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Development and evaluation of orally disintegrating tablet containing mosapride resin complex

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The purpose of this study was to make mosapride citrate−resin (Amberlite®IRP 88) complex and orally fast-disintegrating tablets of the resin complex. The resinate complex of mosapride−Amberlite®IRP 88 with weight ratio of 2:1 was prepared in ethanol-water solution. The effects of alcoholic concentration, temperature, and pH of the solution on complex formation were evaluated. The physicochemical properties of complexes were characterized by differential scanning calorimetry, X-ray diffraction and scanning electron microscopy. Orally disintegrating tablets were prepared by direct compression and optimized by the response surface method. The optimized orally fast-disintegrating tablets disintegrated within 18 s. The pH dependence of mosapride release from the tablet could decrease drug dissolution in simulated saliva, whereas immediately releasing in pH 1.0 solution. The data reported herein clearly demonstrate that the tablets containing complex of mosapride-Amberlite®IRP 88 complex for oral disintegrating, which 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 that acts as a selective 5HT4 agonist which accelerates 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 daily. MC is a weakly basic drug which formulation available on the market are sustained release tablet, oral disintegrating tablet and chewable tablet (2). MC has a low oral bioavailability of 8% and a bitter taste (3). It is better 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. The application of all these approaches depends on the properties of active compound and the dosage form (4, 5). To cover the bitter taste of the ionic drug, the formation of drug-resinate complex is a simple 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 which bind to resins will be released in GI track through ions

exchange with H^+, Na^+, or K^+ in the gastric and intestinal fluids (6).

The resins have been primarily used to mask taste and control liquid drug delivery systems (7-10). Many studies involved in the use of ion exchange resins for taste masking (11-13). However, few investigations have been reported on poorly water-soluble drug. In order to improve the solubility of MC, ethanol-water solution was used as the ion exchange reaction media 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 paediatric, geriatric and bedridden patients with easy method to take the medication. These tablets disperse in the oral cavity, and then active compose 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 mosapride-Amberlite®IRP88 complex and prepare orally fast-disintegrating tablets to improve taste and palatability. The prepared and optimized drug-resinate complex with maximum drug loading would be subjected to physicochemical characterization after preparation by differential scanning calorimetry (DSC), X-ray diffractometry (XRD), and scanning electron microscopy (SEM). Orally disintegrating tablets were compressed by 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). Micrystalline 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 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 drug ethanol solution with a weight ratio of 1:2 under magnetic until equilibrium state. The influences of concentrations of ethanol (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 unassociated drug and other ions. The complexes were then dried in hot air oven for 4 h at 40°C to a constant weight 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 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 the wavelength of 272 nm. The drug loading capacity (g/g) (Q) and adsorption ratio (E) at loading equilibrium were calculated with the following equation (1) and (2) respectively:

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

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

where C_0 (mg·mL^{-1}) is initial concentration of MC 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 weight of dry resin.

Drug–polymer interaction studies

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

The morphologies of MC, resin, MR, and physical mixture of MC and resin were investigated by SEM. Dried samples were added to specimen stubs by 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 the tablets

LH-21, CEOLUS® PH-301, Pearlitol® 300DC were chosen as the fillers and sodium stearyl fumarate (PRUV®) was used as the 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 both a binder due to its excellent compatibility and also known to be self-disintegrating in 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 response variables. As shown in Table 1, five formulations with different MCC/Man ratios were compressed with diameter of 8 mm using a single punch tablet machine and compression pressure at 20~30N with a weight about 200 mg. The different kinds of tablets with various porosity and oral disintegration times were obtained. Based on these data, response surface and contour plots of disintegration were obtained by Origin 8.0.

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).

$$T = \frac{2F}{\pi DH} \qquad (3)$$

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

Measurement of tablet porosity

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

$$\varepsilon = \frac{d_1^2 h_1 - d_2^2 h_2}{d_1^2 h_1} \qquad (4)$$

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). The tablet diameter and thickness were determined using a micrometer caliper (Shenyang measurement factory, China).

Disintegration test

Disintegration test was conducted according to the method 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 water at 37 ± 0.2°C. The time was recorded when the tablet was fully disintegrated.

Dissolution test

The dissolution test was conducted using a dissolution apparatus type II (ZRS-8G, Tianjin university instrument factory, China) in triplicate at 250 mL dissolution media in 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 of distilled water; pH 6.8) (18) at 37 ± 0.5 °C with rotation speed of 50 rpm according to the Pharmacopoeia of the People's Republic of China. The sample 2 mL was replaced with dissolution medium at predetermined time and it was filtered through a 0.45 μm film. The concentration was analyzed using spectrophotometer at the wavelength of 272 nm.

RESULTS AND DISCUSSION

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

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

Figure 3 shows the effects of temperature on adsorption ratio and adsorption capacity. It was found that the adsorption capacity was about 1.0 ~ 1.5 $g \cdot g^{-1}$ with the temperature from 30°C to 15°C. Due to the increment in adsorption ratio with decreased temperature, the 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$g \cdot g^{-1}$ was the smallest because Amberlite® IRP88 is available as unionized molecular 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 $g \cdot g^{-1}$) in Figure 4. At pH 4.2, both the drug and the resin are ionized in sufficient quantity and interacted to form resin complex.

Differential scanning calorimetric

DSC curves of MC, resin, MR, physical mixture are presented in Figure 5. MC shows a melting endothermic peak at 119.04°C (Figure 5c). The DSC thermogram of resin shows broad endotherm peak at 95.54 °C due to the dehydration of resin (Figure 5d). The melting endothermic peak of drug and broad endothermic peak were observed in the thermograms of the physical mixture (Figure 5b). A sharp endothermic peak of mosapride in MR (Figure 5a) weas observed at 155.38 °C, could be due to the bonding force of mosapride and 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 is shown in Figure 6. The XRD pattern of MC in Figure 6 showed the strong intensity of the diffraction peaks. For physical mixture in Figure 6, drug molecules are outside the resin and crystalline sharp peaks appeared in diffractogram. The XRD pattern of MR in Figure 6

indicated some disappearance of crystalline in case of drug resinate complex compared to the drug alone or its physical mixture. The resin Amberlite®IRP 88 X-ray diffractogram displayed diffused peak due to their amorphous state in Figure 6.

The morphology

Scanning electron microscopy (SEM) images of MC, Amberlite®IRP 88 resin, MR, and MC resin physical mixture were presented in Figure 7. It appeared that the drug crystals size range from 1-2 μm to even more than 100 μm in size (Figure 7c). The Amberlite IRP 88 resin is irregular in shape and appears as separate pieces (Figure 7d). The SEM image of physical mixture (Figure 7b) presents embedded particles of MC and Amberlite IRP 88 with a comparable morphology to pure components, which reveals no apparent interaction between both species in the solid state. After forming resin-complex, the morphology MR (Figure 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.

Optimization of Formulation

LH-21, CEOLUS® PH-301, Pearlitol® 300DC were chosen as the excipients, sodium stearyl fumarate (PRUV®) was used as the lubricant to prepare the orally disintegrating tablets and 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 time was set as response variables. The response surface and contour plots of disintegration were obtained by origin 8.0 and demonstrated in Figure 8. The plot of response surface and contour indicates that disintegration time decreases with increase in porosity at the same MCC/Man ratio. It 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

ratio of 0.75. Consequently, the combination of Man and MCC showed the desired flow ability, compressibility and rapid disintegration.

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

The 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 conditions of storage, transformation or handling but they should also have no problem in disintegrating or dissolving. It is generally recognized that the sufficient hardness would be 2 kP or higher. In addition, the desirable oral disintegration time would be generally 30 s or shorter in case of orally disintegrating tablets. The desirable disintegration time was 25 s, the contour plots shows 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. MCC/Man ratio was at 0.75, tablets were prepared at 3 kP with disintegration time of 18 s.

Dissolution Study

Drug release from the drug resin complex depends on the environment pH and ionic strength within the gastrointestinal tract, as well as 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, the drug release in the simulated saliva (pH 6.8) was also

studied.

The dissolution profile (Figure 9) of mosapride from the MR-ODT in varies pH aqueous solution indicated that mosapride was released rapidly and completely at solution 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 even in 30 min at solution of pH > 5.5. All the results demonstrated that release of drug from the tablets was strongly pH dependent. The pH dependence of mosapride release from the complex could decrease drug dissolution in the mouth cavity, whereas immediately releasing in the stomach (20). At pH 6.8 (salivary pH) and the drug release was delayed and it is effective for taste masking. Amberlite® IRP88 is a weak acidic, potassium form cation-exchange resin (21). The high affinity of Amberlite® IRP88 to hydrogen ions can yield fast desorption of bound ions when they were exposed to an acidic environment such as the stomach (22).

The dissolution profile of MR-ODT in simulated saliva is presented in Figure 10 and MC-ODT was used as a reference tablet. In four minutes, the drug released from MR-ODT and MC-ODT 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 would be investigated in future time.

Conclusion

In this study, the resin complex and orally disintegrating tablets using mannitol, L-HPC and MCC as excipients were successfully produced. Differential scanning calorimetry, X-ray diffraction and scanning electron microscopy demonstrated the forming of complex and

indicated the drug was dispersed evenly into the resin to form resine complex and showed some disappearance of crystalline. The oral disintegrating tablet disintegrated within 18 s. This oral disintegrating tablet can be used as potential drug delivery systems of mosapride citrate, especially for the pediatrics, geriatrics and patients with swallowing difficulties.

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Conflict of interest

The authors report no declarations of interest.

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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