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Development and evaluation of orally disintegrating tablets containing the mosapride resin complex

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The purpose of this study was to prepare a mosapride citrate-resin (Amberlite® IRP 88) complex and orally fast-disintegrating tablets of the resin complex. The resinate complex of mosapride-Amberlite® IRP 88, mass ratio 2:1, was prepared in an ethanol-water solution. The effects of alcohol concentration, temperature, and pH of the solution on complex formation were evaluated. The complex physicochemical properties were characterized by differential scanning calorimetry, X-ray diffraction and scanning electron microscopy. Orally disintegrating tablets were prepared by direct compression and were optimized using the response surface method. Optimized orally fast-disintegrating tablets disintegrated within 18 s. The pH dependence of mosapride release from the tablet decreased drug dissolution in simulated saliva, whereas it promptly released in the pH 1.0 solution. The data reported herein clearly demonstrate that tablets containing the mosapride-Amberlite® IRP 88 complex for oral disintegration could be particularly useful for patients with swallowing difficulties.

Keywords: mosapride citrate, Amberlite® IRP 88 resin, resin complex, orally disintegrating tablet, physicochemical characterization, dissolution

Mosapride citrate (MC) is a gastroprokinetic agent, which acts as a selective 5HT4 agonist accelerating gastric emptying and is used for the treatment of acid reflux, irritable bowel syndrome and functional dyspepsia (1). The dose of MC is either 5 or 10 mg given three times a day. MC is a weakly basic drug available on the market as sustained release tablets, oral disintegrating tablets and chewable tablets (2). MC has low oral bioavailability of 8 % and a bitter taste (3). It is recommendable to mask the bitter taste of MC in order to achieve patient compatibility.

There are numerous effective taste masking technologies, such as common granulation, coating processes and microencapsulation. Application of these approaches depends on the properties of the active compound and the dosage form (4, 5). To cover the bitter

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taste of an ionic drug, the formation of a drug-resinate complex is the simplest method. Drug molecules interact with ion exchange resins and hence decrease its exposure to the taste buds while maintaining the concentration of the drug in saliva below the taste threshold value. It is expected that the drugs that bind to resins will be released in the GI tract through ion exchange with H^+, Na^+, or K^+ in gastric and intestinal fluids (6).

Resins have been primarily used to mask taste and control liquid drug delivery systems (7–10). Many studies addressed the use of ion exchange resins for taste masking (11–13). However, few investigations have been reported on poorly water-soluble drugs. In order to improve the solubility of MC, an ethanol-water solution was used as the ion exchange reaction medium to form the mosapride-Amberlite® IRP complex. Amberlite® IRP is a weak acidic potassium cation exchange resin. It is widely used as a disintegrating and taste masking agent in oral dosage formulations (14).

Orally disintegrating tablets (ODT) provide pediatric, geriatric and bedridden patients with an easy method for taking medication. These tablets disperse in the oral cavity, and then the active ingredient dissolves in saliva to be absorbed. For some drugs, disintegrating tablets may have higher bioavailability than the conventional formulation (15, 16).

The aim of this work was to design a mosapride-Amberlite® IRP 88 complex and prepare orally fast-disintegrating tablets to improve taste and palatability. The prepared and optimized drug-resinate complex with maximum drug loading was subjected to physicochemical characterization by differential scanning calorimetry (DSC), X-ray diffractometry (XRD), and scanning electron microscopy (SEM). Orally disintegrating tablets were compressed by the direct method and optimized by a response surface method. The hardness, disintegration time and dissolution properties of the tablets were evaluated.

EXPERIMENTAL

Materials

Mosapride citrate was a gift from Lunan Pharmaceutical Group Corporation (Linyi, China). Polacrilin potassium NF (Amberlite® IRP 88) was kindly supplied by Rohm and Haas Company (Shanghai, China). Microcrystalline CEOLUS® PH-301 was supplied by AsahiKASEI (Japan). Low-Substituted Hypromellose-21 (LH-21) was supplied by Shin-Etsu (Japan). Pearlitol as mannitol was supplied by Roquette (France). All reagents and solvents were of analytical grade.

Preparation and optimization of drug-resin complexes

Mosapride-resin complex (MR) was prepared by a simple aqueous binding process. The ion-exchange resin particles were dispersed in a drug ethanol solution with a mass ratio of 1:2 under magnetic stirring until equilibrium state. The influences of ethanol concentrations (40, 50, 60 and 75 %), pH 2.0, 3.0 and 4.2 of the solution, temperature (15, 20, 25 and 30 °C) on drug loading were investigated. The complexes were separated by filtration and washed with deionized water to remove unbound drug and other ions. The complexes were then dried in hot air oven for 4 h at 40 °C to constant mass and stored in a tight glass vial. Unbound drug was estimated by UV spectrophotometry at 272 nm and drug loading efficiency was calculated. To determine the equilibrium rate, 1 mL of supernatant

was collected and diluted with water at predetermined time intervals to monitor the changes of the MC content concentration in the solution by UV at a wavelength of 272 nm. The drug loading capacity (*m*/*m*) (*Q*) and adsorption ratio (*E*) at loading equilibrium were calculated using the following equations *(1)* and *(2)*, respectively:

$$Q = \frac{(C_0 - C_t)V}{W_R \times 1000} \quad (1)$$

$$E = \frac{C_0 - C_t}{C_0} \times 100\% \quad (2)$$

where C_0 (mg mL^{-1}) is the initial MC concentration in solution and C_t is the concentration of MC at time *t*, V (mL) is the initial sample solution volume, W_R (g) is the mass of dry resin.

Drug-polymer interaction studies

The thermal behavior of MC, resin, physical mixture of MC and resin (2:1), and MR was determined with the aid of a DSC Analyzer (Shimadzu, TA-60WS, Japan). The temperature was increased to 250 °C at the rate of 15 °C min^{-1}.

The XRD patterns of MC, resin, MR, and physical mixture of MC and resin (2:1) were analyzed with an X-ray diffractometer (D/MAX-3C, Riguku Co., Japan) at a 56 kV voltage and 35 mA current. Samples were finely ground and irradiated with monochromatized Cu-Ka radiation after passing through Nickel filters and analyzed between 2 and 40° (2θ).

Morphologies of MC, resin, MR, and physical mixture of MC and resin were investigated by SEM. Dried samples were attached to specimen stubs with a double-sided copper tape and sputter coated with gold-palladium in the presence of argon gas using a Hummer sputter coater (Anatech Ltd., Denver, NC). The samples were recorded with a JEOL JSM-840 scanning electron microscope (JEOL USA Inc., Peabody, MA) at a 5 kV accelerating voltage and a probe current of 3×10^{-11} A.

Preparation and experimental design of tablets

LH-21, CEOLUS® PH-301, Pearlitol® 300DC were chosen as fillers and sodium stearyl fumarate (PRUV®) was used as lubricant to prepare the orally disintegrating tablets. The percent of LH-21 in the formulation was determined by the single factor experiment. Microcrystalline cellulose (MCC) is a binder, owing to its excellent compatibility, and is also known to be self-disintegrating in the direct compression process. Mannitol (Man) was used as a diluent because of its sweet taste and cooling sensation. To optimize the formulation, MCC/Man ratio and tablet porosity were chosen as controlling factors, and oral disintegration time was set as the response variable. As shown in Table 1, five formulations with different MCC/Man ratios were compressed with a diameter of 8 mm using a single punch tablet machine and compression pressure at 20~30 N with about 200 mg mass. The different kinds of tablets with various porosity and oral disintegration times were obtained. Based on these data, the response surface and contour plots of disintegration were obtained with Origin 8.0.

Table I. Tablet formulations for optimization

Ingredients (mg/tablet)	F1	F2	F3	F4	F5
Ceolus® PH-301	110	104	90	62	50
Pearlitol® 300DC	70	76	90	118	130
LH-21	20	20	20	20	20
PRUV®	1	1	1	1	1

Measurement of tablet hardness

The hardness/crushing strength (17) measured in kg cm^{-2} of six tablets were determined using a Hardness Tester (78X-2, Huanghai Instrument Co., Ltd., China). The tensile strength, T, for crushing (MPa) was measured using the following equation *(3)*:

$$T = \frac{2F}{\pi DH} \tag{3}$$

where F is the crushing load (N), d is the diameter (m) and t is the thickness (m).

Measurement of tablet porosity

Tablet porosity was measured with an oil pressurized single punch tablet press under the pressure of 5000 MPa and the porosity (ε) was calculated using the following equation *(4)*:

$$\varepsilon = \frac{d_1^2 h_1 - d_2^2 h_2}{d_1^2 h_1} \tag{4}$$

where d_1 (mm) is the original tablet diameter, h_1 (mm) is the original tablet thickness (mm), d_2 (mm) is the tablet diameter and h_2 (mm) is the tablet thickness (mm). Tablet diameter and thickness were determined using a micrometer caliper (Shenyang Measurement Factory, China).

Disintegration test

Disintegration test was conducted according to the method described in the Pharmacopoeia of the People's Republic of China (2010). Six tablets were separately put into the test apparatus. The basket was put into 800 mL of water at 37 ± 0.2 °C. Time was recorded when the tablet was fully disintegrated.

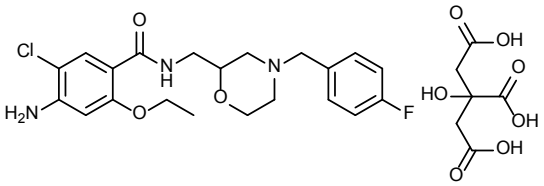

Fig. 1. Chemical structure of mosapride citrate.

Dissolution test

Dissolution test was performed using a dissolution apparatus type II (ZRS-8G, Tianjin University Instrument Factory, China) in triplicate in 250 mL dissolution media of various pH 1.0, 1.5, 2.5 (hydrochloric acid solution), pH 3.5, 4.5 (acetate buffer solution), pH 5.5, 6.5 (phosphate buffer solution) and simulated saliva (NaCl 8.00 g, KH_2PO_4 0.19 g, Na_2HPO_4 2.38 g, in 1 L distilled water; pH 6.8) (18) at 37 ± 0.5 °C at a rotation speed of 50 rpm according to the Pharmacopoeia of the People's Republic of China. 2 mL of sample was replaced with dissolution medium at predetermined time and was filtered through a 0.45 μm film. The concentration was analyzed using a spectrophotometer at the wavelength of 272 nm.

RESULTS AND DISCUSSION

Effects of ethanol concentration, solution pH and temperature on drug loading

MC concentration was 0.8 mg mL^{-1} in a 100 % ethanol solution while the drug-resin ratio was 2:1. Mosapride could not be loaded on Amberlite® IRP 88 in anhydrous ethanol, but it could form a complex in aqueous alcoholic medium. Increasing the ethanol concentration could decrease the drug adsorption capacity (*Q*). The significant improvement of drug adsorption ratio in 40 % aqueous alcoholic medium (92.2 %) compared to that of 75 % aqueous alcoholic medium (8.4 %) is depicted in Fig. 2. The solubility of mosapride was increased in the alcoholic solution to form a complex and reduce the equilibrium time.

Fig. 3 shows the effects of temperature on the adsorption ratio and adsorption capacity. It was found that adsorption capacity was about 1.0~1.5 g g^{-1} at the temperature from 30 to 15 °C. Due to the increment in adsorption ratio with decreased temperature, further experiments were carried out at 25 °C.

The pH of the solution is a very important parameter in drug adsorption on resin. At pH 2.0, the drug adsorption capacity of 0.13 g g^{-1} was the lowest because Amberlite® IRP 88 is available in unionized molecular form in an acidic aqueous solution. By increasing the pH from 2.0 to 4.0, an increase in drug loading is observed (pH 4.0, 2.0 g g^{-1}) in Fig. 4. At pH

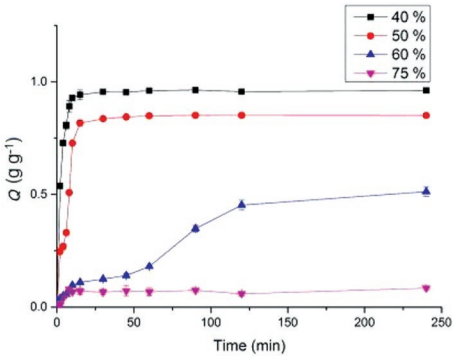

Fig. 2. Effect of ethanol concentration on the drug adsorption capacity, *Q* at 25 °C. Data are expressed as the mean ± SD (n = 3).

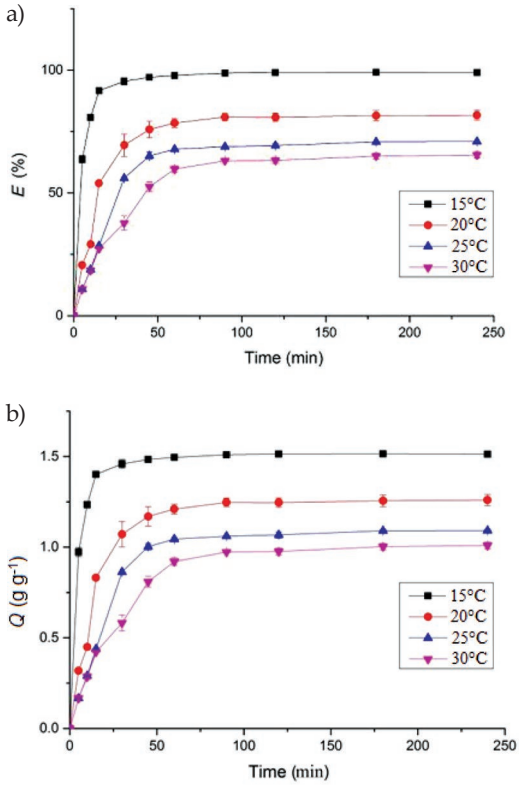

Fig. 3. Effects of temperature on: a) drug adsorption ratio (*E*), and b) the drug adsorption capacity (*Q*). Data are expressed as the mean ± SD (n = 3).

4.2, both the drug and the resin were ionized in a sufficient quantity and interacted to form the resin complex.

Differential scanning calorimetry

DSC curves of MC, resin, MR, and physical mixture are presented in Fig. 5. MC shows a melting endothermic peak at 119.04 °C (Fig. 5c). The DSC thermogram of resin shows a broad endotherm peak at 95.54 °C due to the dehydration of resin (Fig. 5d). The melting endothermic peak of the drug and a broad endothermic peak were observed in the thermograms of the physical mixture (Fig. 5b). A sharp endothermic peak of mosapride in MR (Fig. 5a) was observed at 155.38 °C, probably due to the bonding force of mosapride while resin was so weak that it was discomposed by heating.

X-ray diffractometry studies

The powder XRD patterns of MC, Amberlite® IRP 88 resin, MR, and physical mixture are shown in Fig. 6. The XRD pattern of MC in Fig. 6 shows the strong intensity of the

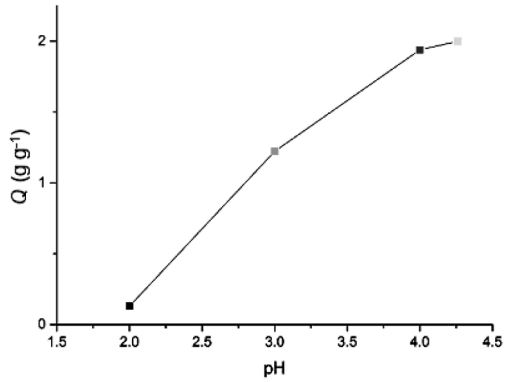

Fig. 4. Effect of pH on drug loading capacity, *Q*. Data are expressed as the mean ± SD (n = 3).

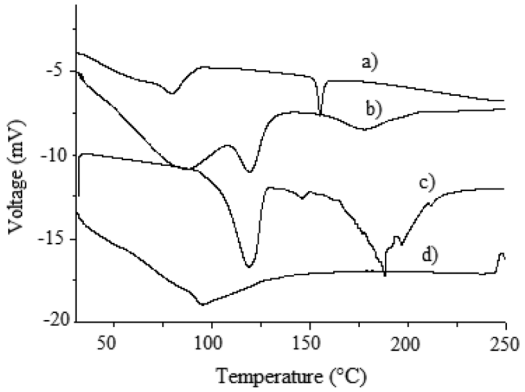

Fig. 5. DSC thermograms of: a) MR, b) physical mixture, c) MC and d) Amberlite® IRP 88.

diffraction peaks. For the physical mixture in Fig. 6, drug molecules were outside the resin and crystalline sharp peaks appeared in the diffractogram. The XRD pattern of MR in Fig. 6 indicated the disappearance of crystalline form in case of the drug resinate complex compared to the drug alone or its physical mixture. The resin Amberlite® IRP 88 X-ray diffractogram displays a diffused peak due to their amorphous state in Fig. 6.

Morphology

Scanning electron microscopy (SEM) images of MC, Amberlite® IRP 88 resin, MR, and MC resin physical mixture are presented in Fig. 7. It appears that the size of drug crystals ranged from 1–2 μm to even more than 100 μm (Fig. 7c). The Amberlite® IRP 88 resin is irregular in shape and appears as separate pieces (Fig. 7d). The SEM image of physical mixture (Fig. 7b) shows embedded particles of MC and Amberlite® IRP 88 with a morphology comparable to pure components, revealing no apparent interaction between both species

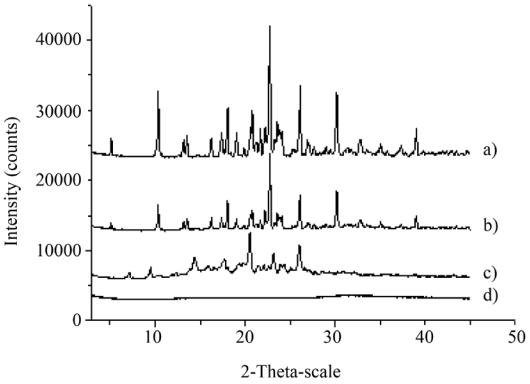

Fig. 6. X-Ray diffractograms of: a) MR, b) physical mixture, c) MC, d) Amberlite® IRP 88.

in the solid state. After forming the resin-complex, the morphology MR (Fig. 7a) appeared different from the drug, the resin or their physical mixture. The features of drug crystals were not easily detectable, indicating formation of a different compound.

Formulation optimization

LH-21, CEOLUS® PH-301, Pearlitol® 300DC were chosen as excipients, sodium stearyl fumarate (PRUV®) was used as lubricant to prepare the orally disintegrating tablets and

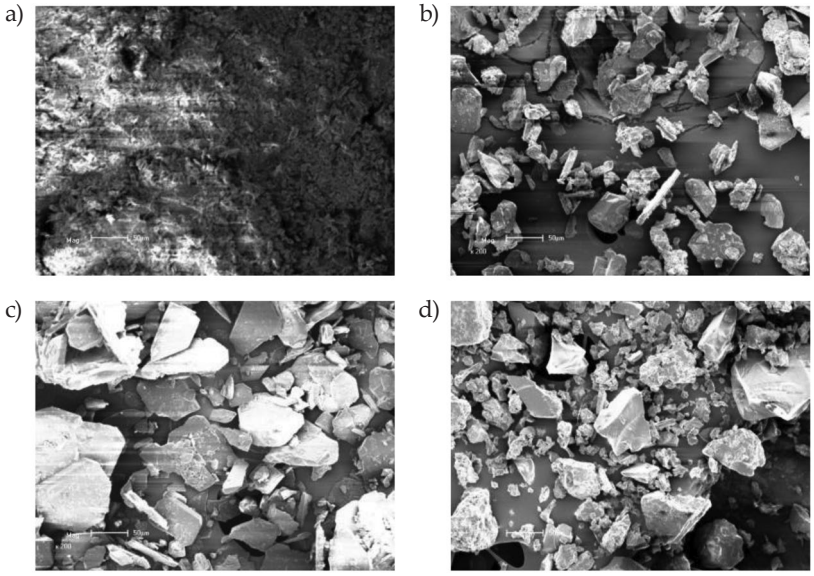

Fig. 7. Scanning electron micrographs of: a) MR, b) physical mixture, c) MC, d) Amberlite® IRP 88.

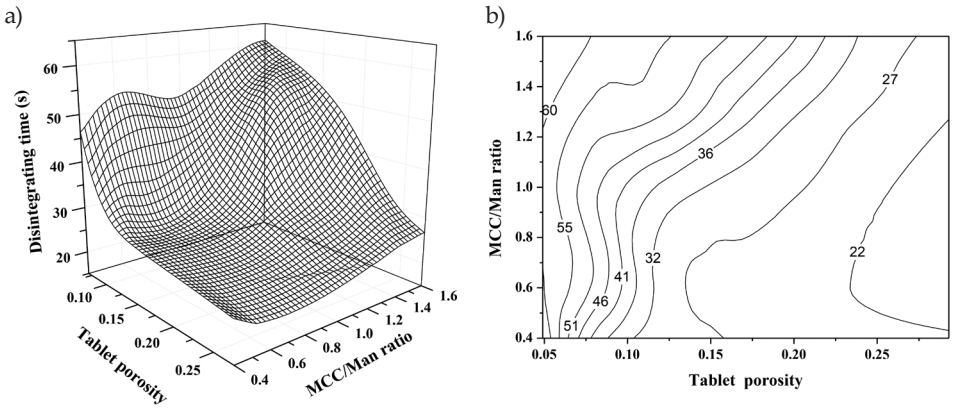

Fig. 8. Response surface and contour plots of disintegration time. MCC/Man ratio is ratio of microcrystalline cellulose and mannitol.

the percent of LH-21 in the formulation was determined by the single factor experiment. To optimize the formulation, MCC/Man ratio and tablet porosity were selected as controlling factors, and oral disintegration times were set as response variables. The response surface and contour plots of disintegration were obtained with Origin 8.0 and are given in Fig. 8. The plot of the response surface and contour indicates that disintegration time decreased with an increase in porosity at the same MCC/Man ratio. This may be explained by the fact that tablets with high porosity can uptake water rapidly and the L-HPC can swell to break the solid bridge. For tablets with the same porosity, the disintegration time was the shortest with MCC/Man at the 0.75 ratio. Consequently, the combination of Man and MCC showed the desired flowability, compressibility and rapid disintegration.

The swelling of L-HPC had less effect on the disintegration of the tablet compared to tablets containing more insoluble MCC. There are about 2.0 % water-soluble substances in CEOLUS® PH-301, and a gel-like layer will be formed when water penetrates into tablets with an increased MCC/Man ratio. In a viscous gel layer, the diffusion rate of water should be reduced. As the mean diameter of CEOLUS® PH-301 and Pearlitol® 300DC is 50 μm and 250 μm, respectively, the contact surface with higher MCC/Man ratio formations may be much larger than that of a low MCC/Man ratio. The bonding force was enhanced and the disintegration time was also decreased.

Hardness of a tablet is defined as the force applied across its diameter in order to break the tablet. Tablets should be able to resist chipping, abrasion or breaking under the conditions of storage, transformation or handling, but there should be no problems in their disintegration or dissolution. It is generally recognized that sufficient hardness would be 2 kP or higher. In addition, the desirable oral disintegration time would generally be 30 s or shorter in case of orally disintegrating tablets. The desirable disintegration time is 25 s, and the contour plots show that all the formulations with porosity above 0.225 can achieve this requirement. Mannitol is commonly used in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness and better mouth feel. The MCC/Man ratio was 0.75 and tablets were prepared at 3 kP with a disintegration time of 18 s.

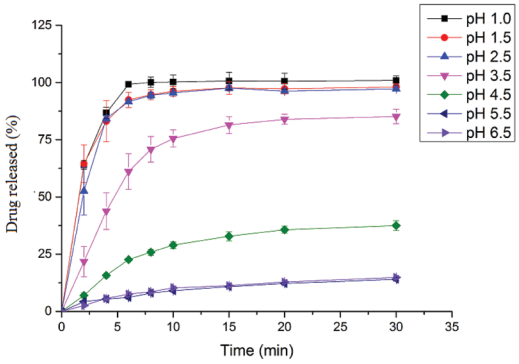

Fig. 9. Effect of solution pH on the dissolution of mosapride from mosapride-resin complex orally disintegrating tablets (MR-ODT). Data are expressed as the mean ± SD (n = 3).

Dissolution study

Drug release from the drug resin complex depends on the environment pH and ionic strength within the gastrointestinal tract, as well as on the properties of the resin (19). The pH, ionic species and strength effects on drug dissolution from MR-ODT were studied. In order to confirm the taste masking results, drug release in simulated saliva (pH 6.8) was also studied.

The dissolution profile (Fig. 9) of mosapride from the MR-ODT in various pH aqueous solutions indicated that mosapride was released rapidly and completely in solutions of pH < 2.5. More than 75 % of bound mosapride was released in 10 min at pH 3.5, but less than 10 % of bound mosapride was released in 30 min in solutions of pH > 5.5. All the results demonstrated that drug release from the tablets was strongly pH dependent. The pH dependence of mosapride release from the complex could decrease drug dissolution in the

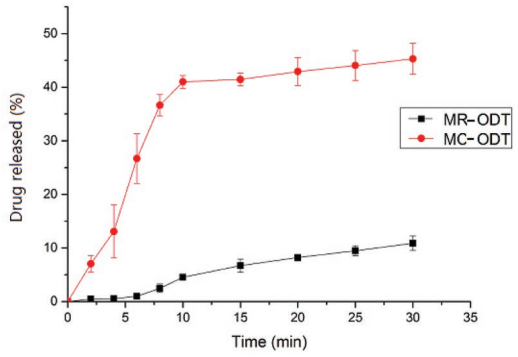

Fig. 10. Dissolution profiles of mosapride citrate orally disintegrating tablets (MC-ODT) and mosapride-resin complex orally disintegrating tablets (MR-ODT) in simulated saliva. Data are expressed as the mean ± SD (n = 3).

oral cavity, whereas it immediately releases in the stomach (20). At pH 6.8 (salivary pH), drug release was delayed and was effective for taste masking. Amberlite® IRP 88 is a weak acidic, potassium form cation-exchange resin (21). The high affinity of Amberlite® IRP 88 to hydrogen ions can lead to fast desorption of bound ions when they are exposed to an acidic environment such as the stomach (22).

The dissolution profile of MR-ODT in simulated saliva is represented in Fig. 10 and MC-ODT was used as a reference tablet. In four minutes, the drug released from MR-ODT and the MC-ODT content in simulated saliva was about 0.5 and 15 %, respectively. The delayed dissolution observed with the resin complex can be attributed to the resin-complex formulation. This result suggested that there should be less drug release in the oral cavity when taking optimized MR-ODT than MC-ODT. The bitter taste masking effect will be investigated in future studies.

CONCLUSIONS

In this study, a resin complex and orally disintegrating tablets were successfully produced using mannitol, L-HPC and MCC as excipients. Differential scanning calorimetry, X-ray diffraction and scanning electron microscopy demonstrated the complex formation and indicated that the drug was dispersed evenly into the resin to form the resin complex and showed some disappearance of crystallinity. The oral disintegrating tablet disintegrated within 18 s. This oral disintegrating tablet can be used as a potential drug delivery system of mosapride citrate, especially for the pediatric and geriatric patients and those with swallowing difficulties.

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