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Influence of selected surfactants on the tackiness of acrylic polymer films

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Abstract

Anti-tacking agents are always necessary in polymeric film coating formulations in order to prevent substrate agglomeration. The objective of this study was to investigate the abilities of certain nonionic surfactants in a group of sorbitan ester in reducing the tackiness of the films obtained from aqueous acrylic polymer dispersions (Eudragit®), compared with those of talc and glyceryl monostearate (GMS). The results from the peel tests demonstrated that GMS, Span 60 and Span 40 could significantly reduce the tackiness of both Eudragit NE 30D and Eudragit RS 30D films. The mechanisms in reducing the film tackiness were investigated by analyzing the film compositions, using attenuated total internal reflectance infrared spectroscopy (ATR-IR) and optical microscopy. The storage modulus of the films was also examined. The results indicated that GMS, Span 60, and Span 40 could reduce the film tackiness by decreasing the polymer contents at the film surfaces, resulting in a notable reduction in the contact area of the polymers between the surfaces. The use of only 5% (w/w) of either GMS, Span 60 or Span 40 in the coating formulations is enough to prevent pellet agglomeration without adverse effects on film flexibility. The pellets coated with Eudragit RS 30D/RL 30D (9:1, w/w) did not exhibit any difference in the drug release profiles when either 100% (w/w) talc or 5% (w/w) GMS was used, whereas the formulations containing Span 60 or Span 40 gave a slightly faster release rate.
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Keywords: Tackiness; Acrylic aqueous dispersions; Film coating; Sorbitan ester; Surfactants; Dissolution

1. Introduction

In the coating of solid dosage forms, there is presently no coating methodology that can match polymeric film coating in production capability or economy. The polymeric coating materials may be in a form of solution in organic solvent or water, or

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in a form of aqueous dispersion. Recently, aqueous polymeric dispersions have gained popularity and are replacing solvent-based systems due to their lower toxicity level and environment friendly standpoint (Porter, 1979; Harris and Ghebre-Sellassie, 1997). The film formation mechanism is more complex with latex dispersions than with organic solvent systems, since the coalescence of individual colloidal particles and the inter-diffusion of polymeric molecules must occur to form a continuous film (Fukumori, 1994).

In the coating of dosage forms by aqueous polymeric dispersions, sticking of the coated substrates always occurs simultaneously during the coating or the curing process. This is due to the tackiness of the films. This tackiness creates a tremendous handling problem as the coated substrates stick to each other as well as to the wall of the coating chamber; and sometimes, irreversible agglomeration of several beads or the complete batch can occur, especially at higher product temperatures or higher plasticizer content in the coating formulation (Bodmeier and Paeratakul, 1991). A fine balance has to be found between sufficiently high temperatures and non-agglomeration (Wesseling et al., 1999).

Theoretically, tack is defined as the ability of two materials to resist separation after bringing their surfaces into contact for a short time under light pressure (Wetzel, 1957). Autohesion or autohesive tack is a term used to describe tack between two polymer surfaces having the same chemical identity, such as the surface of the films coated on the drug substrates. Tack of polymers depends on different fundamental mechanisms. First, the development of intimate contact between the surfaces is necessary. This is related to the deformability of the polymer, and the van der Waals' force is a key factor to give bond strength (Anand, 1973). Inter-diffusion across the surfaces can also be involved if both materials are polymers and when the contact time is long enough. In this case, the interface may eventually disappear (Voyutskii, 1971). Usually glidants or anti-tacking agents are added into the coating dispersions to reduce the sticking problem. A variety of materials have been recommended for this purpose. Most commonly, talc is used. However, some adverse effects have been reported, such as, a variation in quality (Dawoodbhai et al., 1987; Phadke et al., 1994), high amounts (20–100% based on polymer mass) used, which causes sedimentation in tanks, tubes and clogging of the spray systems, and incompatibilities with certain drugs, etc. Other substances like magnesium stearate or kaolin have also been used, but are no more advantageous than talc. Colloidal silica is another choice, which can be effective at a lower amount (30–60%). Nevertheless, due to its hygroscopic property, the drug release profile of the coated substrates could be changed (Vecchio et al., 1995; Singh and Khan, 1997). Some hydrophobic non-ionic surfactants with HLB value 2.5–7 also show a positive result in reducing the tackiness of the films. Petereit et al. (1995) found that glyceryl monostearate (GMS), a non-ionic surfactant with HLB 3.8, showed an excellent anti-tacking property when only a low amount was used (2–10%). Thus, the materials in this group are of interest.

The objective of this study was to investigate the anti-tacking property of certain surfactants. A series of sorbitan ester, widely used surfactant in cosmetics, foods and pharmaceuticals, were tested in this study, compared with talc and GMS. Aqueous acrylic dispersions, Eudragit NE 30D and Eudragit RS 30D, were used as film formers. These polymers are known for their stickiness, especially Eudragit NE 30D is known to give a highly flexible film and an agglomeration problem due to its low glass transition temperature (Bodmeier and Paeratakul, 1994). The tackiness of the films was measured by peel tests. The mechanisms of the materials in reducing the film tackiness were also investigated by analysing film compositions with infrared spectroscopy and microscopy, concomitant with the examination of the mechanical properties of the films. The drug pellets were coated and their dissolution was also examined.

2. Materials and methods

2.1. Materials

Acrylic aqueous dispersions (Eudragit NE 30D, Eudragit RS 30D and Eudragit RL 30D) were donated by Röhm Pharma GmbH, Germany. Plasticizers: triethyl citrate (TEC) and acetyltributyl citrate (ATBC) were donated by Morflex Chemical Co., USA. Glyceryl monostearate (GMS), sorbitan monooleate (Span®80), sorbitan monostearate (Span®60), sorbitan monopalmitate (Span®40) and sorbitan monolau-

rate (Span®20) were purchased from Fluka Chemie, Switzerland. Talc was supplied by Merck, Germany. Theophylline anhydrous, microcrystalline cellulose (Avicel® PH101), povidone K30, and lactose anhydrous were purchased from Shanghai Wandai Pharmaceutical Co. (China), JRS GmbH (Germany), BASF (USA), and The Lactose Company (New Zealand), respectively. These materials were used without further treatment.

2.2. Preparation of the polymer films

The surfactants were first prepared in a form of 4% (w/w) dispersion by homogenizing in water for 15 min at temperatures above their melting points. The surfactant dispersions were then added into the Eudragit NE 30D and Eudragit RS 30D dispersions to obtain the polymer dispersions with 5%, 10% or 15% (w/w) surfactants (based on polymer mass). For the Eudragit RS 30D, the polymer was plasticized first with 30% (w/w) ATBC for 48 h. The weight of the dispersions was adjusted to 15% solid content with water prior to stirring for 15 min. The polymer dispersions containing 15%, 50% and 100% (w/w) talc were also prepared.

The films were produced by using a pneumatic nozzle that intermittently sprayed the polymer dispersions onto a sheet of PTFE laid on a glass plate. The dispersions were stirred continuously when spraying. The films were formed on the surface of the PTFE sheet by the intermittently application of warm air. The spray position was constantly changed in order to obtain films with a uniform thickness. After the films, with an approximate thickness of 0.25 mm, had been obtained they were kept under warm air until they felt dry to the touch and then were removed from the PTFE sheet.

Table 1
Effect of talc and GMS on the tackiness of Eudragit NE 30D films

Additive	Force (N, mean ± S.D.)
No additive	11.0 ± 0.6
Talc (%)	
15	11.5 ± 1.0
50	10.8 ± 2.1
100	4.9 ± 1.2
GMS (5%)	6.4 ± 0.9

The films were stored over silica gel until required for the tests.

2.3. Determination of the tackiness of the films

The films were cut into 2.5 cm × 7.0 cm sections and backed with cotton cloth. Two test films were pressed together under a 200-g weight and stored at 40 °C for 1 h. After this treatment, the samples were cooled to room temperature (23 ± 2 °C), 50 ± 5% RH for 1 h and T-peel tests were performed using a tensile tester (texture analyzer, Stable Micro Systems). The films were peeled from each other through one end at a cross-head speed of 15 mm/min. The force–displacement diagrams were recorded. The average values obtained from the constant force portions of the diagrams were used to represent the peel forces. At least five specimens were tested for each sample.

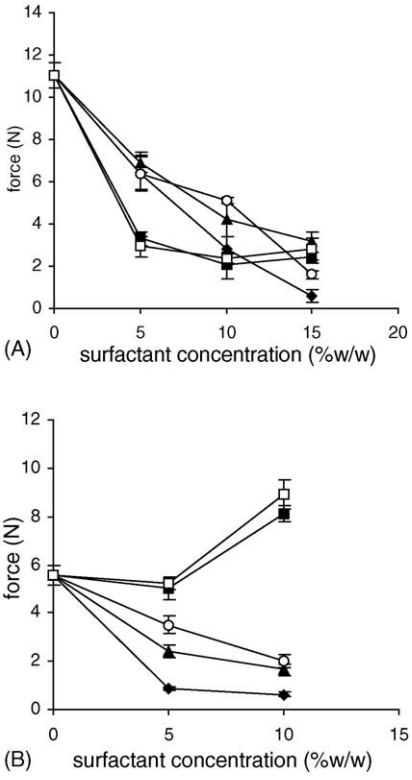

Fig. 1. Effect of surfactants on the tackiness of Eudragit NE 30D films (A) and Eudragit RS 30D films (B): (♦) GMS; (■) Span 80; (▲) Span 60; (○) Span 40; (□) Span 20.

2.4. Analysis of film compositions

2.4.1. Spectroscopic study

The surface components of the test films were examined with a Fourier transform infrared spectrometer (FTIR Spectrum One, Perkin-Elmer) equipped with an attenuated total reflection accessory (FTIR-ATR). Zinc selenide crystal (refractive index, 2.4) having an incidence angle of 45° was used to give a total of 16 reflections. The scanning range was 650–4000 cm^{-1} and the approximate penetration depth was 1.6 μm at 1000 cm^{-1}. Each sample was scanned four times and the spectrum was recorded at a resolution of 4 cm^{-1}

2.4.2. Microscopic study

A thin film was prepared by spreading a drop of polymer dispersion on a glass slide prior to drying at 40 °C for 3 h. The compositions of the films were investigated under an optical microscope (Zeiss®, Germany) using transmittance mode. The images of the films were captured and scanned into a computer.

2.5. Mechanical properties of the films

2.5.1. Storage modulus

Dynamic mechanical measurements were carried out on DMA (GABO Qualimeter®, Germany) in tension mode. The sample films were cut into 8.5 mm × 30 mm sections and clamped between two grips of the machine. The gauge length was 20 mm. The samples were tested at a constant frequency of 10 Hz, under room temperature. The static strain was 20% and the dynamic strain was varied from 0.10% to 10.00%. The modulus of the samples were calculated from the program of the machine.

2.5.2. Film flexibility

The flexibility of the films was determined from their elongation property. A static tensile test was performed using a tensile tester according to ASTM-D882. The sample width was 15 mm and the gauge length was 25 mm. The cross-head speed was 50 mm/min. The stress–strain profiles were recorded and the values of the elongation at break of the films were calculated. The averages of at least five measurements for each sample were reported.

2.6. Preparation of theophylline pellets

Theophylline anhydrous, microcrystalline cellulose (Avicel PH101) and lactose were mixed in a 20:50:25 ratio for 20 min in a mixing container. A 5% PVP K30 (based on total mixture) was dissolved in a suitable amount of water and the solution was then added to the powder mixture. The moistened mass was extruded through a 1 mm diameter screen and the extrudates were spheronized by setting the spheronization speed and residence time at 950 rpm and 15 min, respectively. The wet spheronized pellets were then dried at 60 °C for 24 h. The dried pellets were sieved using a sieve

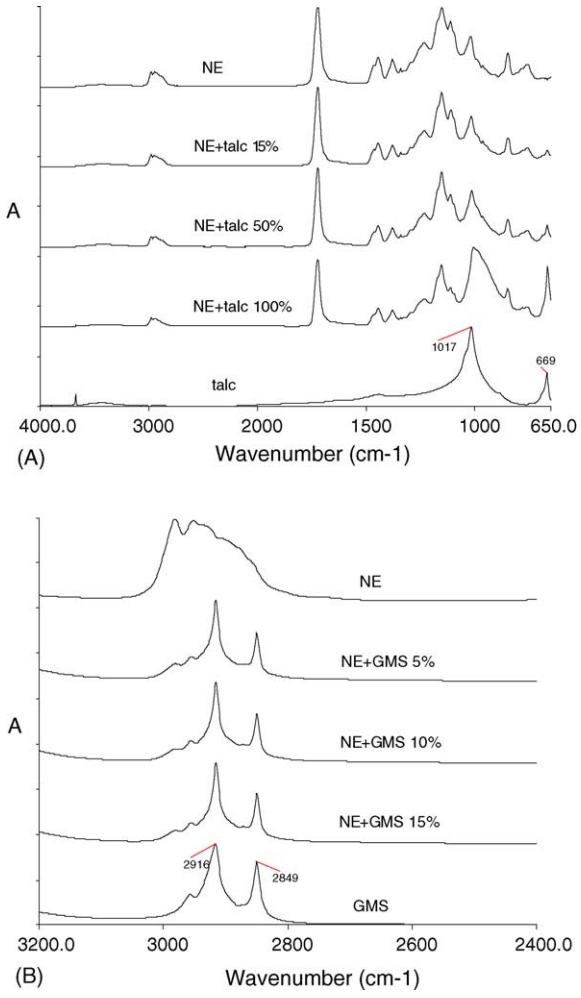

Fig. 2. ATR-IR spectra of Eudragit NE 30D films containing talc (A) and GMS (B).

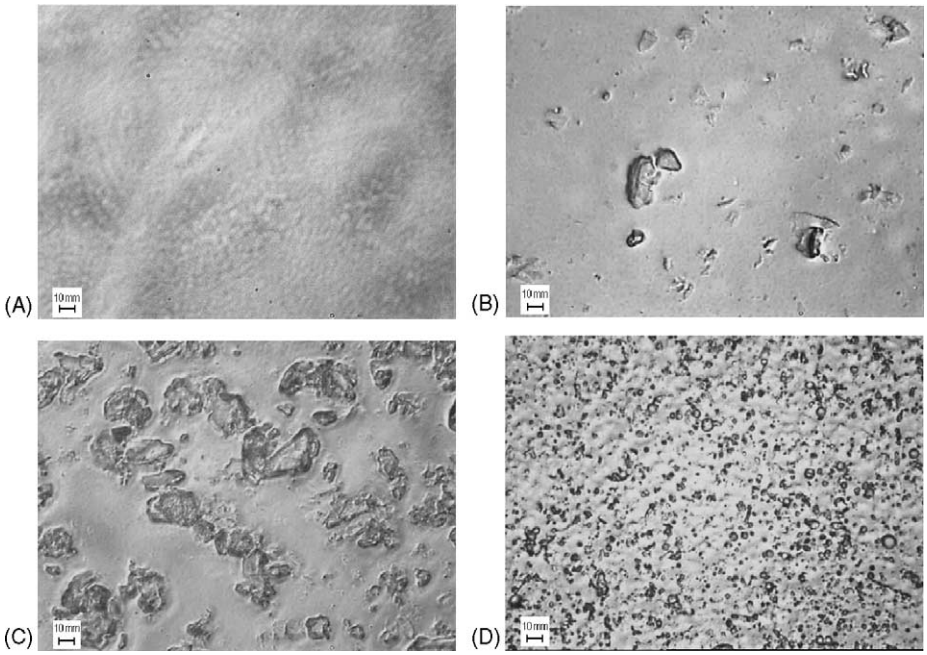

Fig. 3. Microscopic images of Eudragit NE 30D films without additive (A) and the films containing: 5% (w/w) talc (B); 100% (w/w) talc (C); and 5% (w/w) GMS (D).

shaker and the pellets with diameter between 0.71 and 1.25 mm were collected for the further coating process.

2.7. Preparation of coated pellets

Eudragit RS 30D/RL 30D (9:1, w/w) was plasticized with 20% (w/w) TEC (based on polymer mass) for 2 h whereas Eudragit NE 30D was used without plasticization. Talc (100%, w/w) or 5% (w/w) of each surfactant (based on polymer mass) were incorporated into the acrylic dispersions. The polymer content was then adjusted to 12.5% (w/w) by diluting with water. The dispersions were gently stirred for 15 min prior to coating.

The coating dispersions were sprayed (nozzle diameter, 1.0 mm; atomization pressure, 1.8 bar) onto 600 g of the theophylline pellets in a fluidized bed coater (Thai coater®, Wurster insert, PMS Co., Thailand). The spray rate was 2–7 g/min. The inlet air temperatures were 30 and 40 °C, and the product temperatures were held between 26–28 and 32–35 °C for the Eudragit NE 30D coating and the Eudragit RS 30D/RL 30D coating, respectively. The beads were coated until a theoretical polymer weight gain of 10% (w/w) was obtained. After the coating, the coated beads were cured in an oven at 40 °C, 24 h for the Eudragit NE 30D formulations, and at 60 °C, 24 h for the Eudragit RS 30D/RL 30D formulations.

2.8. In vitro dissolution studies

The USP XXIV rotating paddle method (37 ± 0.5 °C, 50 rpm, 900 ml 0.1N HCl, $n = 3$) was used to study the drug release from the coated pellets. The weight of pellets used was equivalent to about 20 mg of theophylline. The automated dissolution-testing machine comprised of a dissolution apparatus, eight-channel peristaltic pump and a UV–vis spectrophotometer equipped with six 1.0-cm quartz cells (VK 7010, Vankel). The instrument was programmed to draw the sample automatically at predetermined time intervals by means of a peristaltic pump, which delivered the samples to the quartz flow cells of the spectrophotometer operating at 271 nm. The concentration of theophylline was detected and the drawn samples were returned to the dissolution vessels.

3. Results and discussion

3.1. The tackiness of the films

In the present study, T-peel tests were used to determine the tackiness of the test films. The force required to peel the pressed films from each other could represent the level of the film tackiness, at least for a comparative study (Wesseling et al., 1999). In order to see the effects of the additives on the tackiness of the polymer films, the films were prepared by spraying, the same process as the coating of the drug substrates. If the films were prepared by casting, the incorporated additives could sediment or move towards the film surface during the evaporation and film formation periods which would make the structure of the cast films different from that of the films coated on the substrates.

The ability of talc and GMS to reduce film tackiness is shown in Table 1. Talc could not significantly decrease the tackiness of the films when less than 50% (w/w) was used. An obvious change was noticed only when up to 100% (w/w) was used. In contrast, only 5% (w/w) of GMS could lower the peel force significantly. This indicates the more powerful anti-sticking property of GMS over talc. Fig. 1 demonstrates the effects of the surfactants on the tackiness of the Eudragit NE 30D and Eudragit RS 30D films. The results showed that GMS, Span 60 and Span 40 could greatly reduce the tackiness of both films, and the film tackiness was lower when higher concentrations of these surfactants were used. Whereas Span 80 and Span 20 could only reduce the tackiness of the Eudragit NE 30D films, but were ineffective for the Eudragit RS 30D films.

3.2. The components of the films

In the current study, the components of the films at the surface were detected by FTIR-ATR technique. The spectra of the Eudragit NE 30D films containing talc are shown in Fig. 2A. The spectra of the films containing talc were not significantly different from that of the original free film, when less than 50% (w/w) of talc were incorporated. The characteristic peaks of talc at 669 and 1017 cm^{-1} became evident, only when 100% (w/w) of talc was added. Compared with the films containing GMS in Fig. 2B, the spectra of these films are very similar to that of GMS, and the characteristic peaks of GMS at 2849 and 2916 cm^{-1} were clearly observed, even though only 5% (w/w) of GMS was incorporated. This indicates that within the same concentration, GMS has much more influence on the structure of the film surface than talc. These findings are supported by the microscopic images of the thin films, as shown in Fig. 3. For the film containing 5% (w/w) talc, only a few particles of talc can be observed. When 100% (w/w) talc was incorporated, more particles of talc can be seen and the area occupied by the polymer is less. In contrast, the film with 5% (w/w) GMS shows a lot of small GMS particles covering a large area of the film. Considering the fact that GMS is practical insoluble in water due to its low HLB (3.8), in the current experiment, GMS was homogenized in water at temperature above its melting point (55–60 °C). As a result, the material turned to be small liquid droplets and became solid when cooled. Thus, the GMS particles were much smaller than talc particles. Within the same volume, a large number of small particles can occupy a greater area than a small number of large particles. In

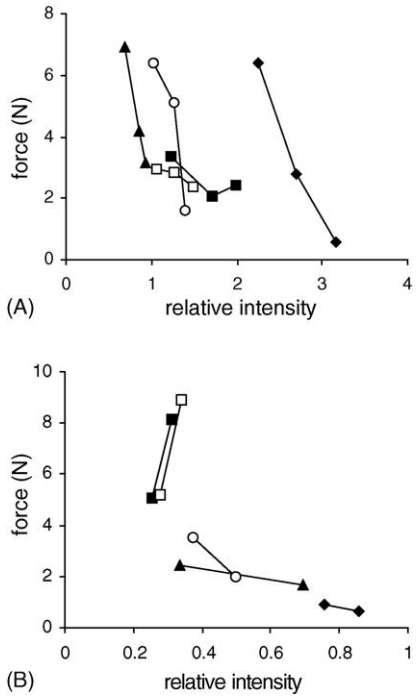

Fig. 4. Relations between relative peak intensity and peel force of Eudragit NE 30D films (A) and Eudragit RS 30D films (B) containing surfactants: (♦) GMS; (■) Span 80; (▲) Span 60; (○) Span 40; (□) Span 20.

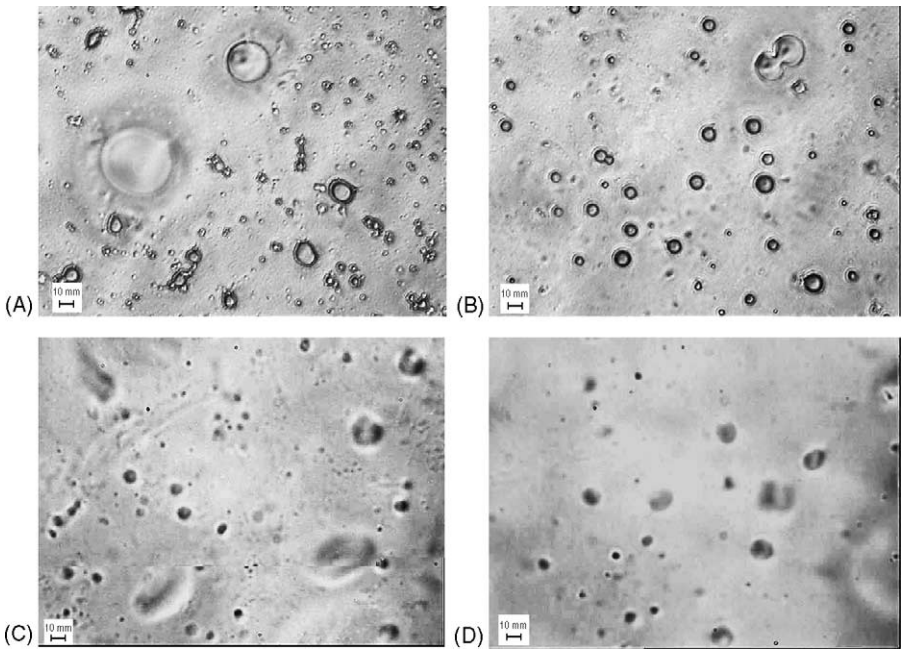

Fig. 5. Microscpic images of Eudragit NE 30D films containing 5% (w/w) Span 80 (A) and 5% (w/w) Span 20 (B), and Eudragit RS 30D films containing: 5% (w/w) Span 80 (C) and 5% (w/w) Span 20 (D).

addition, the specific gravity of GMS is 0.92; whereas, this value of talc is approximate 2.7. Therefore, within the same weight, the volume of GMS is about three times larger than that of talc. This indicates that the efficiency of the materials in reducing the tackiness of the films is related to their capability in reducing the contact area between the polymer. GMS can decrease more polymer contact area than talc, thus the ability in reducing film tackiness of GMS is more powerful.

If the film tackiness is related to the area occupied by the polymer at the surface, when there is a greater concentration of an additive at the surface, the tack should be lower. The additive concentration at the film surface could be determined comparatively from the ATR-IR spectra using the values of the relative peak intensity. These were obtained from the ratio of the characteristic peak intensity of the additives to those of the polymers. The characteristic peaks of the materials used in this experiment were the peaks at 2849 cm^{-1} for GMS, Span 60 and Span 40; 2854 cm^{-1} for Span 80 and Span 20; 2981 cm^{-1} for Eudragit NE 30D; and 2953 cm^{-1} for Eudragit RS 30D. In order to compare the results, the values of the relative peak intensity of the films were plotted against the values of the peel force on the same graph, as shown in Fig. 4. For the films containing GMS, Span 60 and Span 40, it is clear that when the relative intensity is higher, the peel force is lower in both Eudragit NE 30D and Eudragit RS 30D films. The images of the films containing Span 60 or Span 40 (not shown here) also show a lot of additive particles dispersing throughout the film areas, similar to those of the GMS-containing films. This relation, however, cannot be applied for the films with Span 80 or Span 20, especially for the Eudragit RS 30D films, as when the concentration of Span 80 or Span 20 is higher, the film tackiness is also higher. This indicates that the additive concentration at the surface is not the only factor that governs the tackiness of the film.

The images of the Eudragit NE 30D and Eudragit RS 30D films containing 5% (w/w) Span 80 or Span 20 are shown in Fig. 5. Many droplets of the surfactants with various sizes can be obviously seen in the Eudragit NE 30D films containing Span 80 or Span 20. Since both of these surfactants are liquids, it is possible that their solubility in the polymers is limited and some insoluble portions could be exuded towards the surfaces to become a layer of surfactant covering some parts of the film surfaces (Bindschaedler et al., 1987).

This resulted in a notable reduction of the film tackiness, as shown in the peel tests, even though only 5% of them were used. This assumption was proven by wiping the surfaces of the Eudragit NE 30D films containing Span 80 two to three times with cotton wool and comparing the ATR-IR spectra of the film surfaces before and after wiping. The result is shown in Fig. 6A. Before wiping, the characteristic peaks of the surfactants at 2854 cm^{-1} are more dominant than the peaks of the polymer at 2981 cm^{-1}. After wiping, however, the intensity of these peaks is obviously decreased, indicating that some portions of the surfactant were removed. The result is the same for the Eudragit NE 30D film containing Span 20. Nevertheless, the exudation of these surfactants was not evident in the Eudragit RS 30D films. This could be noticed from a slight difference between the spectra of the Eudragit RS 30D films with and without Span 80, as shown in Fig. 6B.

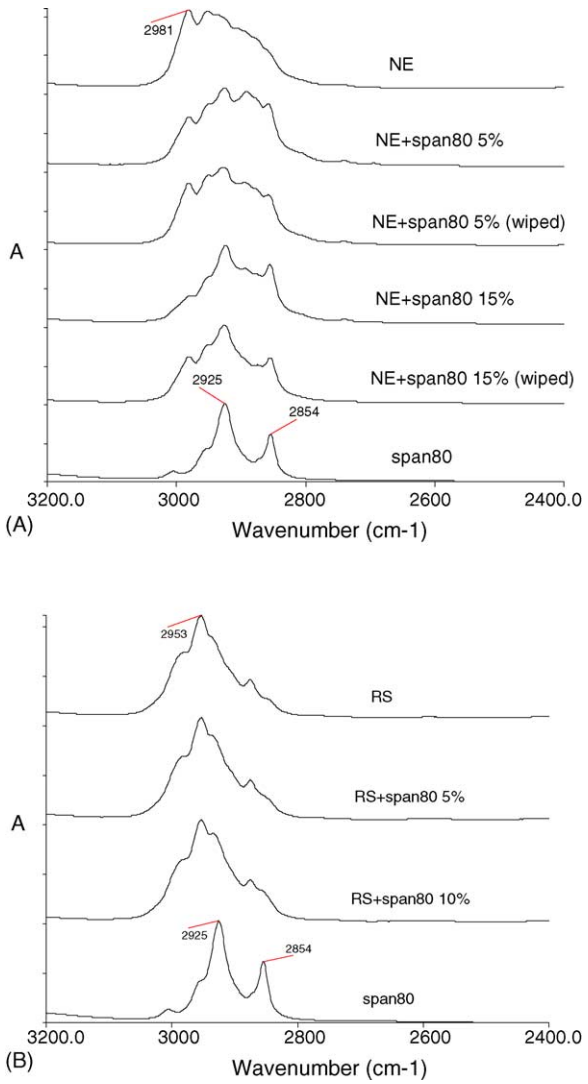

Fig. 6. ATR-IR spectra of Eudragit NE 30D films containing Span 80 (A) and Eudragit RS 30D films containing Span 80 (B).

3.3. Storage modulus of the films

The achievement of intimate contact between the polymer surfaces requires deformation of the materials, which is related to the storage (Young's) modulus (David et al., 2000). In other words, if the additives can soften the polymer films, the tackiness of the films can be higher as the contact between the polymer surfaces is more intimate, resulting in higher bond strength and the inter-diffusion of the polymer molecules across the surfaces may also occur. In the current study, the storage modulus of the films was measured by a dynamic mechanical analyzer at various strain levels, under room temperature and constant frequency. Fig. 7 exhibits the storage modulus of the Eudragit NE 30D films containing 15% (w/w) surfactants, and the Eudragit RS 30D films containing 10% (w/w) surfactants. The results indicate that GMS, Span 60 and Span 40 have slight effects on the modulus of the films, whereas Span 80 and Span 20 can decrease the modulus of the films significantly. From these findings, it could be assumed that Span 80 and Span 20 could increase the film tackiness by decreasing the modulus of the films. However, in the case of the Eudragit NE 30D films, this effect was overcome by the existence of the surfactant layers at the film surfaces, which prevented the direct contact between the polymer at the surfaces.

3.4. Anti-sticking property and the drug release

In order to evaluate the ability of the surfactants as anti-tacking agents in the coating formulations, 5% (based on polymer mass) GMS, Span 60 and Span 40 were incorporated in the Eudragit RS 30D/RL 30D (9:1) coating dispersions (plasticized with 20% (w/w) TEC), compared with the use of 100% (w/w) talc. The sticking of the drug pellets was investigated during the coating and after the curing process. No sticking or agglomeration of the pellets was found within the coating

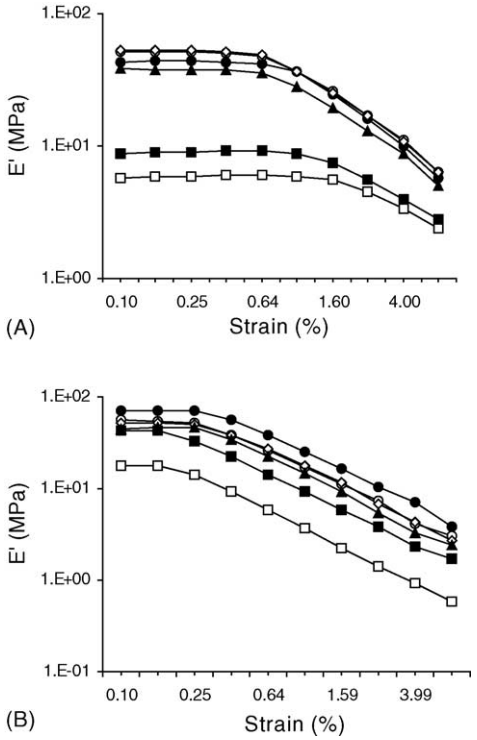

Fig. 7. Storage modulus (E') of Eudragit NE 30D films containing 15% (w/w) surfactants (A) and Eudragit RS 30D films containing 10% (w/w) surfactants (B): (●) no additive; (◯) GMS; (■) Span 80; (◇) Span 60; (▲) Span 40; (□) Span 20.

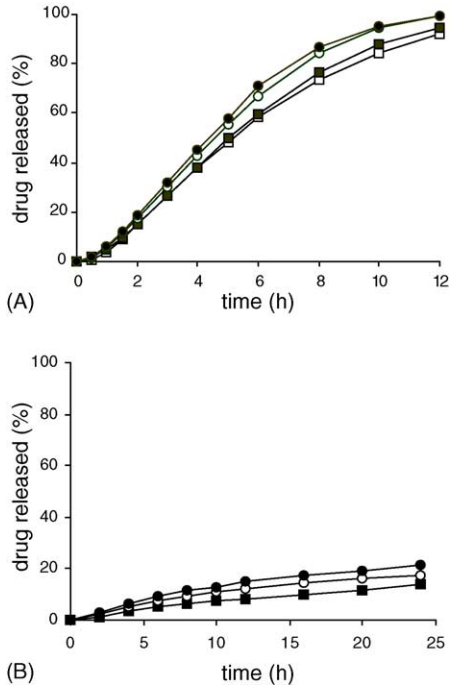

Fig. 8. Dissolution of theophylline from pellets coated with Eudragit RS 30D/RL 30D (9:1, w/w) (A) and Eudragit NE 30D (B) containing additives: (□) 100% (w/w) talc; (■) 5% (w/w) GMS; (◯) 5% (w/w) Span 60; (●) 5% (w/w) Span 40.

level of 10% polymer weight gain when talc, GMS, Span 60 or Span 40 were used in the formulations. However, after curing at 60 °C for 24 h to stabilize the drug release (Amighi and Moes, 1996), the pellet agglomeration was found in the formulations containing GMS, Span 60 or Span 40. To solve this problem, the coated beads were thoroughly blended with 5% talc (based on the pellet weight) prior to curing. This easy step could prevent the agglomeration effectively. The effects of the additives on the drug release were also examined, as shown in Fig. 8A. The formulations containing talc or GMS exhibit similar release profiles, while the formulations containing Span 60 or Span 40 give a slightly faster release rate. This is probably due to the higher hydrophilicity of these two surfactants (HLB of GMS, 3.8; Span 60, 4.7; Span 40, 6.7).

The efficiency of the surfactants to prevent pellet agglomeration was also proven in the Eudragit NE 30D formulations. The films obtained from this polymer are known for their high tackiness. It was found that when the coating formulation without an anti-tacking agent was used, a severe agglomeration of the pellets occurred and the coating process had to stop after only an approximate 3% of polymer weight gain was obtained. When 5% (w/w) GMS, Span 60 or Span 40 were incorporated in the formulations, the sticking problem was eliminated. After curing at 40 °C for 24 h to stabilize the drug release rate (Li et al., 1989), only a slight agglomeration was observed, and the coated beads could be separated easily without film damage. Fig. 8B exhibits the percent theophylline released from the cured–coated pellets. The formulations containing Span 60 or Span 40 give a slightly higher release rate than that containing GMS. This finding is similar to that found from the Eudragit RS 30D/RL 30D formulations. The dissolution stability was also studied, as shown in Fig. 9. The storage at 40 °C for 6 months, or at room temperature for 10 months had no influence on the drug release profiles.

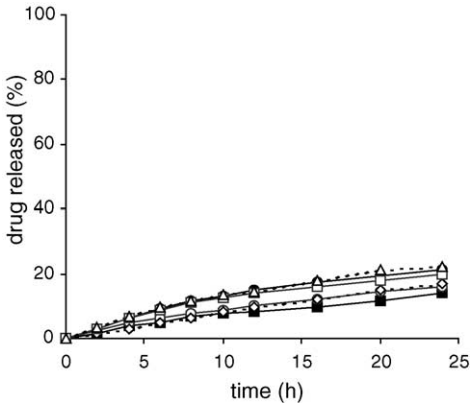

Fig. 9. Dissolution stability of pellets coated with Eudragit NE 30D containing 5% GMS ((■) initial; (◯) room temperature, 10 months; (◊) 40 °C, 6 months) or Span 40 ((●) initial; (□) room temperature, 10 months; (Δ) 40 °C, 6 months).

Flexibility is also an important characteristic of the film coating on the drug substrates. A flexible film is more resistant to mechanical stress as well as being able to maintain the integrity of the coated substrates during passage down the gastrointestinal tract. A high level of talc in the coating formulation can greatly affect the film flexibility (Maejima and McGinity, 2001). The effects of GMS, Span 60 and Span 40 on film flexibility were also examined in this study. The results indicated that these surfactants had no significant effect on the film flexibility, especially when only 5% (w/w) were used.

4. Conclusion

The results from this work indicated that both Span 60 and Span 40 could be used as effective anti-tacking agents in both Eudragit NE 30D and Eudragit RS 30D/RL 30D coating formulations, in addition to talc and GMS. The ability to reduce film tackiness of these surfactants is related to the distribution of small-size particles throughout the film mass, resulting in a notable decrease of the polymer content at the film surface. The use of only 5% (w/w) GMS, Span 60 or Span 40 in the coating formulations was enough to prevent pellet agglomeration during coating without adverse effects on film flexibility. However, when the curing at an elevated temperature for a long time is needed, approximately 5% (w/w) talc should be blended with the coated pellets prior to curing to prevent the pellet sticking. The pellets coated with Eudragit RS 30D/RL 30D (9:1, w/w) did not exhibit any difference in the drug release profile when either 100% (w/w) talc or 5% (w/w) GMS was used in the coating formulation. While the formulations containing either Span 60 or Span 40 gave a slightly faster release rate. The drug dissolution was also proved to be stable, at least for 10 months at room temperature or 6 months at 40 °C.

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