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Hot-melt sub- and outercoating combined with enteric aqueous coating to improve the stability of aspirin tablets

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ABSTRACT

Aspirin is apt to hydrolyze. In order to improve its stability, a new method has been developed involving the application of hot-melt sub- and outercoating combined with enteric aqueous coating. The main aim was to investigate the influence of these factors on the stability of ASA and understand how they work. Satisfactory storage stability were obtained when the aspirin tablet core coated with Eudragit L30D55 film was combined with glycerin monostearate (GMS) as an outercoat. Hygroscopicity testing indicated that the moisture penetrating into the tablet may result in a significant change in the physical properties of the coating film observed by scanning electron microscopy. Investigation of the compatibility between the drug and film excipients shows that the talc and methacrylic acid had a significant catalytic effect on ASA. A hypothesis was proposed that the hydrolysis of ASA enteric coated tablets (ASA-ECT) was mostly concentrated in the internal film and the interfaces between the film and tablet core. In conclusion, hot-melt coating technology is an alternative to subcoating or outercoating. Also, GMS sub-coating was a better choice for forming a stable barrier between the tablet core and the polymer coating layer, and increases the structure and chemical stability.

Abbreviations: **ASA**, acetylsalicylic acid; **SA**, salicylic acid; **GMS**, glycerin monostearate; **ECT**, enteric-coated tablet; **SET**, single enteric-coated tablet; **GST**, double-coated tablet in which GMS is a subcoating; **GOT**, double-coated tablet in which GMS is an outercoating.

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1. Introduction

Acetylsalicylic acid (ASA), a significant pharmaceutical compound commonly known as aspirin [1], is an analgesic-antipyretic agent with a long history of clinical use. Aspirin is an effective platelet aggregation inhibitor, and low daily doses are now used as preventive therapy for cardiovascular disease. However, due to the gastric irritation caused by aspirin, especially during long-term use, and because ASA is a water-sensitive substance, it becomes unstable (i.e. hydrolyzes) in the presence of water [2] and produces salicylic acid (SA), which forms a different geometry and thus gives rise to a degradation chain reaction [3]. It is thus important to consider the stability, release profile, and potential mucosa irritation when developing and optimizing the formulation for oral aspirin. Film coating is thought to circumvent aforesaid problems.

Film coating is a versatile pharmaceutical technology, which may provide modified functions of a formulation, such as controlled or delayed release, taste masking, shading and moisture-proofing, while also stabilizing the main ingredients in a tablet. Compared to organic-solvent, aqueous film coating is safe, economical and environmentally friendly [3]. However, a small change in the film coating formulation or technology may result in marked effect on the chemical stability and release profile, subsequently altering the *in vivo* bioavailability [4]. Therefore, it is important to pay close attention to the film effects in ASA stability. Eudragit L30D55 was selected for the enteric coating film because of its excellent gastro-resistance and stable release in release medium. However, when the tablet core was coated with enteric polymer using aqueous dispersion technique, the content of SA increased markedly after long-term storage under accelerated conditions, which may be attributed to the interaction between the coating film and ASA. However, only a few studies address this problem until now. In the aqueous polymer dispersion coating process, ASA can intensively react with moisture during the atomizing phase, and ASA may also migrate from the tablet core into the applied film [5]. Incorporation of small amounts of diluent or drug may greatly change the intrinsic features of the films, such as softening, glass transition, crystallinity and melting behavior [6]. Moreover, the additives in the polymer aqueous dispersion, such as macrogol and talc, may also have a marked adverse effect in ASA stability [7,8].

An effective way of overcoming these problems is to apply a sub-coating layer between the tablet core and the enteric layer [4,8]. Many materials, such as PVPK30 [9,10], amylopectin [11], Hypromellose [12] and stearic acid [13], have been used as a subcoat to avoid drug migration. In our study, glycerin monostearate with a low melting point of 55–60 °C was chosen as the subcoat using a hot-melt coating technique, which a simple solvent-free coating method suitable for moisture-sensitive drugs and fully complies with regulatory requirements. In hot-melt coating methods, the material is heated to its molten state and evenly spread out over the substrate followed by cooling to form the coating film. Wax including glycerin monostearate, fatty bases, and lipids are the most appropriate coating materials in hot-melt coating. The sub-coat of glycerin monostearate can also avoid any interaction between the drug and the ingredients in the coating film due to the chemical inertness of the wax material [14,15]. An alternative to this technique is to apply a GMS coating in the outer layer of an enteric-coated tablet to figure out the most effective method for moisture-proofing and improving ASA stability.

Considering the moisture content of coated tablets is significantly influenced by the drying efficiency during aqueous film coating, coaters with different ways of moisture removal also have discrepant effects on the ASA degradation as reported [3]. In addition, there are other stability-improving methods than enteric coating, such as reduction of drug solubility, coating of solid dosage forms, moisture-resistant packaging and modification of chemical structure [16].

The primary objective of the present study was to increase the stability of conventional ASA enteric-coated tablets by using two novel kinds of hot-melt coating systems for long-term storage under accelerated conditions. In addition, systematic investigations to the interaction between the film components and ASA and the corresponding hydrolysis mechanism in ASA enteric-coated tablets were performed. The *in vitro* dissolution of a double-coating system was also assessed, compared with a conventional single-coating. These processes can be applied to provide a novel art to facilitate the optimization of aspirin enteric-coated dosage forms with good stability.

2. Materials and methods

2.1. Materials

Acetylsalicylic acid (ASA) was obtained from Huayin Jinqiancheng Pharmaceutical Co. Ltd. (Weinan, China), and the other compounds as indicated: microcrystalline cellulose (MCC, vivipure 200, Germany), Talc (Merck, Darmstadt, Germany), partially pregelation starch (Colorcon, USA), Aerosol (aerosolA200, Rohm, Darmstadt, Germany), Eudragit L30D55 (methacrylicacid-ethyl-acrylate copolymer 1:1, Rohm, Darmstadt, Germany), stearic acid (Tianjin Damao Chemical Reagent Factory, Tianjin, China), triethyl citrate (TEC, Bengbu Fengyuan Medicine Technology Development Co. Ltd., Anhui, China), glyceryl monostearate (Tianjin Bodi Chemical and Engineering Co. Ltd., Tianjin, China). All solvents were of analytical grade and used as received.

2.2. Preparation of tablet cores

The main formulations are listed in Fig. 1 and were a single enteric-coated tablet (SET), a double coated tablet with GMS as a subcoating (GST), and a double coated tablet with GMS as an outercoating (GOT). The basic composition of the tablet cores prepared for film coating was as follows: acetylsalicylic acid 77% (w/w), microcrystalline cellulose MCC 12% (w/w), partially pregelatinized starch 9%, aerosol 1%, stearic acid 1%. The formulation ingredients were dry blended in a twin-shell blender (EYH-300, Shanghai Tianfan Pharmaceutical Machinery Factory), and then directly compressed with an eccentric tablet press (TP-50 tablet press, Shanghai Tianfan Pharmaceutical Machinery Factory) with a constant breaking strength of 6.0-7.0 kp using a 7-mm flat-faced punch. The weight of the targeted tablets was 130 mg.