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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.

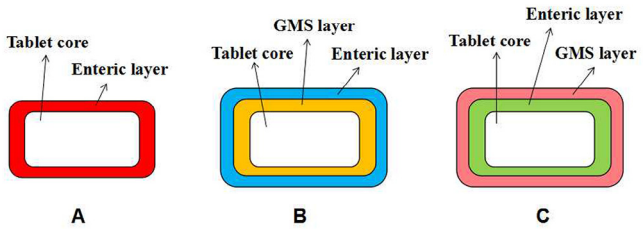

Fig. 1 – Schematic representation of single and double-layer tablets: (A) single enteric-coated tablet (SET); (B) double coated tablet with GMS as a subcoating (GST); (C) double coated tablet with GMS as an outercoating (GOT).

2.3. *GMS subcoating/outercoating*

Tablets which contained two batches of tablet core and a single enteric-coated tablet were coated by hot-melt coating respectively, and a traditional coating pan (B-300 Coating Pan, Baoji JianHua Co. Ltd., Shanxi, China) was used for hot-melt coating. Briefly, 200 g of tablets were transferred to the pan-coating apparatus and slowly rotated until their temperature rose above 70 °C. Then, the GMS was gradually added to the coating pan where it melted quickly and covered the tablet surface uniformly. After all the GMS had been added, the pan was kept rotating for another 10 min, and suitable amount of talc was then added to prevent tablet adhesion. The tablets were cooled down to room temperature under continuous rotation.

2.4. *Eudragit L30D55 coating*

Eudragit L30D55 is a polymer dispersion composed of methacrylic acid-ethylacrylate copolymer in a ratio of 1:1. An enteric layer was as shown in Fig. 1. The talc dispersion (30%, w/w) was first prepared by homogenization in water for 5 min, the talc dispersion was mixed with Eudragit L30D55, the dispersion was plasticized with 10% (w/w) TEC, and the solid content of the dispersion was finally adjusted to 20% with water. The film-coating process was conducted in a traditional coating pan (B-300 Coating Pan, Baoji JianHua Co. Ltd., Shanxi, China), and the process parameters were as follows: pan air temperature 30 °C, coating solution flow rate 3.0 g/min, outlet airflow rate 15L/s, and rotating speed of pan 10 rpm. Each coating batch consisted of 300 g of tablets. The tablets were preheated for 5 min before spraying, and dried for an extra 5 min after spraying. Curing was carried out for 24 h at 40 °C.

2.5. *Evaluation of ASA enteric-coated tablets*

2.5.1. *Storage stability study*

ASA enteric-coated tablets were hermetically packed in aluminum foil pouches under 40 °C/RH75% conditions for 6 months. The content of free salicylic acid was determined to evaluate the stability of the different formulations using a validated HPLC method. The mobile phase was prepared by dissolving 2 g sodium 1-heptanesulfonate in a mixture of 850 ml water and 150 ml acetonitrile, and adjusting the pH to 3.4 with glacial acetic acid at a flow rate of 2.0 ml/min. HPLC analysis was performed using a chromatograph equipped with an L-2400 UV Detector (Hitachi Corporation, Japan). The separation was carried out on a reverse phase Thermofisher C_{18} analytical column (4.6 mm × 100 mm, 5 μm) and the UV detector was set at 280 nm for ASA and salicylic acid. The limit of free salicylic acid in the aspirin enteric-coated tablet was 3% according to USP35/NF30.

2.5.2. *Drug release study*

The *in vitro* drug release study was performed according to the USP35/NF30 "dissolution procedure" for ASA delayed-release tablets. The ASA enteric coated tablets release was determined using an apparatus 1 (ZRS-8LD; Tianda Tianfa Technology Co. Ltd., Tianjin, China) at a rotation speed of 100 rpm. After operation in 0.1 N hydrochloric acid for 2 h, an aliquot of the fluid was withdrawn, and dissolution proceeded immediately as directed under Buffer Stage. Then 250 ml 0.2M sodium phosphate tribasic was added to give a final pH of 6.8 and maintained at 37 ± 0.5 °C (n = 3). An aliquot of samples were withdrawn at 45 min and analyzed using a UV detector (T6-1650E; Beijing Puxi General Instrument Co. Ltd., Beijing, China), set at 280 nm for the acid stage, and 265 nm for the buffer stage.

2.5.3. *Scanning electron microscopy (SEM)*

The surface and internal (Cross-section) morphologies of the tablets were examined under different accelerating voltages of 5.0 kV, 10.0 kV, 20.0 kV (shown in Figs. 3 and 4) using SEM. The cross-sections were obtained by cutting the tablets with a knife. The samples were mounted onto holders, coated with gold in a vacuum evaporator, and subjected to scanning electron microscopy (SU8010; Hitachi High-Technologies Corporation, Tokyo, Japan).

2.5.4. *Hygroscopicity test*

Water adsorption of uncoated and three kinds coated tablets was gravimetrically measured. The tablets without packages were stored in chambers of various relative humidity (RH = 0%, color-variable silica gel; RH = 11%, saturated LiCl solution; RH = 33%, saturated $MgCl_2$ solution; RH = 57%, saturated NaBr solution; RH = 75%, saturated NaCl solution; RH = 92%, saturated KNO_3 solution) at room temperature. The moisture sorption of the samples was determined by weighing the samples at predetermined time intervals and was calculated as percentage based on the initial tablet weight. All experiments were conducted in triplicate.

2.6. *Drug/excipient compatibility*

2.6.1. *Differential scanning calorimetry (DSC)*

DSC measurements (Shimadzu, Japan) were carried out to quickly characterize the compatibility between ASA and GMS, Talc, and dry powder of the same compositions to Eudragit L30D55. Samples (4–6 mg of the 50% drug/excipient physical mixture) were accurately weighed and immediately sealed in alumina pans. The samples were then heated from 25 °C to 180 °C at heating rate of 10 °C/min in nitrogen atmosphere. The heat flow was measured as a function of the temperature.

2.6.2. *Influence factor test*

The physical mixtures of ASA with GMS, Talc, and dry powder of the same compositions to Eudragit L30D55 were prepared

Table 1 – The comparisons of different formulations with and without GMS as a subcoating or outercoating (n = 3, mean ± SD).

Formulation no.[a]	Coating formulation			Drug content (%)	Weight variation (g)	Release	
	Sub coating level (%)	Enteric coating level (%)	Outer coating level (%)			In the acid medium (%)	In PBS medium (%)
F1	—	6	—	100.2 ± 1.2	0.1378 ± 0.37	0	100 ± 0.67
F2	—	9	—	99.0 ± 0.3	0.142 ± 0.27	0	98 ± 1.33
F3	—	13	—	101.2 ± 1.5	0.1462 ± 0.43	0	100 ± 0.27
F4	—	6	2	100.7 ± 0.5	0.1406 ± 0.25	0	99 ± 0.33
F5	—	6	4	101.5 ± 0.9	0.1433 ± 0.65	0	98 ± 0.56
F6	2	6	—	100.4 ± 2.0	0.1403 ± 0.56	0	100 ± 1.56
F7	4	6	—	101.4 ± 1.3	0.1429 ± 0.72	0	69 ± 0.75

[a] The tablet core of all the formulations contains: ASA (77%), partially pregelatinized starch (9%), MCC (12%), stearic acid (1%), aerosol (1%).

in the proportions of 1:1, 2:1, and 3:1, respectively. Then the mixtures were stored in a constant temperature and humidity chamber (LHH-250SD; Shanghai Yiheng Scientific Instrument Co. Ltd., Shanghai, China) under controlled conditions of 40 °C/75% and 25 °C/92.5% for 40 days. The content of free salicylic acid was assayed by HPLC.

3. Results and discussion

3.1. *Optimizing the preparation*

AS for ASA enteric coated tablet, good gastric acid resistance and complete release in the intestinal tract is a benefit of drug efficacy and can reduce any adverse drug reactions to the gastrointestinal tract mucosa. Therefore, the release patterns of different weight gain of the enteric coating films were investigated in this study (F1~F3 listed in Table 1). Table 1 shows that all three formulations exhibited good resistance to gastric acid and produced complete release in the intestinal juices. The tablets with 6% theoretical weight gain (F1) were chosen for further stability study due to the lower amount of polymer material applied and the excellent acid-resistance. To avoid the hydrolysis experienced with ASA enteric-coated tablets, water permeation into the tablet core needed to be prevented. So, we applied a wax-based coating material as a moisture-proofing film using hot-melt coating. GMS is a very commonly used wax material with a low melting point (56 °C) [17], and is especially compatible with ASA in enteric-coated tablets [8]. Hot-melt coating method is attractive for the reason that it offers many advantages over conventional aqueous-based coating systems. Firstly, it does not require the use of any solvent (organic or aqueous), which is especially beneficial for the stability of moisture-sensitive drugs. Accordingly, the elimination of the expensive and tedious processes of solvents makes hot-melt coating cost-effective, time-saving and environment-friendly. Also, the required weight gains with wax are fewer than those of polymers to get the same effect. Further, existing coating equipment can be easily modified to meet the demands of hot-melt coating [14]. GMS was designed as a subcoating film in order to protect the tablet core from the water permeation during the aqueous coating process, and the tablet was then coated with an enteric film. GMS was also designed to act over the enteric film as an outer-coating film to block the effects of moisture in the surrounding environment. GMS used for a coating material is very effective in retarding moisture absorption; however, it also obviously retarded the drug release. Thus, balancing the opposing effects of moisture-proofing and drug release was obtained by adjusting different weight gains of GMS coating. For the enteric-coated tablets with GMS as an outercoating (GOT), the tablets in F1 were coated with GMS at levels of 2% and 4%, respectively (F4, F5 listed in Table 1). The results obtained showed that the GMS coating reduced the drug release rate in the intestinal juices with a longer lag-time (10 min, data not shown here) compared with F1 and F5, but met the criteria in USP35/NF30. Slow release may result to a delayed response to medication and potentially reduce the bioavailability of the drug *in vivo* [18]. According to these results, tablets of F4 were selected for a further stability study involving a fast release in pH 6.8 phosphate buffer. With regard to enteric-coated tablets with GMS as a subcoating (GST) at weight gains of 2% and 4%, respectively (F6, F7 listed in Table 1), the results showed that F6 has a good acid-resistance and exhibits complete and fast release in pH 6.8 PBS buffer. However, F7 displayed incomplete release in pH 6.8 phosphate buffer, and this may be due to the GMS sub-coating retarding the water permeation and slowing the release rate significantly. Accordingly, F6 was selected for the next stability study (Tables 2–5).

3.2. *Characteristics of three formulations*

3.2.1. *Storage stability study*

Stability testing was performed with tablets packed in aluminum foil pouches hermetically under accelerated conditions (40 °C/RH75%) for 6 months using formulation F1 (SET), F4 (GOT), F6 (GST) and the tablet core, and the data are given in Table 2 and Fig. 2. The content of free salicylic acid of the tablets only coated with Eudragit L30D55 increased rapidly from 0.082% to 1.92%. Interestingly, the tablets without any coating film only increased slightly (with the SA content less than 0.46% at 6 months). Also, GOT exhibited similar content of free salicylic acid (0.51%) to that of the tablet core, whereas the content of free salicylic acid in GST (1.02%) was slightly greater than GOT and the tablet core, while the single enteric coated tablets had about two and four times the content of SA, as much as the novel double coated tablets. This shows that the hot-melt coat markedly improved the stability of ASA, especially for GMS used

Table 2 – The percentage content of free salicylic acid in different aspirin enteric-coated tablets under controlled conditions of 40 °C/75% for 6 months (n = 3, mean ± SD).

Storage time (d)	The content of SA (%)			
	Tablet core	SET	GST	GOT
0	0.07 ± 0.018	0.08 ± 0.018	0.08 ± 0.003	0.10 ± 0.013
30	0.13 ± 0.001	0.18 ± 0.014	0.18 ± 0.004	0.31 ± 0.005
70	0.21 ± 0.000	0.28 ± 0.003	0.29 ± 0.003	0.47 ± 0.060
180	0.46 ± 0.006	1.96 ± 0.275	0.51 ± 0.012	1.02 ± 0.030

as an outercoat. Regarding the hydrolysis of ASA, the factors which result in the difference of the stability of ASA-ECT probably involve: (i) the moisture in the environment which permeated into the tablet core and induced hydrolysis [19]; (ii) the residual moisture existing from the interface between the film and tablet core during the aqueous coating process [20]; (iii) the incompatibility between the drug and excipient which may be present in the tablet core [21] or coating film [8]. The compatibility test between the ASA and excipient in the tablet core shows excellent stability under stress conditions for 10 involving a high humidity (25 °C/RH75%), high temperature (60 °C/ambient humidity), and intense light (4500lx ± 500lx) (data not shown here). So, the main reasons for the ASA hydrolysis in tablets might not be the incompatibility between the drug and excipient in the tablet core.

The release of aluminum foil pouches hermetically packed with the three kinds of coated tablet under accelerated conditions (40 °C/RH75%) for 6 months was also evaluated. The three formulations show a good acid-resistance in acidic media and complete release in pH 6.8 phosphate buffer in comparison with the release before storage (data not shown here). This phenomenon shows that GMS as a sub-coat or outer-coat in aspirin enteric-coated tablets can withstand the adverse effects of stressful conditions during drug release, and this novel hot-melt coating technology not only ensures the safety but also the validity of the drug.

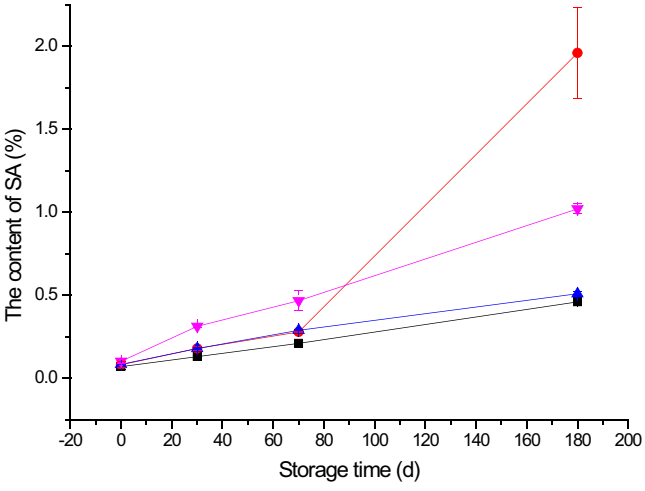

Fig. 2 – The percentage content of free salicylic acid in the aspirin enteric-coated tablets under controlled conditions of 40 °C/75% for 6 months: (■) tablet core; (●) SET; (▼) GST; (▲) GOT.

3.2.2. *Scanning electron microscopy (SEM)*

Observing the structure change in the cross- and surface-sections in different coating film formulations before and after storage at 40 °C/RH75% for 6 months will improve our understanding of the impact of the environment on the structure stability of ASA-ECT. The scanning electron micrographs of the surfaces and cross-sections of the single-coated tablet and double-coated tablets are shown in Fig. 3. The surface and cross-section of all three formulations were almost smooth and compact before storage (Fig. 3A–F). However, after storage at RH75%/40 °C for 6 months (Fig. 4A–F), the surface of the single-coated tablets showed the presence of drug crystals, and a small amount of drug had also migrated to the surface of the GOT, giving an uneven appearance, while no drug crystals were observed on the surface of the GST film. The cross-sectional images of these three formulations were examined after storage at 40 °C/RH75% for 6 months. The SEM images of SET show that the core of the tablet and film became loose and porous, and a clear drug crystal precipitate was observed in the outer region of the enteric film. Compared with the single enteric tablet, the GOT exhibited relatively better integrity and a more dense structure, although damage to the interface structure of the tablet core could also be observed. However, the cross-section of GST remained compact and retained its integrity and there was less damage to the internal structure and interface of the film. The damage to the film may be due to water adsorption and drug immigration [22]. This phenomenon can be explained by water being absorbed and permeating through the polymer film, which increased the mobility of the chain molecules which produced a drug concentration gradient that allowed the drug to migrate from the tablet core to the film surface. The extent of drug migration may be related to the amount of water absorption. Therefore, GMS as a subcoating could be an effective way to improve the structure stability of ASA-ECT. The water absorption of different formulations may be a key factor affecting the structure changes of the film, which may also affect the chemical stability of ASA.

3.2.3. *Water adsorption*

The degree of migration of water molecules from the surface of the film to the surface of the tablet substrate is mostly due to the affinity of the film to water [19], and this may play a key role in the stability of ASA .The water uptake kinetics of the coated and uncoated tablets at RH75%/25 °C was investigated (Table 3, Fig. 5A). It was found that the tablet core quickly reached moisture adsorption equilibrium in only one day, and SET in four days with a higher moisture gain (1.61%) in comparison with that of the tablet core (1.24%). This indicated that the enteric-coated film did not have a moisture-proofing effect; on the contrary, it may increase water adsorption in the film. The moisture absorption behavior of GOT was distinctive in that it exhibited a slow moisture adsorption rate, which reached a relatively lower moisture content (1.47%) in 6 compared with SET, although higher than the tablet core. This showed that GMS as an outer-coat slowed but did not completely retard the moisture penetration due to the abrasion and aggregation of GMS which reduced the capacity of GMS as a moisture-proofing film. GST quickly reached

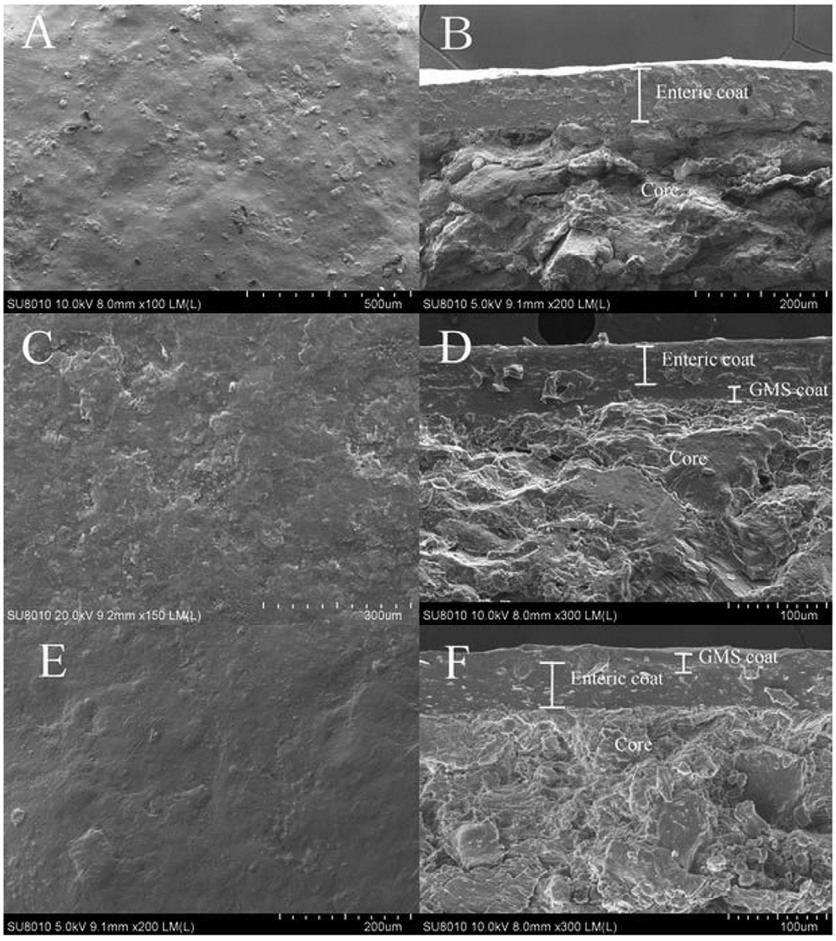

Fig. 3 – Scanning electron micrographs of the surface and cross-section of the single-coated and double-coated tablets before storage at 40 °C/RH75% for 6 months: (A) Surface of SET; (B) Cross-section of SET; (C) Surface of GST; (D) Cross-section of GST; (E) Surface of GOT; (F) Cross-section of GOT.

moisture adsorption equilibrium in the first two days and showed the lowest moisture content (0.53%). In addition, the water uptake content weight gain of GST was almost equal to the difference between the water uptake weight gain of SET and the tablet core, which indicates that the water vapor was unable to penetrate the GMS subcoat and it was mostly concentrated in the enteric film. Thus, GMS as a subcoat is an interesting candidate for moisture-protective polymer coating. The rank order of the degree of water uptake weight gain under this condition was: SET (1.61%, W/W) > GOT (1.47% W/W) > tablet core (1.24%, W/W) > GST (0.53%, W/W). This phenomenon was related to the state of the tablet surface observed after storage at RH75%/40 °C for six months, showing that GST did not appear to be soft or capped with a crystal form and a good tablet surface; also, the surface state of the tablet core was almost unchanged; GOT became slightly capped with a drug crystal form; SET became sticky; and drug crystals appeared around the film coatings in great quantity. This was due to the water uptake which resulted in a structural change in the polymer film and migration of the drug molecules. This further confirmed that the degree of water adsorption controls the structure stability of the film-coated tablet, and GMS as a sub-coating is an efficient way to improve the structure stability.

The three kinds coating formulations and the uncoated tablet were also maintained at a relative humidity of 11%, 33%, 57%, 75%, and 92% at ambient temperature (25 °C) for 10 to allow a more in-depth assessment of their moisture sorption behavior. As shown in Fig. 5B, GST had the lowest water uptake weight gain at each relative humidity in comparison with the other formulations, indicating that GST had a high resistance to moisture uptake under different humidity conditions. The other formulations have similar moisture sorption curves at a low relative humidity (0%–57%). Once the relative humidity reached 92%, the water adsorption increased sharply in all four formulations, and the three coated tablets were soft and capped with evidence of crystal formation. Bley [23] showed that the acrylic resin film may exhibit a critical glass transition RH. When the storage humidity was beyond this threshold value, the polymer film changed from being hard and glassy to soft and rubbery and the water penetration rate increased significantly. The explanation for this phenomenon was that RH of 92% was higher than the threshold value of the acrylic polymers leading to a high degree of water adsorption and drug migration. Although GMS might be used as a subcoat or outercoat, this was not enough to resist such a high relative humidity.

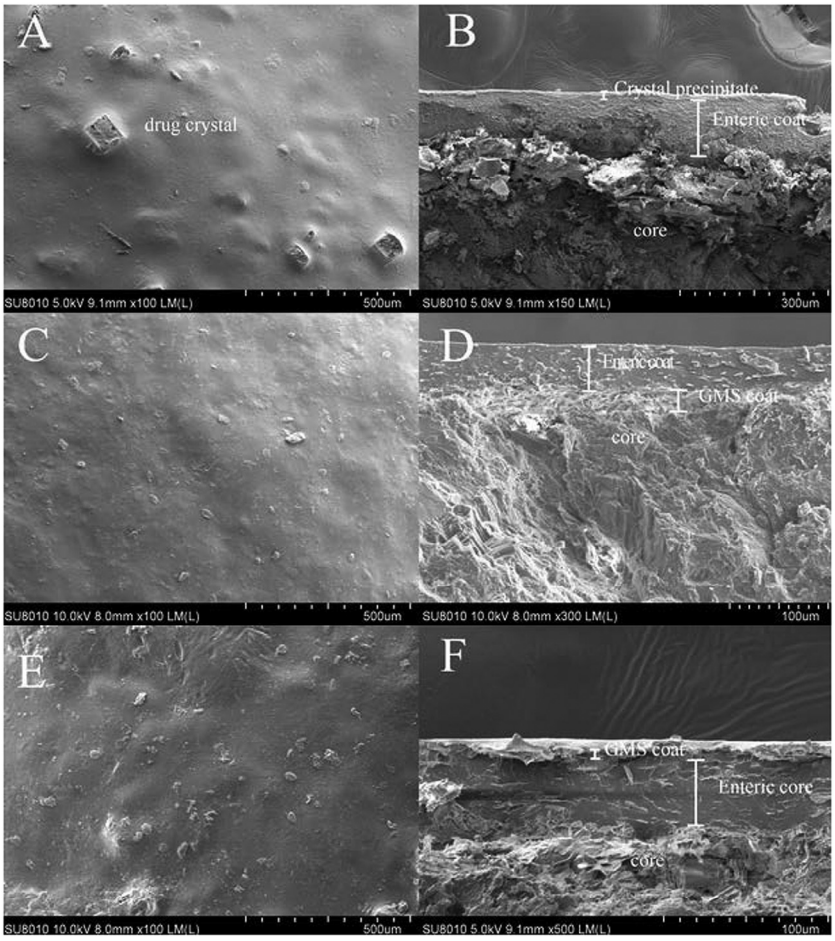

Fig. 4 – Scanning electron micrographs of the surface and cross-section of the single-coated and double-coated tablets after storage at 40 °C/RH75% for 6 months: (A) Surface of SET; (B) Cross-section of SET; (C) Surface of GST; (D) Cross-section of GST; (E) Surface of GOT; (F) Cross-section of GOT.

GST has a lower water absorption than GOT at different relative humidities, but did not have a lower salicylic acid content compared with the tablet core and GOT. This phenomenon supported the fact that increased water uptake does not always lead to more hydrolysis [20]. This suggests that the water uptake must be an instability factor but is not the sole reason for ASA hydrolysis, and the interaction between the ASA and the excipient in the coating film may play a role in the hydrolysis of ASA.

3.3. *The effect of film excipient in the stability of ASA*

3.3.1. *Compatibility study*

Differential scanning calorimetry (DSC) was used to quickly characterize the possible incompatibility between the excipient and drug based on the appearance, shift or disappearance of peaks and/or variations in the corresponding △H [24–26]. DSC scans of crude ASA, three components containing dry powder of Eudragit L30D55, GMS, talc and respective binary mixtures in a proportion of 1:1 and the results obtained are shown in Fig. 6. There are two endothermic peaks in the graphs, representing GMS (56 °C) and ASA (141 °C). The DSC thermograph showed some variations in the thermal profile of the three binary mixtures. A clear reduction in the ASA peak temperature was observed (the physical mixture of GMS/ASA: from 141 °C to 129 °C; the physical mixture of talc/ASA: 141 °C to 124 °C; the physical mixture of dry powder of Eudragit L30D55/ASA: 141 °C to 132 °C). In a previous study it was proposed that a non-eutectic binary mixture may exhibit a lower melting temperature than the individual components [27]. The mechanism for this is not clear. It can be seen from Fig. 6 that the enthalpy values of ASA and the binary mixture of GMS/ASA, Talc/ASA, and dry powder of Eudragit L30D55/ASA were 21.48, 14.79, 25.48, and 19.88J/g, respectively. Binary mixtures do not exhibit any obvious difference compared with crude ASA in the enthalpy values except for the GMS/ASA mixture, and it may be that the slow dissolution of the drug in the melt GMS which partly formed a solid-solvent resulted in a reduction in the enthalpy value in the DSC heat process [27]. However, no new extra thermal effects were observed or the disappearance of component peaks and as a consequence, this method cannot clearly indicate any incompatibility between the film excipients and ASA through transformation of the thermal profile.

HPLC was also used to characterize the interaction between ASA and excipient in the film mixture at 25 °C/92%RH and 40 °C/

Table 3 – (A) Effect of four formulations on water vapor sorption patterns after storage at 75%RH/25 °C for 10 days (n = 3, mean ± SD). (B) Water vapor adsorption isotherms of ASA at the tenth day (n = 3, mean ± SD).

(A)

Time (d)	Weight gain (%)			
	Tablet core	SET	GST	GOT
1	1.23 ± 0.050	1.21 ± 0.033	0.31 ± 0.020	0.73 ± 0.040
2	1.33 ± 0.032	1.55 ± 0 .012	0.34 ± 0.050	1.06 ± 0.031
3	1.35 ± 0.056	1.65 ± 0.026	0.42 ± 0.030	1.23 ± 0.052
4	1.30 ± 0.043	1.74 ± 0.033	0.50 ± 0.020	1.25 ± 0.033
5	1.33 ± 0.067	1.65 ± 0.027	0.43 ± 0.034	1.38 ± 0.047
6	1.24 ± 0.078	1.70 ± 0.038	0.40 ± 0.024	1.45 ± 0.058
7	1.30 ± 0.083	1.67 ± 0.033	0.50 ± 0.033	1.44 ± 0.063
8	1.32 ± 0.099	1.68 ± 0.049	0.51 ± 0.039	1.51 ± 0.049
9	1.24 ± 0.021	1.67 ± 0.021	0.43 ± 0.031	1.45 ± 0.021
10	1.24 ± 0.042	1.61 ± 0.022	0.53 ± 0.012	1.47 ± 0.032

(B)

RH (%)	Weight gain (%)			
	Tablet core	SET	GST	GOT
11	0.06 ± 0.002	0.00 ± 0.000	0.00 ± 0.000	0.00 ± 0.000
33	0.09 ± 0.012	0.06 ± 0.000	0.06 ± 0.000	0.03 ± 0.000
57	0.96 ± 0.042	1.07 ± 0.025	0.46 ± 0.033	0.80 ± 0.015
75	1.24 ± 0.033	1.61 ± 0.032	0.53 ± 0.022	1.47 ± 0.031
92	4.25 ± 0.055	4.83 ± 0.024	4.21 ± 0.043	4.96 ± 0.015

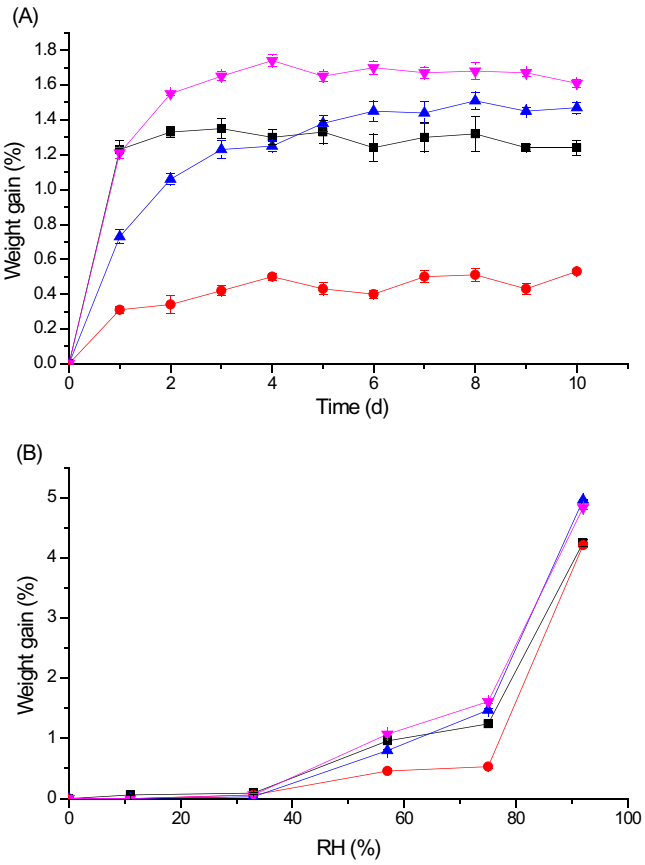

Fig. 5 – (A) Effect of four formulations on water vapor sorption patterns (n = 3) after storage at 75%RH/25 °C for 10 days: (■) tablet core; (▼) SET; (●) GST; (▲) GOT. (B) Water vapor adsorption isotherms of ASA (n = 3) on the tenth day: (■) tablet core; (▼) SET; (●) GST; (▲) GOT.

75%RH conditions over storage for 35 by monitoring the extent of ASA degradation. The SA content variations as a function of the daily profiles of different drug-excipient mixtures are shown in Table 4 and Fig. 7A and B. The figures show that the condition of 40 °C/75% has a more marked effect on the ASA hydrolysis rate than 25 °C/92%RH. This indicates that high humidity and temperature has a greater influence on the stability of ASA than high humidity alone, especially for the dry powder of Eudragit L30D55/ASA mixture. Hence, the mixture under high humidity and temperature satisfactorily and truly reflects the interaction between excipient and drug. The order of the SA content of drug-excipient mixtures in the same proportion after storage at 40 °C/75% for 35 is: Talc, GMS, dry powder of Eudragit L30D55. This indicates that talc has the most adverse effect on the stability of ASA compared with all the others although dry powder of Eudragit L30D55 also adversely affects the stability. When the proportions of excipient/drug increased, the hydrolysis rates of ASA increased in parallel. Interestingly, the raw ASA produced little hydrolysis under the two different conditions. This showed that more excipients being introduced or in contact with ASA may induce more hydrolysis. This phenomenon can be explained by the fact that the raw ASA is hydrophobic and adsorbs very little moisture with a slow hydrolysis rate. However, for the excipients in the film which may contain metal ions, alkaline substrates or may be hygroscopic these can produce hydrolysis of ASA. This would also explain why the tablet core had a better stability at 40 °C/75%RH for six months.

In order to better understand the hydrolysis reaction process, the different time interval (0–5 d; 5–10 d; 10–20 d; 20–35 d) courses of the relevant hydrolysis percentages of ASA/excipient physical mixtures in the proportion of 1:1 in three drug/excipient mixtures at 40 °C/75%RH are shown in Fig. 7C. It can be seen that the ASA/GMS mixture has a fast growth and higher SA content in 10 d, unlike the other two mixtures. However, the hydrolysis of ASA in the GMS/ASA mixture decreased in the medium phase (10–20 d), In contrast, the two other mixtures exhibited gradually increased growth. Also, the growth in the Talc/ASA and dry powder of Eudragit L30D55/ASA mixture was higher than that of the GMS/ASA mixture in later phase (20–35 d).

These findings were expected, since the decomposition of aspirin containing ASA/excipient mixture is the result of various factors, including the humidity and temperature [8,28], and the excipient(s) and its proportions presented. Humidity provides the water and temperature provides the energy needed for the hydrolysis reaction. Different excipients have different pH values [21] and impurities may have marked catalytic effects in the reaction of ASA. The catalytic effect of aspirin mainly involves three kinds: hydronium-ion catalysis, intramolecular-nucleophilic catalysis, and hydroxyl-ion catalysis [29]. The Ea (30–40 °C) values were 19.3, 20.87, and 9.11 kcal/mol, respectively. Talc mainly contains magnesium silicate which is alkaline, so the decomposition of ASA catalyzed by talc is a form of hydroxyl-ion catalysis reaction

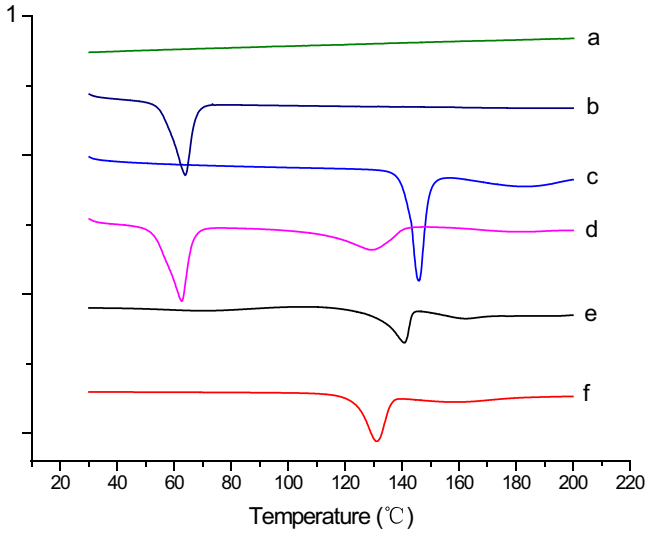

Fig. 6 – DSC thermograms of talc (a), GMS (b), crude ASA (c), 50% ASA-GMS physical mixture (d), 50% ASA-dry powder of Eudragit L30D55 physical mixture (e) and 50% ASA-Talc physical mixture (f).

that is easy to happen due to the low Ea value. Dry powder of Eudragit L30D55 mainly contains methacrylic acid which will produce hydronium-ion catalysis which has a relatively higher Ea value compared with talc, thus the temperature in the environment will have a clear effect on methacrylic acid catalysis. GMS is wax-based and does not contain any acid or alkali groups, and the reason why the mixture had a high hydrolysis rate during the preliminary phase may be because of the residual alkali material which may have been produced during the production of GMS. Once the residual alkali material was consumed completely, the hydrolysis rate will fall. This is accounted for in the result shown in Fig. 7C. This finding can also explain the results of three formulations stored at 40 °C/75%RH for six months showing that the preparation with GMS as a sub-coating initially has a higher SA content compared with the single enteric-coating in three months; also, the SA content of the latter was higher than the former after storage for six months, Finally, in summary, the different compatibilities of the drug and excipients in the film accounts for the differences in chemical stability. Interestingly, GMS, as an outer-coating layer in the tablet, has a lower SA content than the formulation with GMS as a sub-coating. This may be explained by the fact that, although GMS as a subcoat can have a significant moisture-proofing effect, the residual alkali impurities produce some ASA hydrolysis in the preliminary phase. GMS, as an outercoating layer, can partly reduce the water permeation rate, subsequently reducing the catalysis rate of Talc and methacrylic acid in the film due to the absence of water. However, GMS as an outercoat, cannot effectively prevent moisture penetration and is easily influenced by the environment. Thus, it can be speculated that GST will have a lower SA content than GOT over a longer storage period. Furthermore, GMS as a subcoat, can be recommended for improving the chemical and physical properties of ASA enteric-coated tablets.

3.3.2. *The SA content in film-peeling and film-unpeeling tablet analysis*

According the analysis above, one hypothesis is that the hydrolysis of ASA may occur mainly at the interface and within the film because the water penetration is mostly concentrated within the film, with drug migration mainly occurring through the film and hydrolysis mainly occurring in it as well. To prove this point, the SA content of film-peeling and film-unpeeling tablets were determined after storage at 40 °C/75%RH for 6 months. The change of SA content in the tablets is given in Table 5 and Fig. 8. The SA content of SET significantly decreased when the coating films were peeled off, from 1.96% to 0.98%, GST was clearly reduced from 1.02% to 0.66%, and GOT was also reduced but not significantly (from 0.51% to 0.40%). This was due to the low ASA hydrolysis in GOT which further illustrated that the compatibility between ASA and the coating film was very important for the stability of ASA enteric-coated tablets, especially at a high temperature and humidity. Thus, the subcoat existing between the tablet core and the enteric-coated layer is very important and GMS coating is a very useful method. Other macromolecule polymer films can also be used, but it is better if they do not contain any alkaline or acidic groups and related additives. Talc is an excellent and cheap anti-adherent commonly used in polymeric film coating formulations; if talc has to be used, it should be kept to a low level as far as possible or, alternatively, GMS should be used as an anti-adherent in polymer dispersions which can markedly reduce the film tackiness if a low amount is used [30]. Also, GMS can provide a film with better compatibility and moisture-proofing. Coating film in the outer enteric film is also an effective way to maintain drug stability, and GMS hot melt coating can be used, but it is likely to fuse, solidify and cause abrasion, subsequently resulting in structural changes and a loss of efficacy in moisture-proofing due to complete exposure to the outside environment. In addition, the material chosen as an outercoat must have stable property and be very effective in preventing water penetration. An appropriate storage method for ASA tablets, such as storage with a drying agent in a plastic or aluminum pack, may also be an effective method for preventing hydrolysis and ensuring that quality is maintained [31].

4. Conclusion

Aspirin enteric-coated tablets were successfully prepared to avoid drug migration and enhance the stability of ASA involving combination of a GMS hot-melt coat with a level of 2% (w/w) and an acrylic resin polymer coat of 6% (w/w). The key factors that affected the ASA degradation in ASA-ECT were investigated, and it was found that controlling the water uptake in the tablets could improve their structure stability, while improving the chemical stability of ASA-ECT could not be achieved by only controlling the moisture content. The interaction between the film excipient and ASA might be the key reason for this. The compatibility test indicated that Talc had the most adverse effect compared with methacrylic acid copolymer and GMS. However, the effect of methacrylic acid also cannot be disregarded. This phenomenon may be a result of the catalytic effects of alkaline and acidic group present in those

Table 4 – (A) The variation in SA content versus time in ASA and film excipient mixture storage at 40 °C/75%RH (n = 3, mean ± SD). (B) The variations in SA content versus the time in ASA and film excipient mixtures after storage at 25 °C/92%RH (n = 3, mean ± SD). (C) The SA increased rate of ASA/excipient physical mixtures in the proportion of 1:1 over different time intervals at 40 °C/75%RH condition.

(A)

Time (d)	The content of SA (%)								
	Tablet core	ASA and Talc physical mixture			ASA and GMS physical mixture			ASA and L30D55 physical mixture		
		1:1	2:1	3:1	1:1	2:1	3:1	1:1	2:1	3:1
5	0.02 ± 0.002	0.96 ± 0.019	0.46 ± 0.024	0.30 ± 0.070	1.08 ± 0.002	0.70 ± 0.036	0.42 ± 0.055	0.28 ± 0.025	0.13 ± 0.005	0.11 ± 0.008
10	0.02 ± 0.005	1.28 ± 0.194	0.70 ± 0.024	0.47 ± 0.020	2.85 ± 0.061	1.48 ± 0.040	0.88 ± 0.018	0.57 ± 0.078	0.47 ± 0.025	0.34 ± 0.000
20	0.04 ± 0.002	2.74 ± 0.306	1.60 ± 0.061	1.01 ± 0.032	4.51 ± 0.064	2.13 ± 0.086	1.43 ± 0.084	1.99 ± 0.021	1.10 ± 0.017	0.85 ± 0.037
35	0.05 ± 0.007	7.49 ± 0.142	3.61 ± 0.064	2.25 ± 0.036	6.37 ± 0.174	2.93 ± 0.370	1.66 ± 0.121	4.76 ± 0.040	2.67 ± 0.004	1.87 ± 0.029

(B)

Time (d)	The content of SA (%)								
	Tablet core			ASA and Talc physical mixture			ASA and GMS physical mixture			ASA and L30D55 physical mixture
		1:1	2:1	3:1	1:1	2:1	3:1	1:1	2:1	3:1
5	0.02 ± 0.002	0.32 ± 0.009	0.17 ± 0.012	0.12 ± 0.002	0.63 ± 0.043	0.32 ± 0.043	0.24 ± 0.006	0.03 ± 0.008	0.02 ± 0.009	0.02 ± 0.006
10	0.02 ± 0.002	0.47 ± 0.070	0.27 ± 0.006	0.21 ± 0.006	0.75 ± 0.036	0.41 ± 0.013	0.27 ± 0.015	0.04 ± 0.007	0.03 ± 0.002	0.04 ± 0.002
20	0.03 ± 0.006	0.89 ± 0.014	0.44 ± 0.043	0.34 ± 0.008	0.90 ± 0.033	0.43 ± 0.026	0.29 ± 0.020	0.06 ± 0.000	0.05 ± 0.011	0.05 ± 0.006
35	0.04 ± 0.008	1.41 ± 0.040	0.77 ± 0.016	0.52 ± 0.095	1.24 ± 0.043	0.61 ± 0.012	0.38 ± 0.038	0.16 ± 0.003	0.11 ± 0.015	0.10 ± 0.014

(C)

	The SA increased rate (%)			
	0–5 d	5–10 d	10–20 d	20–35 d
ASA/Talc	0.188	0.065	0.145	0.317
ASA/GMS	0.212	0.354	0.166	0.124
ASA/L30D55	0.052	0.059	0.142	0.185

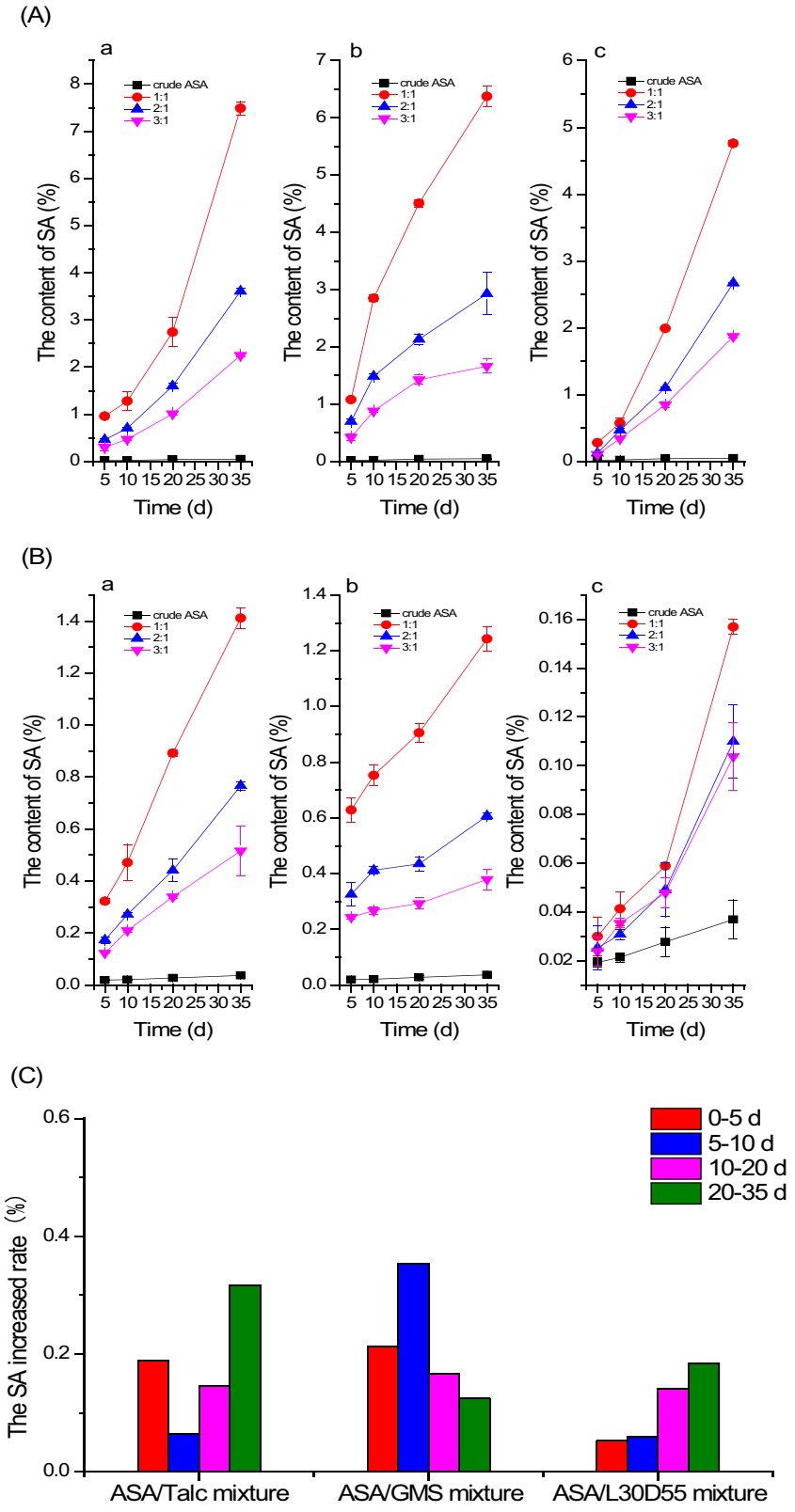

Fig. 7 – (A) The variation in SA content versus time in ASA and film excipient mixture storage at 40 °C/75%RH: (a) ASA and Talc physical mixture; (b) ASA and GMS physical mixture; (c) ASA and dry powder of Eudragit L30D55 physical mixture. (B) The variations in SA content versus the time in ASA and film excipient mixtures after storage at 25 °C/92%RH: (a) ASA and Talc physical mixture; (b) ASA and GMS physical mixture; (c) ASA and dry powder of Eudragit L30D55 physical mixture. (C) The SA increased rate of ASA/excipient physical mixtures in the proportion of 1:1 over different time intervals at 40 °C/75%RH condition.

Table 5 – The percentage content of SA in peeling and unpeeling tablets of three formulations (SET, GST, GOT) after storage at 40 °C/75%RH for 6 months (n = 3, mean ± SD).

	The content of SA (%)	
	Film peel	Film unpeel
SET	0.98 ± 0.27	1.96 ± 0.16
GST	0.66 ± 0.26	1.02 ± 0.20
GOT	0.40 ± 0.13	0.51 ± 0.25

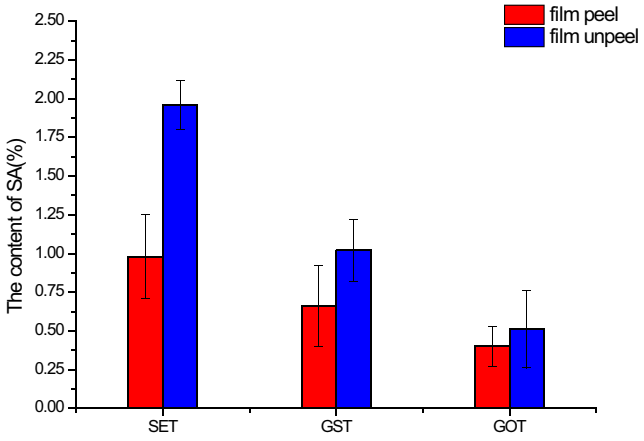

Fig. 8 – The percentage content of SA in peeling and unpeeling tablets of three formulations (SET, GST, GOT) after storage at 40 °C/75%RH for 6 months (*n* = 3, mean ± SD).

additives. GMS hot-melt coating is an alternative to subcoating or outercoating in ASA-ECT, and GMS subcoating is recommended since it exhibits good appearance and chemical stability during long-term storage. Thus, this method is attractive, especially for moisture-sensitive drugs, and it has many advantages including its simplicity, efficiency, and solvent-free coating technology.

Acknowledgments

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