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Preparation and Evaluation of Ketoprofen Hot-Melt Extruded Enteric and Sustained-Release Tablets

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Hot-melt extruded tablets with enteric and sustained-release properties were prepared using ketoprofen as a model drug and Eudragit® L100 as the carrier. Ketoprofen, with a similar solubility parameter to Eudragit® L100, was homogeneously dispersed in the polymer matrix in a non-crystalline state, and was identified by differential scanning calorimetry, X-ray diffraction, and scanning electron microscopy analysis. To compare the enteric and sustained-release characteristics, tablets of physical mixtures and comminuted extrudates were also produced with a tensile strength of 5.0 kg/cm^2. The drug release percentage was below 3% in 0.1 M HCl and a sustained release for 6 to 12 hours was obtained with the tablets prepared by direct cutting of the extrudates and by compressing the pulverized extrudates, while no enteric and sustained-release properties were exhibited by the physical mixture tablets. The release mechanisms of the two types of tablets from their extrudates were different only because of their porosity. For the cut tablets, the drug was released according to the erosion mechanism, whereas in the extruded tablets the release property was controlled by erosion and diffusion mechanisms simultaneously.

Keywords hot-melt extrusion; enteric; sustained-release; ketoprofen

INTRODUCTION

Ketoprofen, a non-steroidal anti-inflammatory drug (NSAID) usually used for the treatment of inflammation, pain, or rheumatism (Chi & Jun, 1990), is known for its harmful side effects in the gastrointestinal tract. Stomach bleeding is a severe side effect that occurs frequently because of the acidity of ketoprofen. As such, it is desirable to produce enteric preparations of ketoprofen to reduce the amount released in the stomach. Meanwhile, frequent administration of the drug is necessary to maintain therapeutic plasma concentrations because the half-life of the drug is only 2 to 3 hours (Ahn, Kim, & Kim, 1998; Liversidge, 1981; Takayama & Nagai, 1991), which adversely affects patient compliance. Therefore, it would be ideal to have a preparation with enteric and sustained-release properties. Unfortunately, although various methods have been used to produce a sustained-release ketoprofen dosage form, an enteric effect with less than 10% of the drug being released in acidic conditions is not always easily obtained. An 8- to 12-hour controlled-release dosage form is the most common one available, such as sustained-release Ibifen® tablets and Orudis® retard capsules (Roda, Sabatini, Mirasoli, Baraldini, & Roda, 2002). If the release rate is less than 10% under acidic conditions, incomplete dissolution may occur under basic conditions within 12 hours since the solubility of the slow-release materials is non-pH dependent. Also, the use of the enteric polymer alone seems to be infeasible because of the high solubility in the basic intestinal fluid. Hence, a combination of sustained-release material and enteric polymer in the matrix or coated layer is needed. To investigate the optimal ratio of the two components complying with the above-mentioned requirements, complicated formulation studies need to be carried out, which researchers have often found to be extremely tedious. Is it possible to prepare an enteric matrix tablet with a super compact and imperforate structure that can resist the rapid penetration of medium under basic conditions, thereby providing the tablet simultaneously with enteric and sustained-release characteristics? Although it is known that holes exist in all tablets, even if they are produced under high pressure, if the distance between the drug and carrier reaches a minimum, that is, that they are in contact with each other at the molecular level, the holes will disappear.

It is an exciting prospect that this may actually be the case when the hot-melt extrusion technique is used. As a mature processing technology, hot-melt extrusion has been used for many years in the plastic, rubber, and food industries. Recently, pharmaceutical scientists have attempted to use this method to improve the dissolution of poorly water-soluble drugs (Hülsmann, Backensfeld, Keitel, & Bodmeier, 2000;

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Nakamichi, Nakano, & Yasuura, 2002; Perissutti, Newton, Podczeck, & Rubessa, 2002; Six et al., 2003; Verreck et al., 2003), to produce controlled-release dosage forms (Crowley, Schroeder, et al., 2004; De Brabander, Vervaet, & Remon, 2003; Follonier, Doelker, & Cole, 1994; Fukuda, Peppas, & McGinity, 2006; Liu, Zhang, & McGinity, 2001; Mehuys, Remon, & Vervaet, 2005; Mehuys, Vervaet, & Remon, 2004; Nakamichi et al., 2001), and to prepare films (Crowley, Fredersdorf, et al., 2004; Prodduturi, Manek, Kolling, Stodghill, & Repka, 2004, 2005; Repka, Gutta, Prodduturi, Munjal, & Stodghill, 2005; Repka & McGinity, 2001). During hot-melt extrusion, the drug and polymer are melted, kneaded, and pressurized at the molecular level, then the homogeneous melt is extruded, and after cooling at an ambient temperature, a compact, even imperforate solid is obtained. Compared with traditional technologies, this process is solvent-free, continuous, and economical in terms of time and money and an excellent mixing is obtained (Breitenbach, 2002). Moreso, its simplicity on an industrial scale makes it popular with pharmaceutical manufacturers.

In this study, the hot-melt extrusion technique was used to prepare ketoprofen enteric and sustained-release tablets. Eudragit® L100, a widely used enteric polymer, was selected as the drug carrier.

MATERIALS AND METHODS

Materials

Ketoprofen was purchased from Hubei Wuxue Pharmaceutical Company (Hubei, China). Eudragit® L100 was kindly provided by Röhm (Germany); all other reagents were of analytical grade.

Methods

Preparation of the Physical Mixture

Three formulations were designed with drug-to-polymer ratios of 1:1, 1:1.5, and 1:2, respectively. Diethyl phthalate (DEP) was used as the plasticizer to reduce the processing temperature. The components of each formulation were weighed as shown in Table 1. The Eudragit® L100 was pre-plasticized with DEP by kneading in a mortar and was then mixed with ketoprofen by hand in a polyethylene bag for 10 minutes to obtain a uniform mixture.

TABLE 1
The Formulation of Ketoprofen for Hot-Melt Extrusion

	1	2	3
ketoprofen	1	1	1
Eudragit® L100	1	1.5	2
DEP	0.1	0.3	0.6

Preparation of the Solid Dispersion by Hot-Melt Extrusion

Solid dispersions composed of ketoprofen and Eudragit® L100 were prepared by hot-melt extrusion using a co-rotating twin-screw extruder, TE-20 32:1 (Coperion Keya Co., China), according to Table 1, and DEP was employed as the plasticizer to reduce the processing temperature. The screw configuration consisted of a hopper, barrel, die, kneading screw, and heaters distributed over the entire length of the barrel. The materials introduced into the hopper were carried forward by the feed screw, kneaded under high pressure by the kneading screw, and then extruded from the die. The feeding and screw rates were fixed at 40 rpm. The temperatures were set at 100°, 130°, 130°, 130°, and 135°C from feeder to die. The extrudates were collected after cooling at ambient temperature.

Preparation of the Three Types of Tablets

The cooled extrudates were manually cut into tablets weighting about 420, 560, and 720 mg so that the drug content of each was 200 mg. The same weight of physical mixture was compressed into tablets of 5.0 kg/cm^2 tensile strength using a TDP-50 single punch tablet press (Shanghai Tianfan Pharmaceutical Machine Co., Ltd). The extrudates were then crushed to obtain powders less than 80-mesh (0.18 mm) and these were then compressed into tablets of 5.0 kg/cm^2 tensile strength.

Density Test

A density test was performed to reflect the porosity indirectly. The three kinds of tablets were used as a cylinder or disc and the density was determined according to the following equations:

$$\rho = m / v \quad v = \pi d^2 h / 4$$

where ρ, m, v, d, and h represent the density, mass, volume, diameter, and height of the tablets, respectively.

Thermal Analysis

The thermal stabilities of ketoprofen and Eudragit® L100 were determined using a thermal gravimetric analyzer (TGA 50, Shimadzu). Ultrahigh-purity nitrogen was used as the purge gas at a flow rate of 150 mL/min. Samples were analyzed using a heating rate of 5°C/min from 30° to 300°C. Plots of weight versus temperature were recorded.

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of the polymer, drug, physical mixtures, and hot-melt extrudates. The DSC analysis was carried out on a DSC 60 differential scanning calorimeter (Shimadzu). Ultrahigh-purity nitrogen was used as the purge gas at a flow rate of 150 mL/min. Samples were weighed to 10 ± 5 mg, crimped in hermetic aluminum pans with lids, and analyzed using a heating rate of 5°C/minute from 30° to 300°C. Plots of heat flow versus temperature were recorded.

Powder X-Ray Diffraction Analysis

The powder X-ray diffraction profiles were obtained using an X-ray powder diffractometer (type D/Max-2400, Rigaku Instrument, Japan). The samples were exposed to CuKa radiation under 56 kV and 182 mA over the 2-theta range from 3° to 45°C at increments of 0.5º/minute every 0.04°. The extrudates were ground into a fine powder before analysis.

Scanning Electron Microscopy (SEM) Analysis

Scanning electron microscopy was used to study the surface morphology of the hot-melt extrudates. The samples were mounted on an aluminum stage using adhesive carbon tape and placed in a low humidity chamber prior to analysis. Scanning electron microscopy was performed using a Hitachi Tabletop Microscope operated at an accelerating voltage of 15 kV.

Dissolution Tests

The drug release properties of the tablets were determined using a ZRS-8G dissolution apparatus according to the dissolution test method one as described in the British Pharmacopoeia (BP) with a basket rotation speed of 100 rpm. The dissolution medium was maintained at 37°C throughout the test. In the first 2 hours 750 mL 0.1M HCl was used to simulate the gastric fluid without pepsin. After 2 hours, the pH of the medium was increased to 6.8 by the addition of 250 mL 0.2 M sodium triphosphate buffer to simulate the intestinal juice without trypsin. Samples equivalent to 200 mg ketoprofen were added to the dissolution apparatus and test fluid was withdrawn at different times. Samples of the dissolution medium were passed through a 0.45-μm millipore filter and assayed for ketoprofen according to the BP 2002 edition by spectrophotometry and a UV wavelength of 260 nm (U2800, Hitachi Corp. Japan).

RESULTS AND DISCUSSION

Miscibility of Drug, Carrier, and Plasticizer

The solubility parameter has been used to evaluate the miscibility of drugs and ingredients. Greenhalgh, Williams, Timmins, and York (1999) demonstrated that compounds with $\Delta\delta_t < 7MPa^{1/2}$ were likely to be miscible while compounds with $\Delta\delta_t > 10MPa^{1/2}$ were likely to be immiscible, while Forster, Hempenstall, Tucker, & Rades (2001) have pointed out that good miscibility occurs when $\Delta\delta_t < 2MPa^{1/2}$. The solubility parameters of ketoprofen, Eudragit® L100, and DEP were 21.99, 21.36, and 20.22, respectively, calculated based on the Hoftyzer/Van Krevelen method (Van Krevelen, 1990). A favorable miscibility can thus be determined. To maintain the current of the motor, the ratio of plasticizer to Eudragit® L100 decreased as the ketoprofen content increased, which meant that the drug can also play the role of plasticizer due to its good miscibility with Eudragit® L100.

Hot-Melt Extrusion Process

There are two ways to produce enteric preparation; one is coating and the other is mixing the drug with enteric carrier. Mehuys and colleagues (2005) premixed enteric coating polymer with plasticizers and extruded them into hollow cylinders. The hollow pipes were filled with a model drug and both open ends of the cylinders were closed, yielding hot-melt extruded enteric capsules. This is a time-consuming process that is difficult to manage in an industrial setting. So, in this experiment, the other way was utilized to prepare enteric tablets by hot-melt extrusion. As can be seen from the result, this process is simple and excellent enteric effect was obtained. Furthermore, sustained-release characteristics were exhibited when the tablet entered the analogical intestinal juice.

Thermal Analysis

Ketoprofen and Eudragit® L100 are thermally stable under 180°C, as can be seen in Figure 1. The pure ketoprofen exhibited a melting peak at about 95°C,which can be detected in the three ratios of the physical mixtures without DEP, but this had subsequently disappeared in all the extrudates (Figure 2), indicating the formation of solid dispersions. However, when DEP

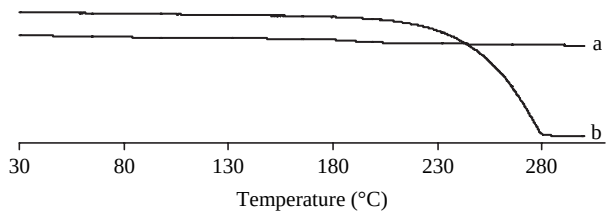

FIGURE 1. The TGA thermograms of Eudragit® L100 and ketoprofen: (a) Eudragit® L100; (b) ketoprofen.

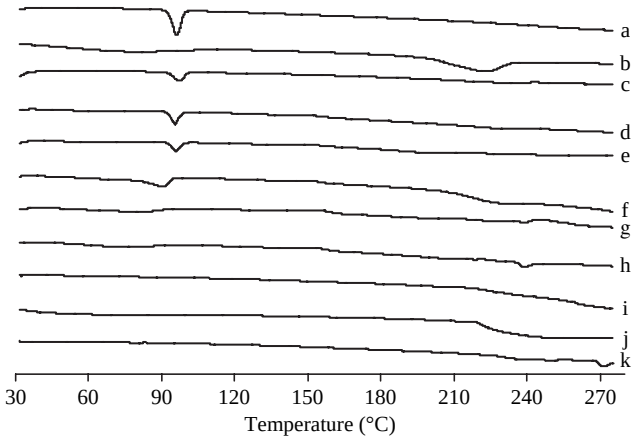

FIGURE 2. DSC thermograms of ketoprofen-Eudragit® L100 systems: (a) ketoprofen; (b) Eudragit® L100; (c) 1:1 physical mixture without DEP; (d) 1:1.5 physical mixture without diethyl phthalate; (e) 1:2 physical mixture without DEP; (f) 1:1 physical mixture; (g) 1:1.5 physical mixture; (h) 1:2 physical mixture extrudate; (i) 1:1 extrudate; (j) 1:1.5 extrudate; (k) 1:2 extrudate.

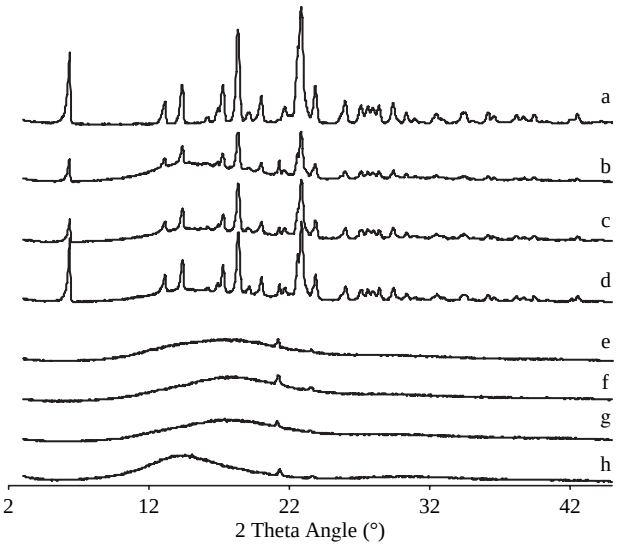

FIGURE 3. Powder XRD patterns of ketoprofen-Eudragit® L100 systems: (a) ketoprofen; (b) 1:1 physical mixture; (c) 1:1.5 physical mixture; (d) 1:2 physical mixture; (e) 1:1 extrudate; (f)1:1.5 extrudate; (g) 1:2 extrudate; (h) Eudragit® L100.

was added to the physical mixtures according to Table 1, the endothermal peak of ketoprofen was reduced or even disappeared entirely. Compared with ketoprofen, Eudragit® L100 melts at a higher temperature, but the glass transition point can be reduced by DEP. As a result, drug and carrier melt almost simultaneously at the elevated temperature in the DSC tests, which is similar to the melting method and leads to the partial formation of solid dispersions.

Powder X-Ray Diffraction

The X-ray diffraction patterns of ketoprofen, Eudragit® L100, physical mixtures, and extrudates are presented in Figure 3. Pure ketoprofen showed numerous distinctive peaks (Figure 3a) at 6.3, 13.1, 14.4, 17.3, 18.4, 20.0, 22.9, 23.9, 26.0, and 29.4°C, which indicated the high crystallinity of the drug. As an amorphous polymer, Eudragit® L100 only exhibited two slender peaks at 21.3° and 23.7°C. The diffraction patterns of the physical mixtures with apparent peaks were similar to that of the pure drug, suggesting the simple mixing of drugs and carriers. As far as the extrudates were concerned, no drug peaks can be seen. Since powder X-ray diffraction is a sensitive technique for crystals, it can be concluded that ketoprofen is dispersed in an amorphous or molecular state in Eudragit® L100.

SEM

SEM was used to examine the surface morphology of the preparations. The particle morphology of ketoprofen can be observed in the SEM micrographs in Figure 4a. The extrudates

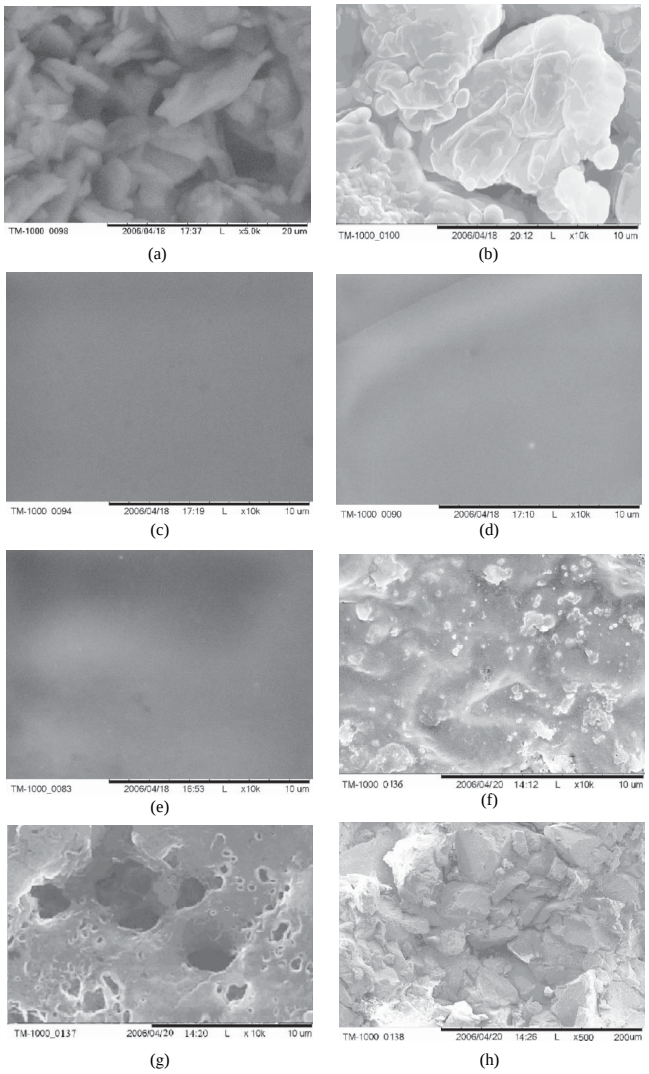

FIGURE 4. SEM micrograph of the morphology for ketoprofen-Eudragit® L100 systems (×10,000): (a) pure ketoprofen (×5,000); (b) 1:2 physical mixture tablet; (c) 1:1 extrudate; (d) 1:1.5 extrudate; (e) 1:2 extrudate; (f) 1:2 extrudate after a 6-hour dissolution test in pH 6.8 PBS; (g) 1:2 tablet using the pulverized extrudate after a 6-hour dissolution test in pH 6.8 PBS; (h) 1:2 tablet using the pulverized extrudate before dissolution (×500).

exhibited clear and homogenous surfaces at various ketoprofen levels (Figure 4c–4e). However, there are apparent drug crystals in the micrographs of the tablets from physical mixtures. These results agree with the DSC and X-ray analysis results, confirming the non-crystalline state of the drug in the extrudates.

Density Test

Porosity is an important parameter for a sustained-release matrix formulation. For the simple purpose of comparing different preparations, the specific value of the porosity is not

TABLE 2
The Density of Three Types of Preparations (n = 3)

	Tablets from Extrudates	Tablets from Pulverized Extrudates	Tablets from Physical Mixtures
Formulation 1	1.06 ± 0.02	0.94 ± 0.03	0.81 ± 0.01
Formulation 2	1.07 ± 0.04	0.91 ± 0.02	0.89 ± 0.04
Formulation 3	1.10 ± 0.01	0.95 ± 0.05	0.85 ± 0.03

needed. Accordingly, the density method was used to evaluate the porosity and avoid the toxicity associated with the mercury injection method. It is obvious that there was a negative correlation between density and porosity for the preparations produced from the same formulation. The density of the three kinds of tablets is listed in Table 2.

It can be inferred that the porosity order of the tablets, from smallest to greatest, is tablets from extrudates; tablets from pulverized extrudates; then tablets from physical mixtures, because of the reverse sequence of the density. Tablets from the extrudates were compact and hard. In fact, their tensile strength was so high that they remained intact even when the indicating pointer of the hardness meter (Shanghai Huanghai Pharmaceutical Test Instrument Company) reached the top of the scale. There was clear porosity in the SEM micrographs of the tablet from the physical mixture (Figure 4b) and the tablet from the pulverized extrudates (Figure 4h), but no porosity was seen in the SEM micrographs of tablets from the extrudates (Figure 4c–4e). So, it appears that the extrudates are compact and aporous solids.

Dissolution Test

Dissolution profiles of tablets from the physical mixtures are shown in Figure 5. No enteric or sustained-release characteristics can be seen with a drug release above 10% in the first 2 hours in 0.1 M HCl solution and 100% drug release in the following hour in pH 6.8 PBS. As far as the tablets from extrudates are concerned (Figure 6), less than 1% of the drug was released in 0.1 M HCl solution, showing the enteric function of the extrudates. Ketoprofen was released slowly in the hours that followed from the extrudate tablets, and there was a difference between the extrudate of formulation 3 and that of formulation 2 or formulation 1. Drugs exhibited sustained release for 6, 7, and 9 hours from formulation 1, 2, and 3, respectively, in pH 6.8 PBS. The dissolution profile of the tablet from formulation 3 extrudate has been simulated with the use of conventional models (Table 3). The highest related coefficient, the Ritger-Peppas equation, seemed to be suitable. In this case, the value of n was 0.92, exceeding 0.89, and indicating that the release mechanism is matrix erosion. To confirm this, the extrudate of formulation 3 was removed from the dissolution cup after a 6-hour dissolution in pH 6.8 PBS, dried in a vacuum, and analyzed by SEM. The uneven surface swirl induced by the washing of the fluid can be seen in Figure 4f, as well as the erosion fragment. However, no holes due to medium penetration or drug release were found. These results are compatible with the extremely compact and hard structure of the extrudate, which is a major barrier to the permeation of water. So, the only way to release the drug left is by denuding the surface layer by layer.

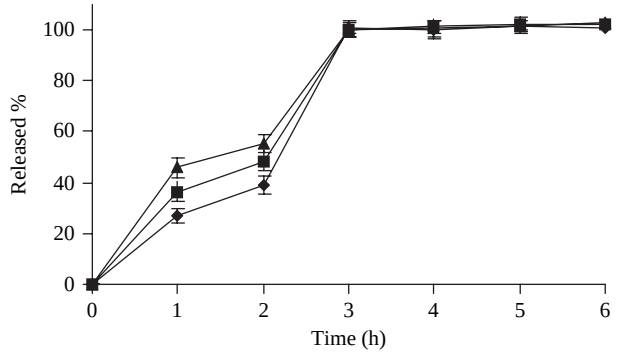

FIGURE 5. Dissolution profiles of ketoprofen-Eudragit® L100 physical mixture tablets in 0.1 M HCl for the first 2 hours, then in pH 6.8 PBS for subsequent hours ($M \pm SD$, n = 6).

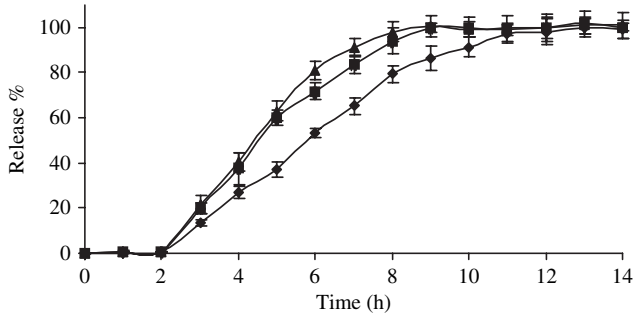

FIGURE 6. Dissolution profiles of ketoprofen-Eudragit® L100 tablets from extrudates in 0.1 M HCl for the first 2 hours, then in pH 6.8 PBS for subsequent hours ($M \pm SD$, n = 6).

TABLE 3
Simulated Model for the Release Profile of Ketoprofen-Eudragit® L100 1:2 Extrudate

Model	Equation	r
Zero-order	$Q = 0.1087t + 0.0686$	0.9879
First-order	$\ln(1 - Q) = -0.4048t + 0.6446$	0.9586
Hixson-Crowell	$(1 - Q)^{1/3} = 0.3105 - 0.0362t$	0.9879
Higuchi	$Q = 0.4477t^{1/2} - 0.3481$	0.9945
Baker-Lonsdale	$3/2\ [1 - (1 - Q)^{2/3}] - Q = -0.063t + 1.0872$	0.9922
Ritger-Peppas	$\ln Q = 0.9217 \ln t - 1.9601$	0.9963

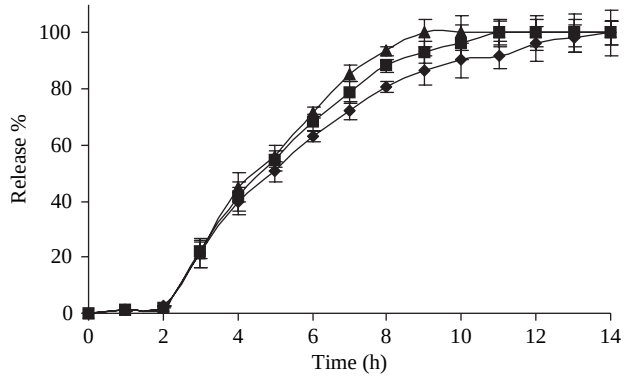

FIGURE 7. Dissolution profiles of ketoprofen-Eudragit® L100 tablets using pulverized extrudates in 0.1 M HCl for the first 2 hours, then in pH 6.8 PBS for subsequent hours ($M \pm SD$, $n = 6$).

Figure 7 shows the dissolution profiles of tablets from pulverized extrudates. When exposed to 0.1 M HCl solution, no more than 3% of the drug is released within 2 hours. Then, in pH 6.8 PBS, there is prolonged release of drug for 7, 9, and 12 hours, respectively, from formulation 1 to formulation 3. Compared with tablets of extrudate from the same formulations, only a little more drug is released in 0.1 M HCl solution while a similar quantity or less drug is released in pH 6.8 PBS. It was surprising that the slow release time of tablets from pulverized extrudates is longer than that of tablets from extrudates because the former have a looser structure with lots of holes, as can be seen in the SEM micrograph in Figure 4h. If the same mechanism controls the release of tablets from pulverized extrudates, that is, erosion, the dissolution rates should be faster than that of tablets from extrudates with regard to the rapid medium penetration rate because of the higher number of holes. Thus it can be deduced that both erosion and diffusion control the drug release from pulverized extrudate tablets, which can be confirmed by the exponential term of the Ritger-Peppas equation. Formulation 3 was simulated by conventional models (Table 4) for its longer sustained-release time. Unfortunately, it does not fit the Ritger-Peppas equation but is first-order release, which does not allow a release mechanism to be identified. So the tablet was removed from the dissolution cup after a 6-hour dissolution in pH6.8 PBS, dried in a vacuum, and analyzed by SEM. Besides the erosion, trace showed the diffusion holes extensively distributed in Figure 4g, suggesting that two mechanisms of drug release are involved. This is due to the particular structure of the tablets of pulverized extrudate, which are composed of numerous 80-mesh no-porosity particles with tiny crevices between particles. When placed in 0.1 M HCl solution, the rapid permeation of HCl solution into the crevices leads to a greater release rate of drug because of the greater contact surface compared with the tablet from the extrudate. When the medium pH value was changed to 6.8, the carrier dissolved. Although the holes permitted access of the basic medium, the amount was too small for the polymer to dissolve completely. Moreover, the polymer often undergoes swelling before dissolving (Miller-Chou & Koenig, 2003; Van Krevelen, 1990). So, sufficient space is needed for the unfolding of the polymer chains, but the crowded configuration in the tablet from the extrudate makes this impossible. Consequently, restricted by the solvent and space, the partially unfolded macromolecular chains of Eudragit® L100 are wound together loosely and form a gel layer enclosing the periphery of each particle, into which the medium comes in contact. This is another barrier to drug release since it has to permeate the gel layer before passing through the cracks between particles, reaching the surface of the tablet, and entering the bulk solution. Therefore, the dissolution rate in pH 6.8 PBS is slower in comparison with that of the tablet from the extrudate.

TABLE 4
Simulated Model for the Release Profile of Ketoprofen-Eudragit® L100 1:2 Tablet Using Pulverized Extrudate

Model	Equation	r
Zero-order	$Q = 0.0797t + 0.2546$	0.9623
First-order	$\mathrm{Ln}\,(1 - Q) = -0.3195t + 0.2086$	0.9921
Hixson-Crowell	$(1 - Q)^{1/3} = 0.7454 - 0.0797t$	0.9620
Higuchi	$Q = 0.3506t^{1/2} - 0.0948$	0.9907
Baker-Lonsdale	$3/2[1 - (1 - Q)^{2/3}] - Q = 0.0398t + 0.1273$	0.9627
Ritger-Peppas	$\ln Q = 0.6438 \ln t - 1.4236$	0.9887

CONCLUSION

Enteric and also sustained-release preparations can be produced by the HME technique. Drugs are dispersed in noncrystalline state in ketoprofen extrudates. The only difference in the release behavior between tablets from pulverized extrudates and tablets from extrudates is due to porosity. Tablets from extrudates release ketoprofen by means of the erosion mechanism, whereas the releasing behavior in tablets from pulverized extrudates came simultaneously through erosion and diffusion mechanisms.

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