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The Influence of Drug-Excipient and Drug-Polymer Interactions on Butt Adhesive Strength of Ranitidine Hydrochloride Film-Coated Tablets

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ABSTRACT The influence of fillers and polymeric films on adhesive strength of hydroxypropyl methylcellulose (HPMC) and Eudragit E100® films coated on ranitidine HCl tablets containing either spray-dried rice starch (SDRS) or lactose monohydrate as fillers after storage at 45°C/75% RH for four weeks was investigated by the use of butt adhesion technique. The adhesive strength of film-coated tablets of fillers without drug was found to slightly decrease after storage. In contrast, the adhesive strength of drug-containing film-coated tablets significantly reduced, the degree of which was higher for Eudragit E100® than HPMC. Physicochemical characterization by employing differential scanning calorimetry (DSC) and diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) revealed that the drug was obviously incompatible with lactose and possibly mild interaction with Eudragit E100® was suggested. The results indicated that the adhesive strength of film-coated tablets would be affected not only by the drug-excipient interaction, but also by the drug-polymeric film interaction.

KEYWORDS Film-coated tablets, drug-excipient interaction, drug-polymer interaction, adhesive strength, ranitidine HCl, hydroxypropyl methylcellulose, Eudragit E100®

INTRODUCTION

Adhesive strength or adhesiveness may be defined as the force required to remove the film coating vertically from a unit area of tablet surface. The adhesive strength of polymeric film to tablet surface has been receiving considerable attention as a useful parameter in evaluating film coating formulations and processes, properties of core tablets, and end-use properties of film-coated tablets (Missaghi & Fassihi, 2004; Felton & McGinity, 1997; Okhamafe & York, 1985). Proper adhesion of a polymeric film coating to a tablet is an important requirement in film coating in practice because complete loss of adhesion will not only adversely affect the appearance of the film-coated tablets, but also reduce the ability of the film to retain its integrity in protecting

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the dosage form and drug release characteristics. In addition, substantial quantity of moisture could accumulate at the interfacial void space between the film coating and the tablet surface, a situation that is likely to accelerate the degradation of moisture sensitive drugs.

For the past decade the studies on drug-excipient as well as drug-polymer interactions have brought about increasing cautions and awareness in film coating applications. Physicochemical characterizations of some drug-polymer interactions have been carried out for ibuprofen-methylcellulose and ibuprofen-hydroxypropylcellulose (Vueba et al., 2005), triptolide-poly (D,L-lactic acid) (Liu et al., 2005), theophylline-Eudragit L100® (Sarisuta et al., 2000), ibuprofen-Aquacoat CD® (Schmid et al., 2000), erythromycin-Eudragit L100®, and erythromycin-shellac (Sarisuta et al., 1999), carteolol-Eudragit L30D® (Holgado et al., 1995). Such interactions could be any type of chemical interactions caused by redox reaction, acid–base reaction, hydrolysis, or the combination of these and the physical interactions caused by change in solubility, phase transition, polymorphic transition, adsorption, etc. Since adhesion between the polymeric film and tablet surface is primarily due to the intermolecular hydrogen bonding force (Rowe, 1977), the drug-excipient and/or drug-polymer interactions may possibly lead to the deterioration of adhesive properties of the film-coated tablets.

Since ranitidine HCl is a moisture sensitive drug and its generic products are commercially available in film-coated tablets and often exhibit stability problems, it would be a good model drug to be studied (Hohnjec et al., 1986; Uzunarslan & Akbuga, 1991). In this study an instrumented tablet-film adhesion tester was designed to measure the butt adhesive strength of ranitidine HCl film-coated tablets and their changes upon storage were correlated to any possible drug-excipient and/or drug-polymer interactions.

MATERIALS

Ranitidine HCl (batch number 201899) was obtained from Ranbaxy, India. Spray-dried rice starch (SDRS) (Era-Tab® batch number T990810) was obtained from Erawan Pharmaceutical Research and Laboratory, Nakorn Pathom, Thailand. Lactose monohydrate (Tablettose 70® batch number 0102537) was purchased from Meggle, Wasserburg, Germany. Hydroxypropyl methylcellulose 15 cps (HPMC) (Methocel E15LV® batch number OD13012N31) and polymethacrylate (Eudragit E100® batch number 8390101009) were the gift from Dow Chemicals, Midland, MO, USA, and Rohm Pharma, Darmstadt, Germany, respectively.

METHODS

Preparation of Film-Coated Tablets

The 302-mg tablets containing either filler alone or filler mixed with 150 mg ranitidine HCl with 5–6 kg hardness were prepared by direct compression method using SDRS or lactose as filler and 0.7% magnesium stearate as lubricant. Batches of 1 kg core tablets were subsequently coated with 900 mL of film coating solution containing 5% of either HPMC or Eudragit E100®, 1.5% PEG 4000, 3.5% talcum, and 3% titanium dioxide in 1:1 methylene chloride–ethanol using a 15″ perforated pan coater (Thai Coater®, Pharmaceutical and Medical Supply, Bangkok, Thailand). The inlet air temperature was controlled at 50°C, while the outlet air temperature was 30–40°C. The spray rate of the coating solution was 15 mL/min and the atomizing air pressure was 1.0 kg/cm^2. The rotating speed of the coating pan was set at 10 rpm. The total coating time was 1 h.

Determination of Physical Properties of Film-Coated Tablets

Other physical properties such as weight, thickness, hardness, and disintegration time of core and film-coated tablets were evaluated. The weights of 20 tablets were determined individually by using electronic precision balance (Model AA200DS, Denver Instrument, Arvada, CO, USA). Thicknesses and hardnesses of 10 tablets were determined by using & hardness testing accessories (Model PTB311, Pharmatest, Hamburg, Germany). The disintegration times (six tablets) in distilled water at 37 ± 2°C were determined using the USP XXII disintegration test apparatus.

Determination of Butt Adhesive Strength of Film-Coated Tablets

A simple tablet-film adhesion tester as shown in Fig. 1 was developed in-house by utilizing the air

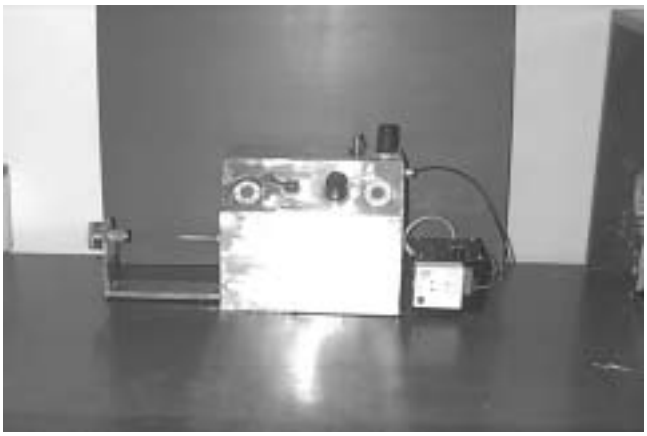

FIGURE 1 **Photograph of the Tablet-film Adhesion Tester.**

pressure to drive the pneumatic piston cylinder in order to pull the film coating out in the normal direction to the surface of coated tablet (Tourtip et al., 1999). The adhesive strength was recorded by analog mini-logger (ML-20, Wisco, Hialeah, FL, USA) via the pressure transmitter (PA-3024, Elector, Essen, Germany), and the recorded data were subsequently retrieved and analyzed in a personal computer. The regulating air pressure used in the system is 6 bar.

In preparation for testing, the film coating on the edge of the tablet was removed with a sharp blade. This would ensure that the force measured was that required for removing the film from the tablet surface and not that required for tearing the coating at the tablet edge. The tablet was then placed into the mounting which was the stainless steel screw cap with open window for exposing the film surface to be measured. The two-sided adhesive foam tape was patched on the surface of the plunger at the end of pneumatic piston cylinder which was afterward driven inward by regulating the air pressure until it was pressed firmly onto the film coating with the force of around 2 kg. The tablet was kept under pressing for 2 min to allow intimate bonding between the tape and the film coating. The plunger was then driven outward until the film coating separated from the tablet and the breaking force was measured via the pressure transmitter and recorded in the data logger. The recorded data were then retrieved and analyzed afterward by a program on a personal computer. A total of 15 tablets for each formulation was employed in the determination.

Physicochemical Characterization of Drug-Polymer and Drug-Excipient Interactions

Preparation of Drug-Polymer and Drug-Excipient Mixtures

Both types of mixtures were prepared by different means according to their relevant methods actually employed in preparation of film-coated tablets in this study, and also in routine production. The film coating polymers are usually applied to the surface of tablets in the form of solutions in practice and so they were in this study. It has previously been suggested that dissolution of a small amount of drug (contained in a solid dosage form) in a film coating solution during a coating operation, and/or migration of the drug into the applied coating over a period of time following the coating application could occur in practice (Okhamafe & York, 1989). In order to simulate such situation the 1:1 drug-polymer mixtures were therefore prepared by incorporating solutions of 5% HPMC or Eudragit E100® in 1:1 methylene chloride–ethanol into the drug powder, and then evaporating the solvent out until dryness in a vacuum oven at room temperature. Likewise, the 1:1 drug-excipient mixtures were prepared by physically mixing them together, the same ratio and the way by which they were actually prepared in direct compression tablets.

Differential Scanning Calorimetry

Samples of 2–3 mg were placed into standard aluminum pans with encapsulated lids and scanned using DSC (DSC7, Perkin Elmer, Norwalk, CT, USA) with heating rate of 10°C /min for a temperature range of 40–300°C under nitrogen gas purge at a flow rate of 25 mL/min. The measurements were performed in triplicates.

Diffuse Reflectance Infrared Fourier Transform Spectroscopy

The diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) spectra measurement was carried out using a Fourier transform infrared spectrophotometer (Magna-IR 550, Nicolet, GMI, Ramsey, MN, USA) equipped with a DTGS detector

and diffuse reflectance cell (Collector cell, Spectra Tech, GMI, Ramsey, MN, USA). Samples were triturated with the previously milled and sieved (<125 μm) KBr powder at 5% concentration which were then filled and spread uniformly into the 10-mm diffuse reflectance cell. Spectra were scanned from 4000 to 400 cm^{-1} with average scanning 32 times, 4.0 cm^{-1} resolution, and a detector gain of 1.0. The measurements were performed in triplicates.

RESULTS AND DISCUSSION

Physical Properties of Film-Coated Tablets

In order for comparison purpose, the percent by weight of film coating on tablets were controlled to be within the same order of magnitude as much as possible which were found to be within the range of 5.40–7.87% as shown in Table 1. The average thicknesses of

TABLE 1 Physical Properties of Various Formulations of Core and Film-coated Tablets

Film-coated tablet formulation	Weight[a] (mg)	Thickness[b] (mm)	Hardness[b] (kg)	Disintegration time[c] (min)
HPMC film				
SDRS				
Core tablets	305.4 ± 2.4	4.00 ± 0.03	5.0 ± 0.7	1.31 ± 0.03
Film-coated tablets	325.0 ± 3.9	4.07 ± 0.10	11.1 ± 1.1	2.71 ± 0.10
% or value increased	6.42%	0.07 mm	6.1 kg	1.40 min
Ranitidine HCl/SDRS				
Core tablets	307.6 ± 4.4	3.76 ± 0.04	5.1 ± 0.5	3.11 ± 0.11
Film-coated tablets	328.6 ± 4.8	3.84 ± 0.02	11.3 ± 1.3	11.44 ± 0.98
% or value increased	6.83%	0.08 mm	6.2 kg	8.33 min
Lactose				
Core tablets	308.4 ± 3.2	3.13 ± 0.02	5.7 ± 0.5	5.66 ± 0.05
Film-coated tablets	327.8 ± 3.9	3.32 ± 0.05	10.3 ± 0.8	13.50 ± 0.81
% or value increased	6.29%	0.19 mm	4.6 kg	7.84 min
Ranitidine HCl/lactose				
Core tablets	303.7 ± 3.1	3.48 ± 0.04	5.9 ± 0.5	3.28 ± 0.07
Film-coated tablet	327.6 ± 3.5	3.71 ± 0.07	10.9 ± 1.0	7.00 ± 0.32
% or value increased	7.87%	0.23 mm	5.0 kg	3.72 min
Eudragit E100® film				
SDRS				
Core tablets	305.4 ± 2.4	4.00 ± 0.03	5.0 ± 0.7	1.31 ± 0.03
Film-coated tablet	321.9 ± 5.5	4.03 ± 0.02	8.5 ± 0.3	3.66 ± 0.19
% or value increased	5.40%	0.03 mm	3.5 kg	2.36 min
Ranitidine HCl/SDRS				
Core tablets	307.6 ± 4.4	3.76 ± 0.04	5.1 ± 0.5	3.11 ± 0.11
Film-coated tablet	329.9 ± 6.1	3.86 ± 0.03	8.0 ± 0.7	35.96 ± 1.54
% or value increased	7.25%	0.10 mm	2.9 kg	32.85 min
Lactose				
Core tablets	308.4 ± 3.2	3.13 ± 0.02	5.7 ± 0.5	5.66 ± 0.05
Film-coated tablet	318.6 ± 3.7	3.19 ± 0.02	7.5 ± 0.7	48.61 ± 2.15
% or value increased	5.84%	0.06 mm	1.8 kg	42.95 min
Ranitidine HCl/lactose				
Core tablets	303.7 ± 3.1	3.48 ± 0.04	5.9 ± 0.5	3.28 ± 0.07
Film-coated tablet	323.2 ± 5.6	3.57 ± 0.02	7.4 ± 1.0	39.03 ± 1.44
% or value increased	6.42%	0.09 mm	1.5 kg	35.75 min

[a]Mean ± SD of 20 tablets.
[b]Mean ± SD of 10 tablets.
[c]Mean ± SD of 6 tablets.

various formulations of film coating on tablets were found to vary within the range of 0.03–0.23 mm depending on their differences in film density. The hardnesses of all formulations of film-coated tablets appreciably increased which was higher for tablets coated with HPMC film (4.6–6.2 kg) as compared to those coated with Eudragit E100® film (1.5–3.5 kg). The disintegration times of the film-coated tablets increased within the range of 1.25–42.95 min from those of core tablets.

Physicochemical Characterization of Drug-Excipient and Drug-Polymer Interactions

The differential scanning calorimetry (DSC) thermogram of pure drug showed a sharp endothermic melting peak at 151°C, whereas that of pure SDRS exhibited no sharp peak. There was no alteration in thermogram of the 1:1 drug-SDRS mixture compared to those of the pure compounds as shown in Fig. 2. The diffuse reflectance infrared Fourier transform (DRIFTS) spectrum of pure drug as illustrated in Fig. 3 showed the strong peak at 1046 cm^{-1} indicating the crystal form II of ranitidine HCl used in this studied (Hohnjec et al., 1986; Carstensen & Franchini, 1996). The crystal form I, which is less stable, showed no peak at this wave number. There was neither new band nor shifting in peak of spectrum of the mixture which suggested no direct molecular interaction between ranitidine HCl and SDRS.

The differential scanning calorimetry (DSC) thermograms of pure drug and lactose are compared with that of their 1:1 binary mixture in Fig. 4. Lactose monohydrate

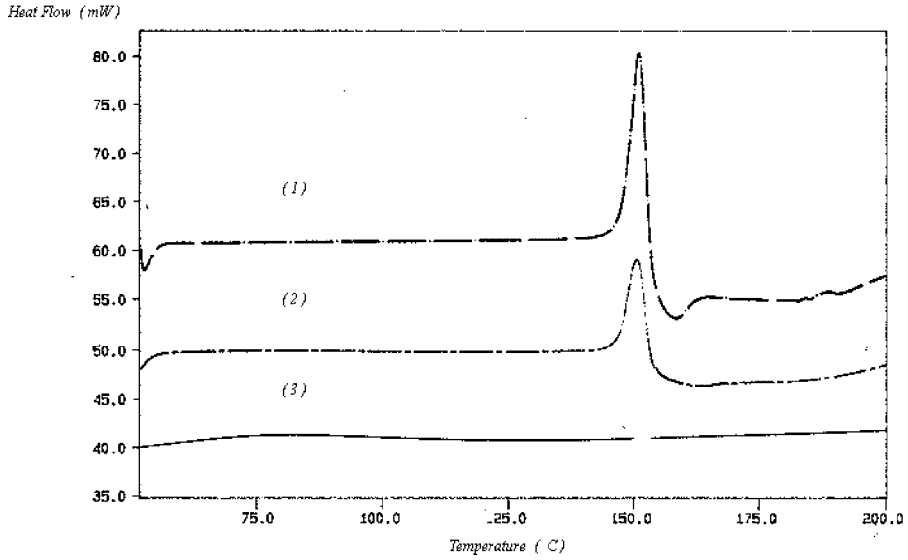

FIGURE 2 DSC Thermograms of (1) Ranitidine HCl, (2) 1:1 Ranitidine HCl-SDRS Mixture, and (3) SDRS.

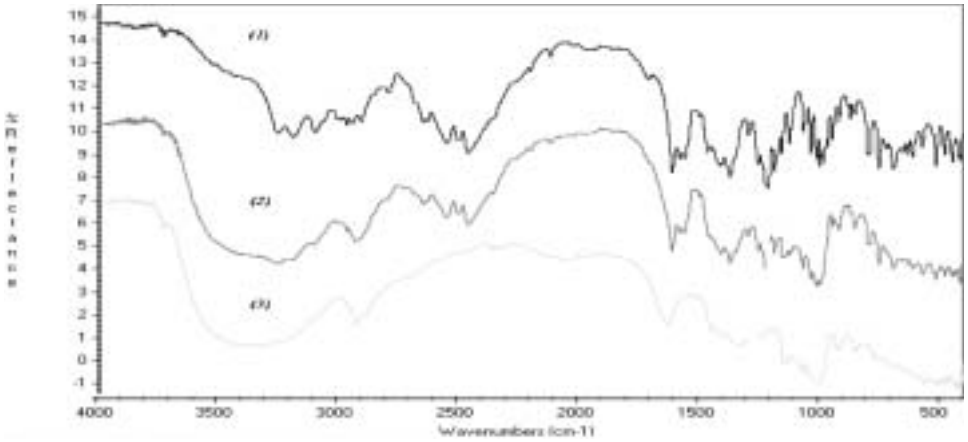

FIGURE 3 DRIFTS Spectra of (1) Ranitidine HCl, (2) 1:1 Ranitidine HCl-SDRS Mixture, and (3) SDRS.

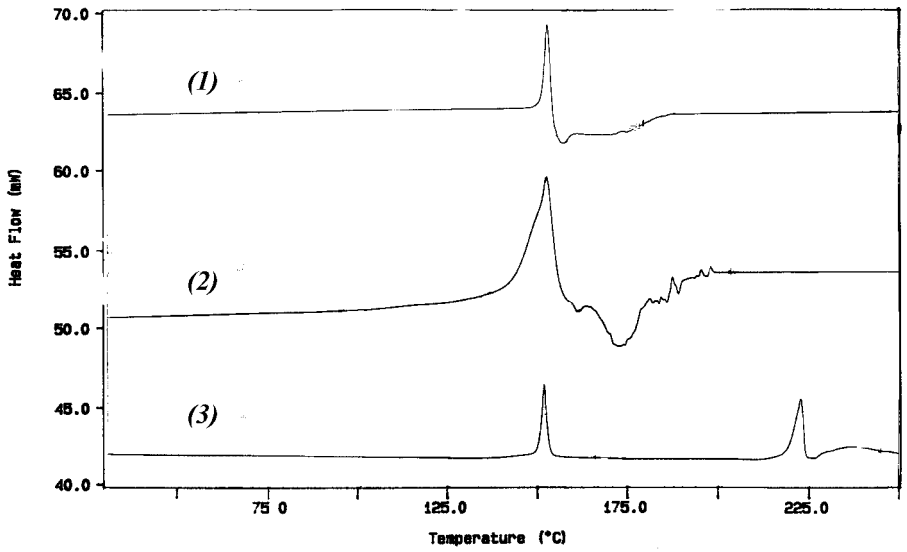

FIGURE 4 DSC Thermograms of (1) Ranitidine HCl, (2) 1:1 Ranitidine HCl-lactose Mixture, and (3) Lactose.

showed a dehydration peak at 150°C followed by endothermic melting peak at 222°C. However, the thermogram of the mixture showed a broader peak at 150°C accompanied with the disappearance of melting peak of lactose at 222°C, indicating possible ranitidine HCl-lactose interaction. The most probable mechanism may be the reaction between amine group of ranitidine HCl and aldehyde group of lactose. Such behavior of disappearance of the DSC peak of lactose at 222°C in the presence of drug was also found in the case of aminophylline–lactose mixture, the interaction mechanism of which was proposed to be through a Schiff base intermediate (Hartauer & Guillory, 1991). However, the DRIFTS spectrum of their mixture showed neither new band nor shifting in peak as illustrated in Fig. 5.

The differential scanning calorimetry (DSC) as well as DRIFTS results of the 1:1 drug-HPMC mixture as illustrated in Figs. 6 and 7, respectively, showed neither alteration nor shifting in their peaks and spectra, clearly indicating no interaction between ranitidine HCl and HPMC.

Although there was no alteration in DSC thermogram of the mixture compared to those of pure compounds as shown in Fig. 8, careful examination of the DRIFTS spectrum of 1:1 drug-Eudragit E100® mixture

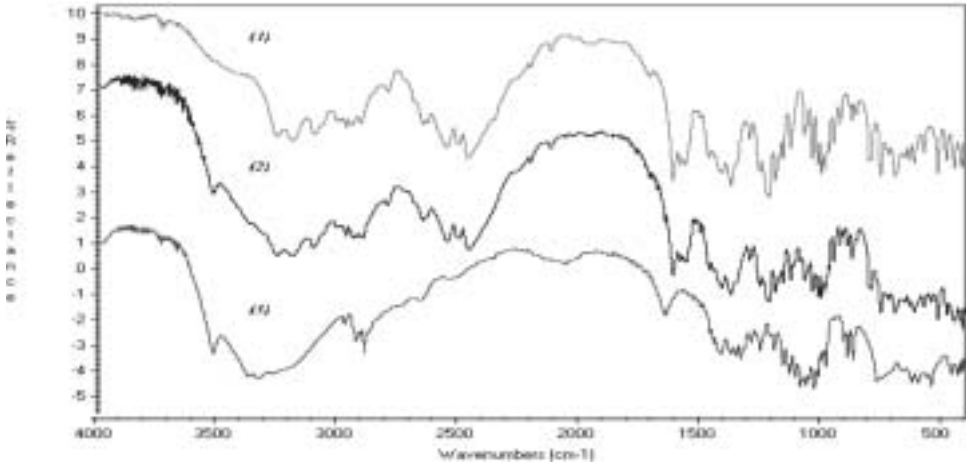

FIGURE 5 DRIFTS Spectra of (1) Ranitidine HCl, (2) 1:1 Ranitidine HCl-lactose Mixture, and (3) Lactose.

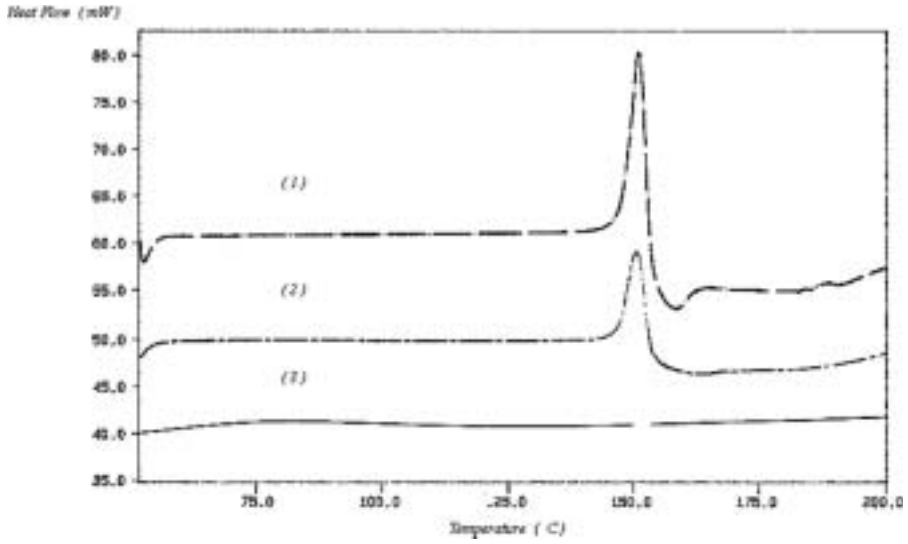

FIGURE 6 **DSC Thermograms of (1) Ranitidine HCl, (2) 1:1 Ranitidine HCl-HPMC Mixture, and (3) HPMC.**

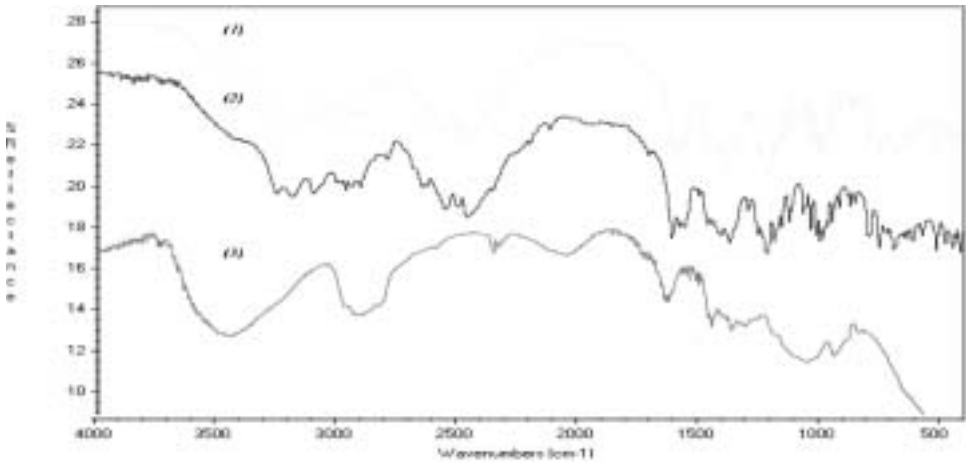

FIGURE 7 **DRIFTS Spectra of (1) Ranitidine HCl, (2) 1:1 Ranitidine HCl-HPMC Mixture, and (3) HPMC.**

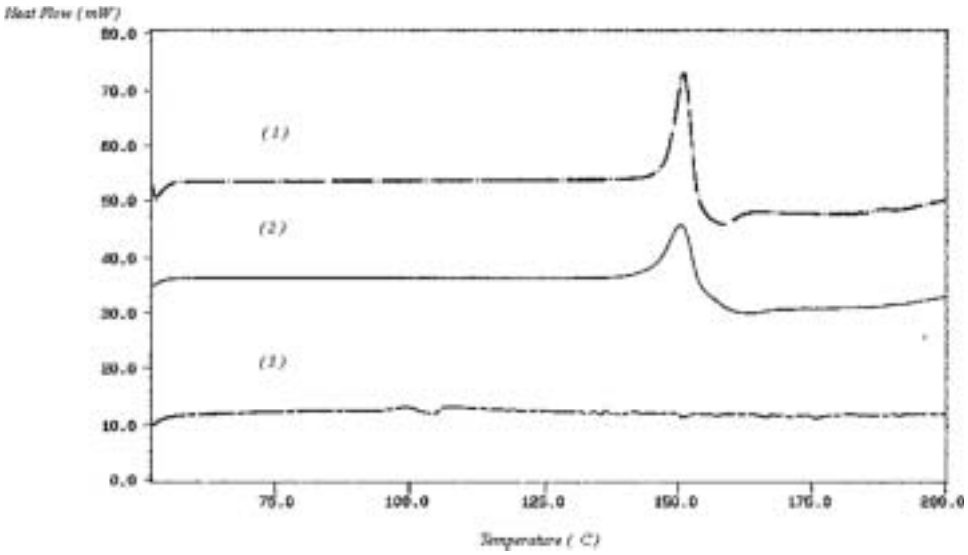

FIGURE 8 **DSC Thermograms of (1) Ranitidine HCl, (2) 1:1 Ranitidine HCl-Eudragit E100® Mixture, and (3) Eudragit E100®.**

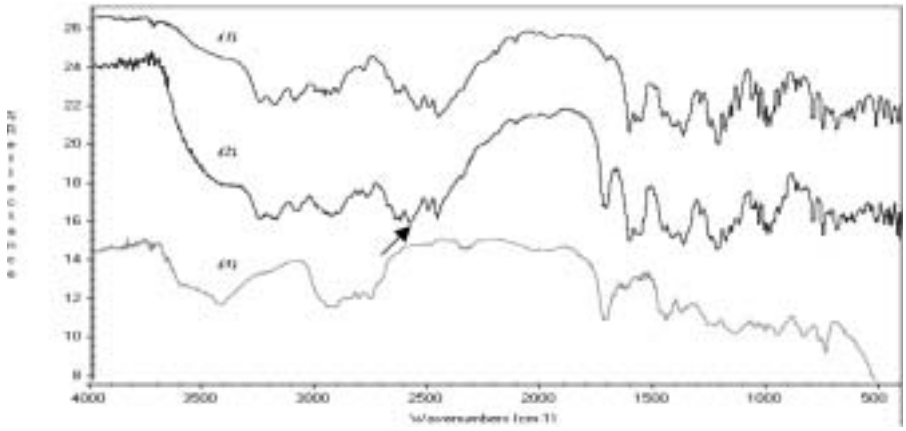

FIGURE 9 DRIFTS Spectra of (1) Ranitidine HCl, (2) 1:1 Ranitidine HCl-Eudragit E100® Mixture, and (3) Eudragit E100®.

revealed a slight shift of the band of protonated tertiary amine group R_3-NH^+ of ranitidine HCl at 2560 cm^{-1} to a higher wave number as illustrated in Fig. 9. This suggested mild interaction such as hydrogen bonding between protonated tertiary amine group of the drug and a certain group of the polymer (Willard et al., 1974; Smith, 2000).

Adhesive Strength of Film-Coated Tablets

It is now generally accepted that adhesion between the polymeric film and the surface of a tablet is due to the interaction of the intermolecular bonding forces. These forces consist primarily of hydrogen bonds, and, to a lesser extent, the weaker dipole–dipole and dipole–induced dipole interaction, involving such functional groups as –OH, –COOH, –C=O and $-COCH_3$ (Rowe, 1977). Therefore, the adhesion of HPMC films, which contain both primary and secondary hydroxyl groups in the molecule, was found to be considerably strong on the surfaces of both SDRS and lactose tablets as shown in Table 2. This is in accord with those results previously reported (Lethola et al., 1995). Furthermore, comparison between the adhesive strength of HPMC film and that of Eudragit E100® film coated on various types of ranitidine HCl core tablets as shown in Table 2 indicated that the latter generally adhered to the tablet surface stronger than the former. As expected, the methacrylic acid and its ester functional groups could readily form stronger hydrogen bonds with the surface of SDRS and lactose tablets.

Storage at 45°C/75% RH for up to 1 month was found to have negligible effect on weights of film-coated tablets for all formulations. Generally, all formulations of film-coated filler tablets without drug showed a slight decrease in adhesive strength under storage conditions studied, whereas those containing drug exhibited a significant reduction in adhesive strength except Eudragit E100® film-coated SDRS tablets (Table 2). Such results could not be attributed to the volumetric expansion of the tablets as a result of moisture uptake and stress relaxation during storage since there was no correlation between changes of tablet weight and adhesive strength. On the other hand, there seemed to be a correlation between types of excipient and/or polymer used and their changes in adhesive strength of film-coated tablets. Comparison between the ranitidine HCl/SDRS tablets coated with HPMC film and those coated with Eudragit E100® revealed that the former showed less percentage of reduction in their adhesive strengths. Such behavior may be attributed to the mild interaction between ranitidine HCl and Eudragit E100® as mentioned above which would probably affect the adhesion between the film and the tablet surface.

The adhesive strength of film-coated tablets in this study was found to be affected not only by interactions between the drug and the polymeric film coat, but also the drug and the filler used in the core tablets. This could be demonstrated by the decrease in adhesive strength of the HPMC film-coated ranitidine HCl/lactose tablets at much higher percentage than that of HPMC film-coated ranitidine HCl/SDRS tablets. The drug was found to undergo interaction with lactose but not SDRS as discussed above. The situation was even

TABLE 2 **Adhesive Strength of Film-coated Tablets After Storage at 45°C/75% RH for one Month**

Film-coated tablet formulation	Adhesive strength[a] (kg/cm^2)		
	Initial	After	% Difference
HPMC film			
SDRS	1.47 ± 0.33	1.23 ± 0.15	−16.0
Ranitidine HCl/ SDRS	1.36 ± 0.30	1.02 ± 0.14	−25.0[b]
Lactose	1.87 ± 0.34	1.75 ± 0.16	−6.8
Ranitidine HCl/lactose	1.96 ± 0.31	1.19 ± 0.09	−40.0[b]
Eudragit E100® film			
SDRS	2.66 ± 0.42	1.94 ± 0.33	−25.9[b]
Ranitidine HCl/SDRS	2.04 ± 0.29	1.05 ± 0.10	−48.6[b]
Lactose	2.07 ± 0.32	1.92 ± 0.21	−7.3
Ranitidine HCl/lactose	2.80 ± 0.28	1.23 ± 0.10	−55.9[b]

[a]Mean ± SD of 15 film-coated tablets.
[b]Significant difference ($P < 0.05$, *t*-test).

worse in the case of Eudragit E100® film-coated ranitidine HCl tablets since the drug could interact simultaneously with both the polymer and the filler.

CONCLUSION

The butt adhesive strength of ranitidine HCl film-coated tablets was demonstrated to significantly decline upon storage while that of film-coated tablets without drug slightly reduced. Ranitidine HCl was found to undergo interactions with lactose and Eudragit E100®, but not with SDRS and HPMC. The drug-polymer and/or drug–excipient interactions seemed to be responsible for the deterioration of tablet-film adhesion.

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