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Research paper

Mucoadhesive amorphous solid dispersions for sustained release of poorly water soluble drugs

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ABSTRACT

The oral delivery of mucoadhesive patches has been shown to enhance the absorption of large molecules such as peptides. We hypothesized that this mechanism could have utility for poorly soluble small molecules by utilizing a mucoadhesive polymer as the matrix for an amorphous solid dispersion. Binary dispersions of itraconazole and carbomer (Carbopol 71G) were prepared utilizing a thermokinetic mixing process (KinetiSol Dispersing) and the physicochemical properties were investigated by powder X-ray diffraction, calorimetry, and liquid chromatography. Adhesion of the dispersions to freshly excised porcine intestine was investigated with a texture analyzer. Minitablets were compressed from the optimal dispersion and further investigated *in vitro* and *in vivo* in rats. Thermokinetic mixing successfully processed amorphous dispersions up to 30% drug loading and each dispersion exhibited works of adhesion that were approximately an order of magnitude greater than a negative control *in vitro*. Ethylcellulose (EC) coated and uncoated minitablets prepared with the 30% drug load dispersion were delivered orally to rats and exhibited sustained release characteristics, with overall bioavailability greater for the uncoated minitablets compared to the EC-coated minitablets, similar to the rank order observed in our *in vitro* dissolution experiments. Necropsy studies showed that minitablets delivered with enteric-coated capsules targeted release to the distal small intestine and adhered to the intestinal mucosa, but the rat model presented limitations with respect to evaluating the overall performance. Based on the *in vitro* and *in vivo* results, further investigations in larger animals are a logical next step where fluid volumes, pH, and transit times are more favorable for the evaluated dosage forms.

1. Introduction

Oral delivery of lipophilic, poorly water-soluble small molecules continues to be a significant endeavor across pharmaceutical development pipelines [1,2]. Over the last decade, amorphous solid dispersions (ASDs) have emerged as a preferred technology to overcome solubility limitations, with several commercially approved examples [3]. Dosage forms based on ASDs release predissolved drug, typically at supersaturated concentrations that may be orders of magnitude higher than the thermodynamic solubility of the drug [4]. Additionally, supersaturating systems can result in higher flux across the intestinal membrane, as the increase in apparent solubility does not result in a concomitant decrease in permeability that affects other solubility-enabling platforms (e.g. surfactants, cyclodextrin, co-solvent systems) [5]. These latter complexing systems fail to increase the concentration of molecularly dissolved drug [6]. For slow crystallizing drugs, this flux advantage can be maintained up to a maximum level in which a drug's "amorphous solubility" is reached [7], and through diligent formulation design, ASDs have leveraged these advantages to allow for convenient oral dosing of several life-saving drugs [8–10].

The oral delivery of large molecules such as peptides and proteins is even more challenging and has spawned innovative drug delivery platforms of its own in order to overcome absorption barriers such as low permeability and enzymatic degradation to enhance bioavailability [11,12]. Some examples include the use of permeation enhancers, enzyme inhibitors, microsphere encapsulation, liposomes, and others [13–15]. One promising technology under development uses mucoadhesive patches that are delivered to the small intestines via enteric-coated capsules [16]. These patches consist of drug dispersed in a matrix of mucoadhesive polymers and coated on all sides but one with an impermeable,

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insoluble backing layer of ethylcellulose. The mucoadhesive side of the patch adheres to the intestinal mucosa, promoting drug release unidirectionally for several hours with enhanced transport due to the high concentration gradient of drug between the patch and the membrane, as demonstrated with model peptides such as insulin and salmon calcitonin [17,18]. We hypothesized that this concept could be applied to an ASD by utilizing a mucoadhesive polymer as the matrix for a molecularly dissolved, poorly water-soluble small molecule, providing mucoretentive and sustained delivery of drug. For rapidly crystallizing drugs, this may be an attractive option to deliver supersaturated drug at a moderate rate into the GI lumen, reducing the driving force for recrystallization compared to an immediate release formulation [19], or alternatively, promoting transport of drug directly from the dosage form to the mucous membrane.

Cross-linked poly(acrylic) acids such as carbomer have widely been reported to adhere to mucosal membranes [20–22] through a two-stage contact (wetting) and consolidation process [23]. However, carbomer has not been extensively investigated as the predominant matrix polymer in ASDs, which is likely due to the difficulty in processing the polymer with the two most common production methods for ASDs: hot-melt extrusion and spray-drying [3]. The difficulty to process arises from the exceptionally high molecular weight of the cross-linked particles that result in melt or solution viscosities that practically limit the concentrations that can be used in extrusion and spray-drying applications [24,25]. Recently, KinetiSol Dispersing (KSD) has emerged as an alternative manufacturing process for ASDs [26]. It is based on a thermokinetic mixing process that converts friction to heat over short residence times and is not practically limited by viscosity, as demonstrated through processing of multiple viscous, high molecular weight polymers [10,27,28].

The objectives of this study were to (1) demonstrate that ASDs could be manufactured from binary mixtures of itraconazole and carbomer using the KSD process, (2) demonstrate that these dispersions exhibit adhesion *in vitro* to intestinal mucosa, even with relatively high concentrations of hydrophobic drug, and (3) confirm that mucoadhesion and sustained drug delivery is observed *in vivo*. Itraconazole was chosen as the model poorly water-soluble drug due to its very low aqueous solubility and its wide comparative use as a model in ASDs, including demonstrated processability by thermokinetic mixing, enabling rapid proof-of-concept for this study [29–36]. Two approaches were evaluated *in vivo* in this study. The first utilized uncoated minitablets that were delivered via immediate release capsules, which were hypothesized to be mucoretentive, providing sustained release of itraconzole into the GI lumen. The second approach utilized minitablets that were coated on all sides but one with ethylcellulose and were delivered by capsules coated with an enteric polymer. These were hypothesized to release the minitablets at the site of absorption in the small intestines, and transport itraconazole unidirectionally through the mucoadhesive side of the tablet through the mucous membrane.

2. Materials and methods

2.1. Materials

Itraconaozle (EP, >99% purity) was purchased from Shenzhen Nexconn Pharmatechs Ltd (Shenzhen, China). Carbopol 71G was kindly donated by Lubrizol Advanced Materials (Brecksville, Ohio). Ethylcellulose 7cp was kindly donated by Colorcon (West Point, PA). Simulated intestinal fluid powder (FaSSIF v1) was purchased from Biorelevant.com (Surrey, United Kingdom). High performance liquid chromatography grade acetonitrile and methanol, along with all other reagents were purchased from Fisher Scientific (Pittsburg, PA).

2.2. KinetiSol processing of amorphous dispersions

KSD processing was conducted with a compounder developed by DisperSol Technologies, L.L.C. (Georgetown, Texas). Physical mixtures of itraconazole and carbomer (Carbopol 71G) were prepared in the ratios outlined in Table 1 by dispensing each component with a top-loading balance, followed by mixing with a mortar and pestle for 30 s. Batch sizes of 100 g were added to the compounder for processing. KSD ejection temperature was set at 105 °C and the rotation speed was set at 2800 RPM for 30 s (stage 1), followed by 3000 RPM for 30 s (stage 2). Stage 2 is only initiated if the ejection temperature is not reached within the first stage. The material was ejected upon reaching the temperature set point (measured in-line) and quenched between two aluminum plates. The KSD processed batches were milled with a Fitzpatrick L1A Fitzmill (Elmherst, IL, USA) operated at 8000 rpm with a 0.020″ round-hole screen with impact forward impellers.

2.3. Physicochemical characterization

The physical characteristics of the processed dispersions and raw materials were analyzed by powder X-ray diffraction (PXRD) and modulated differential scanning calorimetry (mDSC). PXRD was performed on a Rigaku Miniflex 6000 (Tokyo, Japan) equipped with CuKα radiation at 40 kV, 15 mA. Data was collected in a scan mode with a step size of 0.02° and a step time of 2 s over a 2θ range of 5–60°. Modulated differential scanning calorimetry (MDSC) analysis was performed with a TA Instruments Model Auto Q20 DSC (New Castle, DE, USA). Samples were placed into standard aluminum pans and crimped using a TA instruments sample press (New Castle, DE, USA). Processed samples were equilibrated at 0 °C, followed by heating to 200 °C at a ramp rate of 5 °C/min with a modulation amplitude and period of 1 °C and 60 s, respectively. During analyses, high purity nitrogen flowed through the sample chamber at a rate of 50 mL/min. Analysis was performed with TA Universal Analysis 2000 software.

Thermo Scientific Dionex UltiMate 3000 HPLC system (Thermo Scientific, Sunnyvale, CA, USA) was used to assay the processed dispersions in triplicate using a previously described method [29]. An Ultimate 3000 Autosampler was configured with a Luna 5 μm CN 100 Å, 150 × 4.6 mm column (Phenomenex, Torrance, CA) and a 10 μL injection volume was used. The mobile phase was a mixture of acetonitrile:water:diethanolamine 70:30:0.5 with a flow rate of 1.00 mL/min. An UltiMate RS Variable Wavelength Detector, extracting at 263 nm, was used to quantify the results. The retention time of ITZ was approximately 6 min. All analyses maintained linearity (R^2 = 0.999) in the range tested. Chromeleon Version 6.80 software (Thermo Scientific, Sunnyvale, CA, USA) was used to process all chromatography data.

2.4. Contact angle and adhesion force measurements

Contact angle was measured with water using a FTA200 goniometer (First Ten Angstroms, Inc., Portsmouth, VA, USA) to

Table 1
Batch compositions of itraconaozle and carbomer.

Batch	Itraconazole (% w/w)	Carbomer (% w/w)
1	10	90
2	20	80
3	30	70
4	40	60