surface behavior of

amorphous solids. Many folds higher surface crystallization kinetics exhibited by amorphous APIs can be retarded by capping of the free surface.[3,4] Further, the interfacial interactions can impact surface mediated phenomena such as wettability, disintegration and dispersibility of a dosage form.[5]

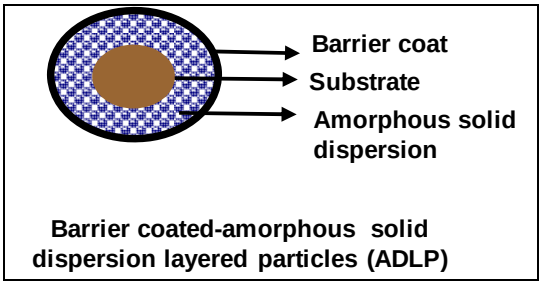
Amorphous celecoxib solid dispersion[6] (ACSD) comprising of amorphous celecoxib (A-CLB), polyvinylpyrrolidone (PVP) and meglumine (MEG) was selected for capsule dosage form development. However, encapsulated ACSD exhibited solid mass agglomeration in aqueous media,[7] and underwent recrystallization on exposure to environmental stress. Thus, in the present work, surface modification was employed to deliver its optimal dosage form. Barrier coated-ACSD layered particles (ADLP) were developed and characterized for solid state stability and dissolution in capsule dosage form.

## 2. Results and Discussion

### *2.1. Barrier coated- amorphous CLB solid dispersion layered particles*

Wurster process facilitated layered deposition of ACSD on substrate particles with rapid evaporation of the spray solution. Microcrystalline cellulose (MCC) particles were used as substrate particles, which was followed by application of an excipient coat of polyvinyl alcohol (PVA), inulin or polyvinyl alcohol phthalate (PVAP). The schematic representation of barrier-coated ADLP is shown in Fig. 1.

**Figure 1.** Schematic representation of barrier coated-ADLP.




#### *2.1.1. Solid state characterization*

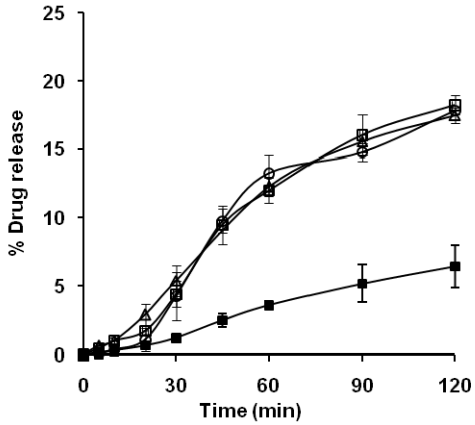
ADLP exhibited amorphous halo X-ray powder diffraction (XRPD) pattern, and showed no CLB melting in the conventional differential scanning calorimeter (cDSC) profile. Modulated DSC (MDSC) measurements of ADLP gave a single glass transition event ($T_g$) at about 69.9 °C. The XRPD and DSC profiles after barrier coating were similar to that of uncoated ADLP, with no significant change in $T_g$ values.

#### *2.1.2. Drug release performance*

Fig. 2 compares drug release behavior of uncoated and coated ADLP filled capsules in water. Uncoated ADLP exhibited poor dispersibility, which led to non-optimal drug release. This was earlier studied to be due to increased interparticle cohesivity.[7] In contrast, all barrier coated-ADLP capsules could impede the unfavorable interfacial interactions and facilitate rapid dispersibility. The release profiles of barrier coated-ADLP capsules could match that of loose uncoated ADLP added to

dissolution vessel (data not shown). Thus, the barrier coated-ADLP per se yielded rapidly dispersing capsule formulations.

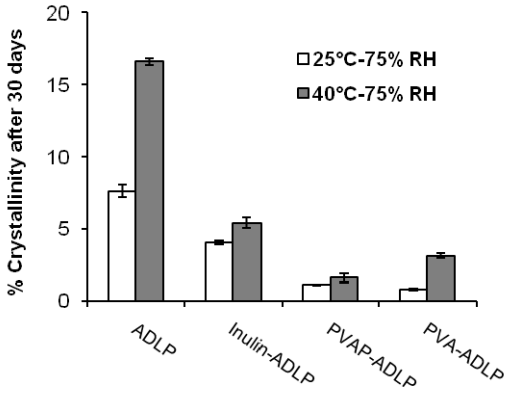
**Figure 2.** Drug release profiles of uncoated and coated ADLP capsules in distilled water (■) ADLP, (Δ) PVA-ADLP, (○) Inulin-ADLP and (□) PVAP-ADLP. (n=3, mean±SD).




*2.1.3. Physical stability testing*

Crystallization inhibition efficiency was monitored under open conditions of (i) 25 °C/75% RH and (ii) 40 °C/75% RH (Fig. 3). Under 25 °C/75% RH conditions, the uncoated ADLP exhibited about 8% crystallinity in one month, while, coated ADLP underwent significantly lesser recrystallization. Under 40 °C/75% RH conditions, uncoated ADLP showed about 17% crystallinity in one month as compared to a maximum of about 5% observed for coated ADLP. Overall the excipients could be rank ordered as inulin<PVA≈PVAP for crystallization inhibition efficiency. Evidently, the barrier coat provided protection to the amorphous particles and enhanced their physical stability.

**Figure 3.** Percentage crystallinity on exposure to 25 °C/75% RH and 40 °C/75% RH. Values are significantly different at $p<0.05$ (n=3, mean±SD).



## 3. Experimental Section

### *3.1. Materials*

CLB was received from Zydus Cadila Healthcare Ltd. (Ahmedabad, India). PVP (K 29/32) and MEG were purchased from ISP Technologies (New Jersey, USA) and Sigma-Aldrich Chemie GmbH (Steinheim, Germany), respectively. MCC particles (Avicel® PH 200, size range of 200-350 μm were obtained from FMC Corporation, Ireland. Inulin was obtained from Hi-Media Laboratories Pvt. Ltd. (Mumbai, India), PVA from Sigma-Aldrich Chemie GmbH (Steinheim, Germany) and PVAP from Colorcon Inc. (West Point, USA). Hard gelatin capsule shells were obtained from Associated Capsules Pvt. Ltd., Mumbai, India.

### *3.2. Generation of amorphous solid dispersion layered particles (ADLP)*

The ADLP were prepared by Wurster process in fluidized bed processor (Microkit, Glatt GmbH, Germany). MCC particles were fluidized at bed temperature of 30-32 °C and methanolic solution of CLB, PVP and MEG (7:2:1 w/w), at 10% w/v solid content, was bottom-sprayed using atomization air pressure of 0.8 bar, feed rate of 0.5 ml/min and airflow of 0.1-0.2 bar. The loading efficiency was 31% w/w. Further, excipient solution (prepared in methanol for PVAP and methanol:water 1:1 v/v for PVA and inulin), at 2.5% w/v solid content, was bottom-sprayed onto the particles at feed rate of 0.3 ml/min to achieve a weight build up of 3% w/w. The coated particles were dried under vacuum at 30 °C for 16 h.

### *3.3. Solid state characterization*

XRPD patterns were recorded using Bruker's model D8 Advance Diffractometer (Karlsruhe, West Germany) over an angular range of 3° to 33° 2θ with a step size of 0.01° and step time of 5 s. Thermal transitions were determined using a Q2000 DSC (TA Instruments, DA, USA), under 50 ml/min nitrogen purge. Percent drug crystallinity was determined based on standard plot of enthalpy of fusion vs. % crystallinity, using cDSC scan (sample 9-11 mg) from -5 to 180 °C at a heating rate of 20 °C/min. The enthalpy of fusion was corrected based on sample drug assay. $T_g$ was determined using MDSC scan (sample 5-6 mg) performed at a heating rate of 2 °C/min, a modulation amplitude of 0.5 °C and a period of 60 s.

### *3.4. Dissolution studies*

Sample equivalent to 100 mg drug were manually filled in hard gelatin capsules of size '00'. Dissolution testing was conducted in using USP dissolution apparatus II (paddle), in 1000 ml of dissolution medium, at a temperature of 37±0.5 °C and rotational speed of 50 rpm. Dissolution media was distilled water and samples were analyzed for drug concentration using HPLC method[8].

## 4. Conclusions

Surface modification was achieved by barrier coating of ASD particles with moisture protective pharmaceutical excipients. The barrier coat enhanced its physical stability and could preclude the unfavorable interfacial interactions of amorphous particles in aqueous environment. Thus, the approach was an efficient means to improve performance of high drug load amorphous dosage form.

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