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Stabilization and sustained-release effect of Misoprostol with Methacrylate copolymer

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Abstract

The use of ammonio methacrylate copolymer (Eudrgit RS, RL) to form a sustained-release solid dispersion of Misoprostol can improve and enhance two important physical and chemical properties of Misoprostol. First, the solid dispersion matrix formed by the copolymer can protect Misoprostol from being degraded by water so that its stability is improved. Second, Misoprostol can be slowly released by diffusion from the copolymer matrix. Accelerated stability studies of Misoprostol–Eudragit solid dispersion after storing at various temperatures for different time periods were carried out. According to high performance liquid chromatography (HPLC) analyses, the stability of Misoprostol in a series of Eudragit appeared significantly improved at different ratios. The Misoprostol–Eudragit dispersion can be used in a powder form, filled in capsules, or compressed into tablets. The dissolution profiles of Misoprostol–Eudragit solid dispersion and its tablets in water, pH 1.2, 4.5 and 6.8, dissolution media show that this stable solid dispersion is a sustained-release type.

Keywords: Misoprostol; Eudragit; Stability; Sustained-release effect; Dissolution profile

1. Introduction

Misoprostol is a synthetic prostaglandin E1 analog, which has proven to be an effective anti-secretary agent for oral use (Collins et al., 1985). The major indications of Misoprostol are in the prevention and treatment of NSAID-induced gastric and duodenal ulcers (Herting and Clay, 1985; Agrawal et al., 1986; Majure, 1987; Birnie et al., 1988; Dajani et al., 1992; Gladziwa and Klotz, 1994). Misoprostol is difficult to formulate due to its instability and the viscous liquid form. Just like all prostaglandin E type drugs, Misoprostol is chemically unstable at room temperature. Under acidic or alkaline conditions with the presence of a very small amount of water, Misoprostol can undergo a dehydration process in which the 11-hydroxy group is eliminated to form an A-type prostagladin. In turn, the A-type prostaglandin can further isomerize to the corresponding

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prostaglandin B-form (Collins et al., 1985). Sanvordeker discovered that a solid dispersion of Misoprostol in hydroxypropyl methylcellulose (HPMC) is much more stable than the neat chemical of Misoprostol alone (Sanvordeker, 1981). Since dehydration of Misoprostol is the first step in the degradation of this compound and it is catalyzed by the presence of a very small amount of water, it is suggested that the improved stability of Misoprostol in HPMC is affected by the polymer–water interaction. It is also proposed that in the low-relative humidity environment, the stability of this compound is greatest due to a decreased mobility of water and Misoprostol in the glassy Misoprostol/HPMC solid dispersion (Kararli and Catalano, 1990). Karali et al. reported the following results from the mechanism study of Misoprostol stabilization in HPMC (Kararli et al., 1991). DSC and DMA measurements indicated that Misoprostol oil was molecularly dispersed in the glassy HPMC matrix and TIR studies indicated no evidence of complexation between Misoprostol and HPMC.

Misoprostol is used for the prevention of gastric and duodenal ulcer caused by non-steroidal anti-inflammatory drugs. The major undesired side effects after oral administration are uterus contractility and diarrhea. It is contraindicated for use in pregnant women. A strategy to reduce these side effects while maintaining the therapeutic efficacy of this drug is controlled or slow delivery of Misoprostol to the gastrointestinal tract. Tremont et al. reported a polybutadiene–base polymer with an acid labile diisopropyl silyl ether linker to the active isomer of Misoprostol (Tremont et al., 1993). This design of slow-release Misoprostol in the stomach is a covalent silicon ether bond to the C-11 hydroxyl group of Misoprostol. The silyl linker releases intact Misoprostol from the polymer matrix under acidic conditions in the stomach. This silyl linker, a design of a slow-release of Misoprostol from a polybutadiene–base polymer, was reported to prevent the GI mucosal damage caused by NSAID while producing fewer diarrhea side effects in animal models (Perkins et al., 1994). Gullikson et al. also reported that the slow release of this silyl linker could result in lower plasma levels of Misoprostol free acid and reduce uterotonic activity (Gullikson et al., 1995).

In attempting to reduce the side effect of diarrhea and uterine contractility, the goal to develop a slow or sustained release dosage form of Misoprostol for oral use becomes an important subject. Oth et al. reported a bilayer floating dosage unit, which was designed to achieve sustained delivery of Misoprostol at the gastric mucosa (Oth et al., 1992). This design is a capsule design, consisting of a floating layer maintaining the dosage unit buoyant upon the gastric content, and a drug layer formulated to act as a sustained-delivery system.

G.D. Searle manufactured a drug called Cytotec by using the pharmaceutical formulation technique to produce a stable Misoprostol/HPMC solid dispersion. Cytotec was successfully developed and made its way into the market in the past decade. Currently, this commercially available dosage form for Misoprostol is an immediate-release type of tablet for oral use. To date, there is no slow-release or sustained-release dosage form of Misoprostol available in the market.

The major objective of this paper is to disclose our invention of preparing a stable, sustained-release solid dispersion of Misoprostol with ammonio methacrylate copolymer (Eudragit RS, RL) (Chen et al., 1997; Chen et al., 1999). The use of an ammonio methacrylate copolymer to form a sustained-release solid dispersion of Misoprostol can improve and enhance two important physical and chemical properties of Misoprostol. First, the solid dispersion matrix formed by the copolymer can protect Misoprostol from being degraded by water so that the stability of Misoprostol is improved. Second, Misoprostol can be slowly released by diffusion from the copolymer matrix. The primary advantage of a sustained-release dosage form should also be addressed here; the dosing frequency for the oral administration of Misoprostol can be greatly reduced to a once-daily form.

2. Materials and methods

2.1. Materials

Misoprostol was supplied by Everlight Chemical Industrial Corporation (Taoyan, Taiwan). Cytotec was purchased from G.D. Searle, Eudragit series were purchased from Rohm Pharma, Avicel PH 102 was purchased from Asahi Chemical, and Sodium starch glycolate was purchased as Primojel from Avebe. Hydrogenated castor oil was purchased from Henkel Corporation. Mannitol, Sodium dihydrogen phosphate monohydrate and absolute alcohol were purchased from Merck Taiwan Ltd. Acetonitrile HPLC grade was purchased from BDH Laboratory. All exicipients were USP Grade and used without further purification.

2.2. Preparation of solid dispersion

The preparation of solid dispersion comprises the following steps:

1. Dissolve Misoprostol in a selected solvent to form a solution.
2. Add an appropriate amount of Eudragit to Misoprostol solution in accordance with the exact ratio (Table 1) to form a mixture and stir for 2 h under cover.
3. Introduce nitrogen to blow-dry the supernatant solvent.
4. Strip solvent in vacuo at 40°C for 2 h.
5. Ground and sieve the solid dispersion through 100 mesh to obtain a resultant product. The final product was stored in an air tight polyethylene container at a temperature ranging from -5 to 20°C.

As shown in Table 1, the solvent used in step 1 included ethanol, such as ethanol 200 proof grade, ethanol 3A grade, ethanol USP, ethanol absolute GR; and dichloromethane, such as dichloromethane AR grade, and a mixture of ethanol and dichloromethane at any ratio.

Table 1
Preparation of Misoprostol–Eudragit solid dispersion

Sample no.	Drug: Eudragit	Eudragit type	Solvent
1	Pure	–	None
2	1:150	RSPM	Ethanol
3	1:300	RSPM	Ethanol
4	1:450	RSPM	Ethanol
5	1:300	RSPM	Ethanol:CH_2Cl_2[a]
6	1:300	RSPM	CH_2Cl_2
7	1:10	RSPM	Ethanol
8	1:20	RSPM	Ethanol
9	1:40	RSPM	Ethanol
10	1:50	RLPM	Ethanol
11	1:450	RLPM	Ethanol
12	1:50	RSPM	Ethanol

[a] Solvent containing nine parts absolute ethanol and one part dichloromethane.

2.3. Preparation of tablets

A total of 20.4 mg of Misoprostol–Eudragit solid dispersion (1:50) obtained from the steps described above, 167.6 mg of Avicel PH 102 (Microcrystalline Cellulose), 10 mg of sodium starch glycolate and 2 mg of hydrogenated castor oil were mixed and compressed into tablets. The total weight of each sustained-release tablet was 200 mg. In total, 2000 sustained-release tablets were prepared. Each tablet contained 400 μg of Misoprostol. The tablet compression was made using the Kikusui rotary tablet machine.

2.4. Preparation of capsule

A total of 20.4 mg of Misoprostol–Eudragit solid dispersion (1:50) obtained from the steps described above was weighed and filled into No. 2 gelatin capsules. Each sustained release capsule contained 400 μg of Misoprostol.

2.5. Determination of Misoprostol stability

The stability of Misoprostol in the solid dispersion, the capsules and the tablets was determined after storing at various temperatures for different time periods. A HPLC stability-indicating method for the analysis of Misoprostol in the stability study was developed and validated. The calibration graph was linear from 2.2 to 6.6 μg ml^{-1} of Misoprostol. The square of correlation coefficient of the calibration curve was 0.999 for the above

Table 2
Stability data of Misoprostol alone and its Eudragit solid dispersions (Time: week; Data: %Potency remained)

Sample no.	5°C		30°C	50°C
	0	6	6	6
1	100	94	82.7	64
2	100	99.5	97.7	80.1
3	100	98.6	95.8	81.5
4	100	100	100	83.3
5	100	100	100	95.8
6	100	99.7	100	91.7

concentration range. The detection and quantitation limits were 0.6 and 2.0 μg ml^{-1}, respectively. Inter- and Intra-Assay RSD were 1.21–1.49% ($n = 5$) and 1.20–1.88% ($n = 6$), respectively, for 2.2, 4.4 and 6.6 μg ml^{-1} of Misoprostol. Recoveries in the calibration range were 98.25–100.60%, with a RSD of 1.05–1.71% ($n = 3$). Analysis of thermally stressed active and excipients with this HPLC method and photodiode-array detection (Focus, Spectra Physics) showed that the method was specific. The chromatography was stability-indicating, as demonstrated by the absence of measurable interferences from degradation products of either Misoprostol or the excipients. All assays were performed by using a TSP HPLC equipped with Model P2000 pump, AS3000 autosampler, UV 1000 detector, ISM 100 integrator and SN4000 controller. The wavelength was set at 210 nm and a chart speed was set at 0.5 cm min^{-1}. Assay was achieved by using a COSMOSIL, 5C18-AR, 150×4.6 mm ID column, eluted with a mobile phase containing 40 parts of acetonitrile and 60 parts of pH 2.81 phosphate buffer in volume with a flow rate of 1 ml min^{-1}. The retention time of Misoprostol is ~ 12 min.

2.6. Dissolution study of Misoprostol sustained-release tablets

The dissolution profiles of Misoprostol sustained-release tablets were generated by a USP paddle dissolution tester (Logan DissoRate 8) at 37°C with an agitation speed of 50 or 75 rpm. The dissolution media were pH 1.2 (0.1 N HCl), pH 4.5 (NaH_2PO_4 13.8 g l^{-1} H_2O), pH 6.8 (0.2 N sodium phosphate buffer), pH 7.5 (0.1 N sodium phosphate buffer) and H_2O with 0.044–0.25% sodium lauryl sulfate (SLS). If the dissolution medium were a buffered solution, the solution would need to be adjusted so that its pH is within 0.05 unit of the pH specified. At each time point, dissolution samples were assayed by the HPLC method described above.

2.7. Differential scanning calorimetry analysis (DSC)

Thermal analytical method of DSC was employed to study the thermal properties of Misoprostol, Eudragit and Misoprostol–Eudragit solid disperison. DSC thermographs were obtained by using a Setaram DSC 92 Thermal Analysis System using loosely covered aluminium pans. The DSC apparatus was calibrated using indium. The weights of the samples were 8–20 mg. The scanning rate was 10°C min^{-1}. The samples were scanned first from -70 to 125°C, and then cooled to -70°C. The same samples were rescanned from -70 to 250°C.

3. Result and discussion

3.1. Stability study of Misoprostol–Eudragit solid dispersions

The stability of Misoprostol in different solid dispersions (Samples 1–12) was determined after storing at various temperatures for different time periods. After assaying the remaining percent potency of Misoprostol in each sample by HPLC, the result was summarized in Table 2 for Samples 1–6 and Table 3 for Samples 1 and 7–11. The stability of Misoprostol in the Eudragit solid dispersion matrix at different ratios was significantly improved. Misoprostol is known to be an unstable compound and will degrade on contact with water at room temperature even when extremely small amounts of water exist, to lose its biological activity. In the stable solid dispersion prepared in the present study, the matrix formed by the Eudragit most likely forms a barrier be-

Table 3
Stability data of Misoprostol alone and its Eudragit solid dispersions (Time: week; Data: %Potency remained)

Sample no.	30°C				50°C				70°C	
	0	3	6	12	1	3	6	12	1	2
1	100	92.2	82.7	14.4	93.9	91.7	64	10.9	81.2	41.5
7	100	99.5	102.2	93.0	97.0	97.2	94.8	91.8	–	–
8	100	99.1	98.1	95.6	102	95.8	95.0	93.7	93.9	88.6
9	100	98.8	100.4	97.5	100.7	99.7	98.3	96.5	95.0	92.3
10	100	96.5	94.5	96.6	96.5	97.0	93.0	93.0	94.5	90.5
11	100	102.9	101.5	97	97.9	95.3	95.2	95.7	97.6	92.3

tween water and Misoprostol so as to coat and protect Misoprostol from contact with water and being degraded. Like the stabilization mechanism of Misoprostol/HPMC, it can also be proposed here that the stability of Misoprostol be improved due to the low mobility of water and Misoprostol in the glassy Misoprostol–Eudragit solid dispersion. Since dehydration of Misoprostol is the first step in the degradation of this compound, and since it is catalyzed by a small amount of water, the low mobility of water and Misoprostol in the glassy Misoprostol–Eudragit dispersion matrix leads to a minimal rate of degradation of Misoprostol within the dispersion matrix.

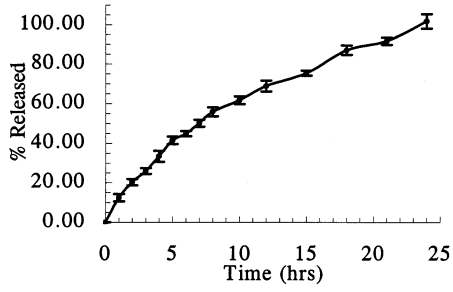

Fig. 1. Dissolution profile of the Misoprostol sustained-release tablets in a 0.25% SLS water solution with an agitation speed of 50 rpm.

3.2. Dissolution profile of Misoprostol sustained-release tablets

The sustained-release dissolution profile of the Misoprostol sustained-release tablets, Prepared by using the Misoprostol–Eudragit solid dispersion (1:50), are shown in Figs. 1 and 2. The dissolution test in Fig. 1 was conducted in a 0.25% SLS water dissolution medium. The dissolution tests in Fig. 2 were conducted in 0.044–0.055% SLS pH 1.2, 4.5, 6.8 and 7.5 dissolution media, respectively.

From Figs. 1 and 2, it is clear that the sustained-release effect of the solid dispersion of Misoprostol of the present invention is better than that of the Misoprostol immediate-release tablet. Since ammonio methacrylate copolymer is insoluble in water, Eudragit RL and RS are copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The ammonium groups are present as salts and give

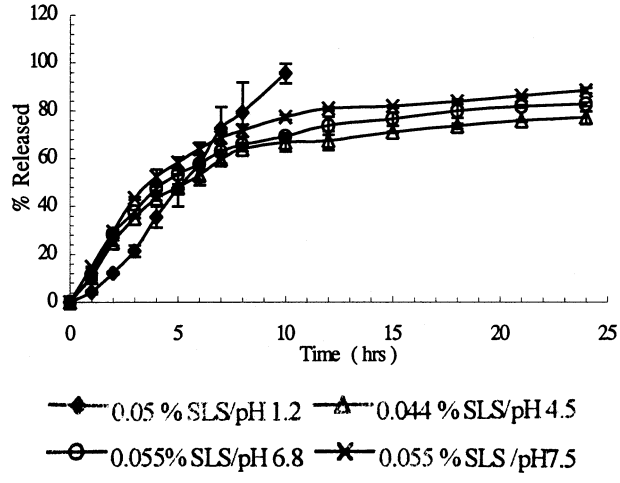

Fig. 2. Dissolution profile of the Misoprostol sustained-release tablets in various dissolution media with an agitation speed of 75 rpm.

Table 4
Comparison of stability data of solid dispersion, tablet and capsule (Time: month; Data: %Potency remained)

Temperature	37°C			43°C			50°C		
Sample	75% RH			75% RH			75% RH		
	1	3	6	1	3	6	1	3	6
Misoprostol–Eudragit solid dispersion (1:50)	95.1	95.9	92.1	96.0	94.7	90.1	93.5	90.7	76
Sustained-release tablet	100	96.6	97.3	100	96.4	91.6	93.8	89.6	56.8
Sustained-released capsules	97.9	–	95.4	95.3	–	92.2	92.8	–	68.8

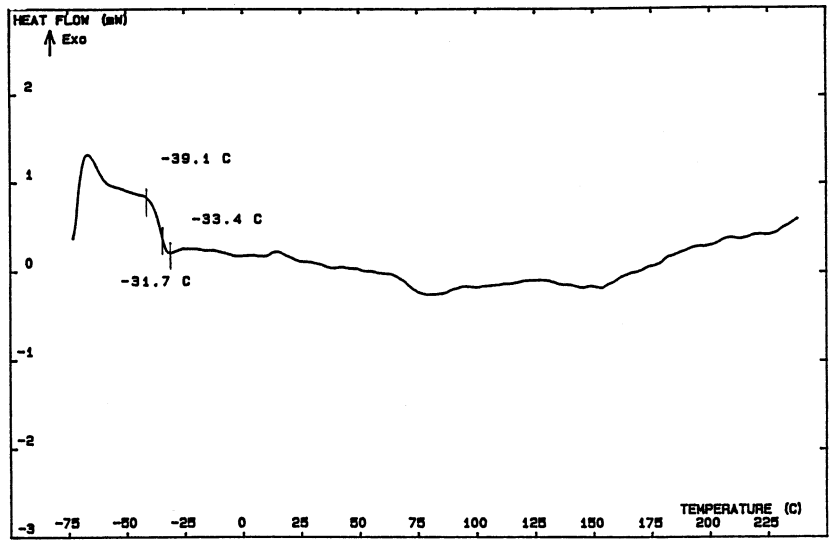

Fig. 3. DSC thermograph for pure Misoprostol.

rise to the permeability of the polymers in aqueous medium. Misoprostol dispersed in these copolymers are gradually dissolved and continuously released by diffusion from the permeable copolymer matrix. In accordance with this study, a 1-a-day tablet or capsule produced from the solid dispersion of Misoprostol could possibly be formulated since the solid dispersion of Misoprostol is a sustained-release type.

3.3. The stability of Misoprostol–Eudragit solid dispersion, tablet and capsule

As shown in Table 4, the tablets compressed from the stabilized solid dispersion of Misoprostol or the capsules filled with the stabilized solid dispersion of Misoprostol are stable at 37 and 43°C, and the potency is still higher than 90% after 6 months. The shelf-life of the product could very well be predicted as close to 2 years.

3.4. DSC thermal analysis on Misoprostol, Eudragit and Misoprostol–Eudragit solid dispersion

DSC thermal analysis was employed to study how the drug is distributed in the Misoprostol–Eudragit dispersion matrix. Figs. 3 and 4 illustrate the DSC thermographs for Misoprostol and Eudragit, respectively. In Fig. 3, a second-order tran-

sition at −33°C as reported in the literature (Kararli et al., 1991), is the characteristic of Misoprostol. The DSC thermographs of Misoprostol–Eudragit solid dispersion (1:50) are shown in Fig. 5.

It has been reported that T_g and melting points in a solid dispersion with miscible components are shifted and lost, corresponding to the pure components (Okhamafe and York, 1988; Kararli et al., 1991). The DSC result in Fig. 5 shows that the second-order transition at −33°C as the characteristic of Misoprostol is lost. No −33°C transition could be detected from the DSC measurement on the Misoprostol–Eudragit solid

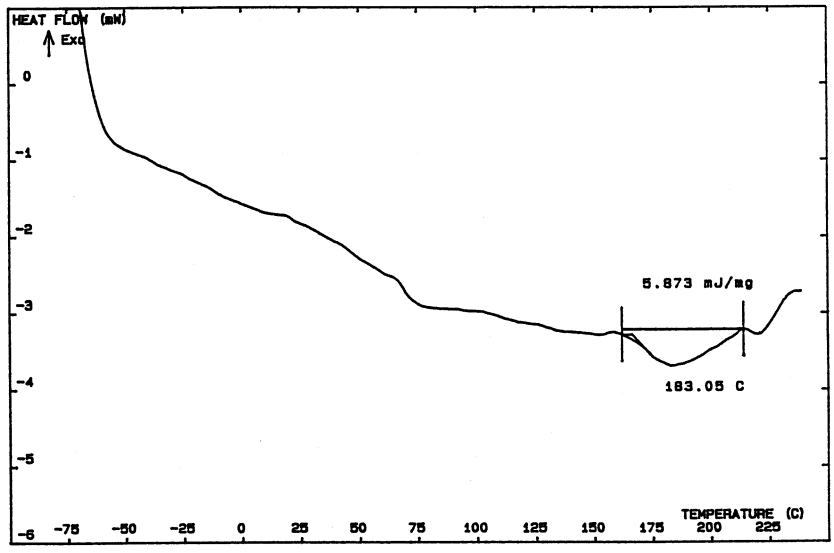

Fig. 4. DSC thermograph for pure Eudragit.

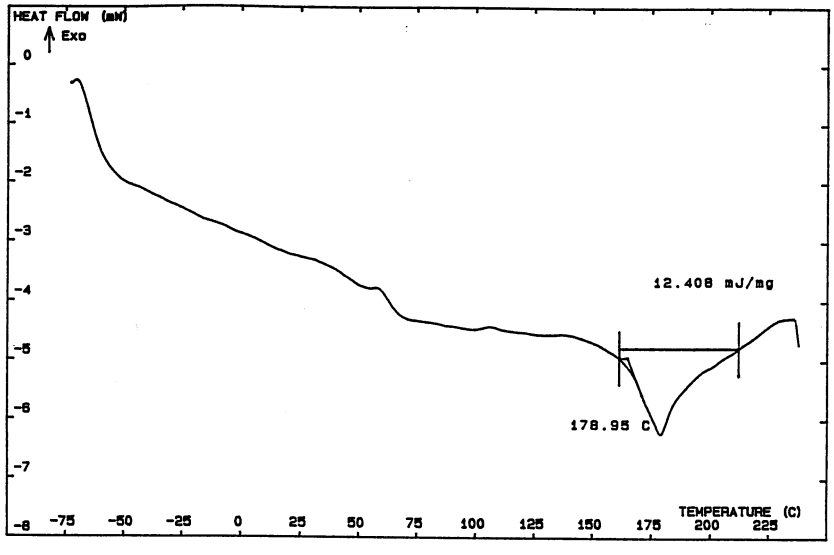

Fig. 5. DSC thermograph for Misoprostol–Eudragit solid dispersion (1:50).

dispersion. Evidence from the DSC measurement indicate that Misoprostol is miscible in Eudragit at the ratio been used. Based on the DSC measurement, it could be suggested that Misoprostol is molecularly dispersed in the glassy matrix of Eudragit. This type of matrix could reduce the mobility of Misoprostol and water, leading to a minimum rate of degradation.

4. Conclusions

The present study makes use of an ammonio methacrylate copolymer (Eudrgit RS, RL) to form a sustained-release solid dispersion of Misoprostol that can improve and enhance two important physical and chemical properties of Misoprostol. First, the solid dispersion matrix formed by the copolymer can protect Misoprostol from being degraded by water so that the stability of Misoprostol is improved. Second, Misoprostol can be slowly released by diffusion from the copolymer matrix.

The stable Misoprostol–Eudragit solid dispersion can be used directly in a powder form, filled in capsules, or compressed into tablets with pharmaceutical excipients. The dissolution profiles of Misoprostol–Eudragit tablets in different media show sustained-release properties and this tablet can be used as a long-acting drug.

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