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Research paper

Site specific solubility improvement using solid dispersions of HPMC-AS/HPC SSL – Mixtures

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ABSTRACT

Many upcoming drug candidates are pH-dependent poorly soluble weak bases in the pH range of the gastrointestinal tract. This often leads to a high *in vivo* variability and bioavailability issues. Aiming to overcome these limitations, the design of solid dispersions for site specific dissolution improvement or maintenance of a potent supersaturation over the entire gastro-intestinal pH-range, is proposed to assure a reliable drug therapy. Solid dispersions containing different ratios of Dipyridamole (DPD) or Griseofulvin (GRI) and the enteric polymer hydroxypropylmethylcellulose-acetate succinate (HPMC-AS) and the water soluble low-viscosity hydroxypropylcellulose (HPC-SSL) were prepared by hot melt extrusion (HME). The solid dispersions were evaluated for their solid state, dissolution characteristics applying a three pH-step dissolution method following an acidic to neutral pH transition and stability. The use of HPMC-AS in binary mixtures with DPD and GRI facilitated increased solubility and supersaturation at pH-controlled release of the preserved amorphous state of the dispersed drug, which even inverted the pH-dependent solubility profile of the weakly basic model drug (Dipyridamole). I.e. a potent site specific delivery system was created. With ternary solid dispersions of API, HPMC-AS and HPC-SSL, tailored release profiles with superior supersaturation over the applied pH-range could be obtained. At the same time, binary and ternary mixtures showed favorable stability properties at a temperature difference between glass transition temperature and the applied storage temperature of down to 16 °C.

1. Introduction

An increasing number of poorly soluble active pharmaceutical ingredients (APIs) [1,2] need an investigation and implementation of new approaches in formulation development in order to increase the chances of a successful biostudy.

Already, a broad range of technologies is available to improve solubility and/or dissolution of poorly water-soluble compounds, including water-soluble salt or co-crystal formation [3–5], particle size reduction [6], self-emulsifying drug delivery systems [7], complexation with cyclodextrins [8] or the incorporation of pH modifiers for ionizable drugs [9,10]. Furthermore solid-state manipulations, i.e. the formation of amorphous solid dispersions are an important formulation approach of increasing interest, to improve the dissolution rate and apparent solubility of poorly soluble compounds [11,12,6,13]. In addition to their solubility enhancing properties these solid dispersions often display supersaturation effects which are seen to be beneficial to overcome solubility-limited absorption [2]. While solubility enhancement and supersaturation form the rationale for choosing an amorphous solid dispersion development, there are also hurdles associated with the amorphous solid state of APIs. Due to its higher energy state compared to the crystalline form, the amorphous form has an increased chemical and physical (re-crystallization tendency) reactivity which may offset its benefits [14–16] by lack of stability. Therefore, the amorphous API is mostly stabilized in a molecular dispersion of the API in a matrix-polymer [17–19], which prevents re-crystallization by kinetic stabilization [20].

Despite the significant influence of product dissolution rate and extent on bioavailability [21], improved solubility solely by solid state manipulation and obtaining supersaturation does not necessarily result in improved bioavailability. Furthermore, two principles in conjunction with enhanced, supersaturated solubility are considered to govern bioavailability [22–27]:

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(a) Maintenance of supersaturation throughout the GI.
(b) Dissolution of solubility enhanced principle at absorption site.

This means the dissolved drug must be delivered out of its formulation over an appropriate period of time to those sites in the GI where the drug is well absorbed [28]. Several authors [22–26] found a significantly improved bioavailability for prolonged supersaturation periods so in particular for poorly soluble drugs for which absorption is limited due to low *in vivo* GI concentrations. Hence, various formulation approaches have been described which result in the generation of a supersaturated solution, employing also polymers to delay precipitation in the GI tract [27]. The first principle (a) can be addressed by formation of modified release products to create a moderate degree of supersaturation in order to decrease the force for recrystallisation. Another approach (b) is the inclusion of a precipitation inhibitor in immediate release drug formulations to decrease the rate of precipitation and hence, ensure high concentrations of dissolved drug to facilitate absorption. Various water soluble polymers, such as hydroxypropylmethylcellulose, hydroxypropylcellulose or polyvinyl pyrrolidone have previously been shown to interact with compounds in solution and slow the rate of precipitation [29,30].

Supersaturation resulting from a pH-dependent drug release of a solid dispersion is typically a transient event. Hence, it can be easily understood that specific targeting of supersaturation until the drug enters the primary site for absorption (i.e. dissolution takes place at absorption site) can improve the bioavailability of a compound [31–33].

Specifically for basic or neutral drug compounds with poor solubility it is important to prevent precipitation and at the same time maintain supersaturation at pH values above pH 5 to possibly improve bioavailability or target the release to the site of absorption. A basic drug or a neutral compound formulated in a supersaturating solid dispersion may dissolve completely in the stomach, but then subsequently precipitate in the intestine due to the increase in pH (and dilution of excipients after disintegration of the drug product).

Enteric polymers, which are practically insoluble in acidic solutions (i.e. gastric fluid), but soluble in buffer solution with a pH above 5.5–7.0, are promising carriers for site specific supersaturation targeting. They can deliver the drug to a particular region of the intestine or colon [34], enhance the bioavailability by increasing the wettability and dissolution rate of the drug [35,36] and stabilize the drug within the matrix [27]. They are further described to protect on the one hand the gastric mucosa from drug irritation and on the other hand prevent drug degradation in the stomach by enzymes or acidic fluids [37].

HPMC-AS is a pH dependent soluble polymer and it is widely described as an enteric coating agent for dry coating [38] or conventional coating processes using aqueous dispersions [39]. The polymer starts to dissolve at pH 5.5 and is at pH 6.8 HPMC-AS readily soluble. There have been several studies of HPMC-AS as suitable matrix in solid dispersions, mainly produced by means of solvent-co precipitation [40], spray drying [41,42] or hot melt extrusion [40,43]. Hence, we used HPMC-AS to generate a pH-depended controlled release dosage form, which might result in improved bioavailability and supersaturation at pH above 5.5. As enteric polymer, it can prevent recrystallisation of the drug in the gastric pH or any acidic decomposition of the drug.

Yamada et al. described that HPC-SSL is able by to maintain supersaturation of a poorly soluble compound over a reasonable period [44]. Due to its chemical similarity to HPMC-AS, we assumed miscibility of HPC-SSL with HPMC-AS. Concerning its lower molecular weight and low T_g, we assigned HPC-SSL to act as a solid state plasticizer decreasing HME processing temperature and/or torque load of extrusion equipment.

Our purpose was to study the pH-dependent *in vitro* dissolution and supersaturation of melt extruded solid dispersions out of a weak base (Dipyridamole) or a neutral compound (Griseofulvin), a pH-dependent soluble polymer (HPMC-AS) and a pH-independent soluble polymer (HPC-SSL). As proposed by Miller et al. for an increased *in vivo* relevance, a partially non-sink dissolution method, following the transition from acidic pH 1.2 over pH 5.5 to neutral pH 6.8, was used to elucidate and characterize the release profiles of our formulations [27]. The release of API from HPMC-AS matrices and mixture thereof with HPC-SSL were compared with the dissolution profiles of API/Copovidone solid dispersions and interpreted for their potential *in vivo* benefits.

2. Materials and methods

2.1. Materials

HPMC-AS LG was obtained from Shin-Etsu Chemical (Tokyo, Japan), HPC-SSL from Nisso Chemical Europe (Düsseldorf, Germany) and Copovidone (Kollidon VA64) was obtained from BASF (Ludwigshafen, Germany), Griseofulvin from Sigma–Aldrich (St Louis, MO, USA) and Dipyridamole from Boehringer-Ingelheim Pharma (Ingelheim, Germany). The materials used were all of pharmaceutical grade. GRI was obtained in laboratory reagent grade (>99%). Used buffers were of analytical grade.

2.2. Preparation of the mixtures

Thy physical mixtures were all prepared by gently mixing the drug and the polymers in a Turbula mixer (Willy A. Bachofen AG, Muttenz, Switzerland) for 15 min after passing the materials through a 0.25 mm sieve.

2.3. Hot melt extrusion

Experiments were conducted on a 12 mm Extruder developed at Boehringer Ingelheim (BI) in cooperation with ThreeTec (ThreeTec, Seon, Switzerland), described in detail previously [45]. The extruder is instrumented to control the temperature profile along the processing barrel, the screw speed, and the feed rate employing a BI developed software (Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany), which simultaneously handles the data acquisition. The extruder was linked to a 9 mm volumetric dosing feeder (ZD9 FB; ThreeTec). For this study, screw speed was kept constant at 100 rpm. Barrel temperatures, feed rates and resulting torque loads are summarized in Table 1. Extrudates were milled with a hammer mill Polymix PX-MFC (Kinematika AG, Lucerne, Switzerland) at 3500 rpm using a 0.5 mm screen. The milled extrudates were sieved and the fraction above 200 μm was used for analysis.

2.4. Stability studies

Stability studies were conducted to determine the effect of aging on the physical stability of the drugs in various formulations. The extrudates were stored in screw-capped glass vials at room temperature and ambient humidity (30–40% r.h.) for 12 months and characterized by XRPD. For accelerated stability studies, the extrudates were stored at 40 °C/75% r.h. in open and screw capped glass vials. The samples were collected at timepoints of 2 and 12 weeks and subsequently characterized by XRD studies.