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Hydrophilic Excipients Modulate the Time Lag of Time-Controlled Disintegrating Press-coated Tablets

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ABSTRACT

An oral press-coated tablet was developed by means of direct compression to achieve the time-controlled disintegrating or rupturing function with a distinct predetermined lag time. This press-coated tablet containing sodium diclofenac in the inner core was formulated with an outer shell by different weight ratios of hydrophobic polymer of micronized ethylcellulose (EC) powder and hydrophilic excipients such as spray-dried lactose (SDL) or hydroxypropyl methylcellulose (HPMC). The effect of the formulation of an outer shell comprising both hydrophobic polymer and hydrophilic excipients on the time lag of drug release was investigated. The release profile of the press-coated tablet exhibited a time period without drug release (time lag) followed by a rapid and complete release phase, in which the outer shell ruptured or broke into 2 halves. The lag phase was markedly dependent on the weight ratios of EC/SDL or EC/HPMC in the outer shell. Different time lags of the press-coated tablets from 1.0 to 16.3 hours could be modulated by changing the type and amount of the excipients. A semilogarithmic plot of the time lag of the tablet against the weight ratios of EC/SDL or EC/HPMC in the outer shell demonstrated a good linear relationship, with $r = 0.976$ and $r = 0.982$, respectively. The predetermined time lag prior to the drug release from a press-coated tablet prepared by using a micronized EC as a retarding coating shell can be adequately scheduled with the addition of hydrophilic excipients according to the time or site requirements.

KEYWORDS: micronized ethylcellulose, press-coated tablet, time lag, spray-dried lactose, HPMC, time-controlled disintegration, weight ratio.

INTRODUCTION

Direct compression is an accepted pharmaceutical manufacturing technique because of its many advantages such as low equipment costs, short processing time and limited steps, low labor and energy requirements, and use of nonsolvent processes.[1-2] Recently, this technique has been applied to prepare different solid dosage forms, such as fast-disintegrating tablets or controlled-release preparations.[3-4] Time-controlled release preparations have been extensively developed to achieve time- and/or site-specific release.[5-7] In order to achieve the chronopharmaceutical design for these time-controlled release preparations, currently formulation design to control the lag time is prior to the substantial release of drug.[8-9] Recently, a TIMERx technology with an erosion mechanism was developed to achieve the chronotherapeutic delivery system.[10]

Ethylcellulose (EC) is a well-known water-insoluble polymer that has long been used as a rate-controlling membrane in medication dosage forms to regulate drug release. EC can be dissolved or dispersed in different solvents by means of coating or granulating processes.[11-14] Several reports have directly addressed the use of EC as a directly compressible excipient in a controlled-release matrix or in an immediate-release tablet.[15-17] In our previous studies, EC powder with different micronized sizes has been directly compressed to form compact EC in which plastic deformation is the predominant consolidation mechanism.[18] Furthermore, the particle size of EC powder and the porosity in compact EC are the major factors that influence the uptake of water and the dissolution of drug from the compacted form.[19-20] Recently, the unique suitability of EC powders to act as an outer shell has also been explored to directly prepare the press-coated tablet with a special time-controlled rupturing function.[21] This function can be further and effectively controlled by modifying the compression force applied to the outer shell, the amount of outer shell used, and the excipients added to the inner core tablet.[22-23]

Many studies have reported that the type and amount of excipients used might affect the drug release profile of controlled-release tablets to influence the drug bioavailability.[24-26] Our previous study results have proven that the type of excipients in the inner core tablet might significantly influence the induction period of the time-controlled disintegration or rupture of a compression-coated tablet.[23] The purpose of this study was to investigate the influence of the type and amount of excipients mixed with micronized EC powder in the outer shell on the time-lag and time-controlled disintegrating or rupturing function of press-coated tablets. Two model excipients, spray-dried

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lactose (SDL) and hydroxypropyl methylcellulose (HPMC), were used. The highly water-soluble SDL might rapidly facilitate tablet disintegration, whereas HPMC belonging to a water-soluble polymer with the viscous property of gelation might delay the tablet disintegration. Sodium diclofenac was used as a model drug.

Materials and Methods

Materials

Micronized EC powder with a particle size of 4.6 μm (grade N-10-F) was kindly supplied by Shin-Etsu Chemical Industries Co, Ltd (Tokyo, Japan). The water content for this EC powder was less than 1.2%, as determined by means of thermal analysis. Sodium diclofenac (<80 mesh, water content <5%) was purchased from Syn-Tech Chemicals and Pharmaceuticals Co, Ltd (Taiwan, Republic of China). Two direct-compressible excipients, SDL (<100 μm, Dairy Crest Ltd, Surrey, England) and HPMC (60SH-4000, <50 μm, Shin-Etsu Chemical Industries, Tokyo, Japan), were used.

Preparation of Press-coated Tablets

The press-coated tablets were prepared by using a tablet press under constant pressure as described in our previous study.[22-23] An inner core of drug tablet (sodium diclofenac 100 mg, 7 mm in diameter) was previously direct-compacted at a pressure of 200 kg/cm^2 for 1 minute. Different weight ratios (wt/wt) of EC/excipient mixtures were previously prepared as follows: 280 mg/0 mg (100%/0%), 250 mg/30 mg (89.3%/10.7%), 200 mg/80 mg (71.4%/28.6%), 150 mg/130 mg (53.6%/46.4%), 100 mg/180 mg (35.7%/64.3%), and 0 mg/280 mg (0/100%). Each EC/excipient mixture (140 mg) was first filled into a die (diameter, 10 mm), and the inner core tablet was then manually placed in the center of the EC/excipient powder bed. The remaining EC/excipient powder (140 mg) was then poured onto the inner core tablet and compressed at a pressure of 300 kg/cm^2 for 1 minute to prepare the compression-coated tablet.

In Vitro Dissolution Study

The release of sodium diclofenac from the press-coated EC tablet was accomplished in distilled water (pH 5.6) with a USP dissolution paddle assembly at 100 rpm and a temperature of 37°C ± 0.5°C. The amount of drug release was measured at the suitable time interval and was then determined spectrophotometrically at 276 nm (UV-160 A; Shimadzu Co, Tokyo, Japan).[22-23] Cumulative percentage drug release was calculated using an equation obtained from a standard curve. The release studies were conducted in triplicate, the mean values were plotted vs time with standard deviations (SD) of less than 3%, indicating the reproducibility of the results.

Results and Discussion

Based on the concept of chronotherapy or chronopharmacology, recent pharmaceutical investigations have focused on developing a site- or time-controlled drug delivery system for the treatment of various diseases.[8-9] Drugs used for the ideal treatment of diseases should be administered only at the required time to maintain a therapeutic blood level. This reveals that the drug release behavior should be controlled by time rather than by rate. In order to achieve the development of chronopharmaceutical dosage forms, currently, the site- and/or time-controlled release preparation with a designated initial lag time phase without drug release followed by a rapid release phase has been investigated.[5-6,14] These preparations enable us to predict and reproduce the drug absorption at the predetermined time and/or site. For this purpose, various designed dosage forms including the time clock system and sigmoidal release systems have been developed by using various unique techniques and functional polymers or additives.[27-28]

The press-coating technique is one of the novel methods and has been applied for many drugs to develop the site- and/or time-controlled release preparation.[5,29] This technique has many advantages such as nonsolvent process, short processing time and limited steps, and low labor and energy requirements. We have used this technique to design a time-controlled disintegrating press-coated tablet by using micronized ethylcellulose (EC) as an outer coating shell.[21-23] In this study, we try to modulate the time lag of drug released from this time-controlled disintegrating press-coated tablet by adding the hydrophilic excipient into the outer coated layer.

It is well known that the addition of SDL can improve the flow and bond properties of other excipients during direct compression.[30-31] In particular, SDL with higher water solubility might also facilitate the disintegration and dissolution of solid dosage forms. Thus, SDL was used to mix with EC, not only to improve the flowability of the mixed powders but also to monitor the time lag and time-controlled disintegration of tablet. It should be noted that the drug released from core tablet (prepared by sodium diclofenac alone) without an outer shell was completed by changing its size within 35 minutes of dissolution course, since there was no barrier to delay the dissolution behavior. Figure 1 shows the dissolution profiles of press-coated tablets prepared by using different weight ratios of EC and SDL in the outer shell. The profiles clearly indicate that sodium diclofenac released from the press-coated tablet exhibited a unique release profile, depending on the amount of SDL used. This profile was composed of an induction period (time lag) followed by a rapid release phase. The drug was rapidly and completely released from the press-coated tablet after a lag period of several hours in the initial drug delivery profile, depending on the weight ratios of EC and SDL. The longest time lag was

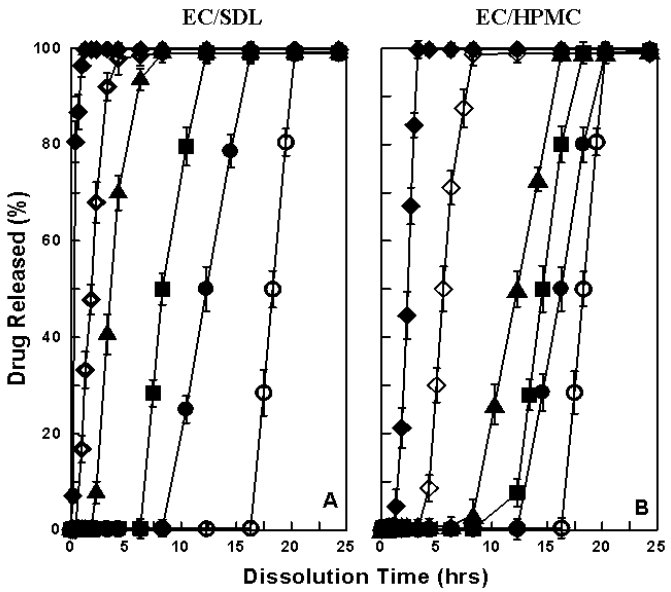

Figure 1. Dissolution profiles of sodium diclofenac from press-coated tablets prepared by using different weight ratios of EC with SDL or HPMC in the formulation of the outer shell. The weight ratios of EC/SDL or EC/HPMC mixture are ○, 100%:0%, ●, 89.3%/10.7%; ■, 71.4%/28.6%; ▲, 53.6%/46.4%; ◇, 35.7%/64.3%; and ◆, 0/100%. Values are the mean ± standard deviation (n = 3).

~16.3 hours for sodium diclofenac released from the SDL-free press-coated tablet, in which the outer shell of the press-coated tablet directly ruptured or broke into 2 halves to permit rapid drug release, similar to our previous studies.[22-23] The sudden splitting of the outer shell of press-coated tablets after the lag period is a key factor to achieve the time-controlled delivery. The drug was immediately released from a core tablet after rupturing the surrounding outer shell, caused by a pressure build-up within the core system. This was different from the TIMERx system in which the erosion of polysaccharide gums was the main mechanism.[9-10] Once SDL was added into the formulation of the outer shell, the time lag was shortened with the increase of the amount of SDL used. The order of the time lag changed according to the weight ratios of the EC/SDL mixture as follows: 35.7%/64.3% (0.67 hour), 53.6%/46.4% (1.83 hours), 71.4%/28.6% (6.3 hours), 89.3%/10.7% (8.3 hours), and 100%/0% (16.3 hours). The finding indicates that the time lag of the press-coated tablet can be modulated from 0.67 hour to 8.3 hours by the addition of amount of SDL. The drug delivery behavior once it started appears to be very comparable, since the time to deliver 5% ~ 90% of drug released is approximately 6 to 8 hours in each case except the outer shell formulation of EC/SDL with 35.7%/64.3%. This implies that SDL might possibly act as a solid pore-forming agent rather than a disintegrant for water penetration before rupturing the surrounding outer shell. This also suggests that when the requirement of a time-programmed therapeutic scheme is less than 8 hours, SDL can be formulated with EC in the outer shell of press-coated tablets to achieve this purpose.

Figure 2 shows the possible scheme of drug released from the compression-coated tablets prepared by EC, EC/SDL, or EC/HPMC in the formulation of outer shell. The release behavior of a press-coated tablet prepared by EC alone in the outer shell might be attributed to the medium penetration from the lateral surface of tablet to destruct the barrier shell, leading to a longer time lag.[21] Once the SDL was added into the formulation of the outer shell, however, the dissolution medium easily dissolved SDL and penetrated into the inner core through the pore of the outer shell formed by dissolved SDL. The drug was rapidly released from the inner core after rupturing the surrounding outer shell, since an inner osmotic pressure caused by dissolving drug was built-up within the core system.[23,32-33] Thus, a shorter time lag before a complete rupture or disintegration of press-coated tablet was proposed.

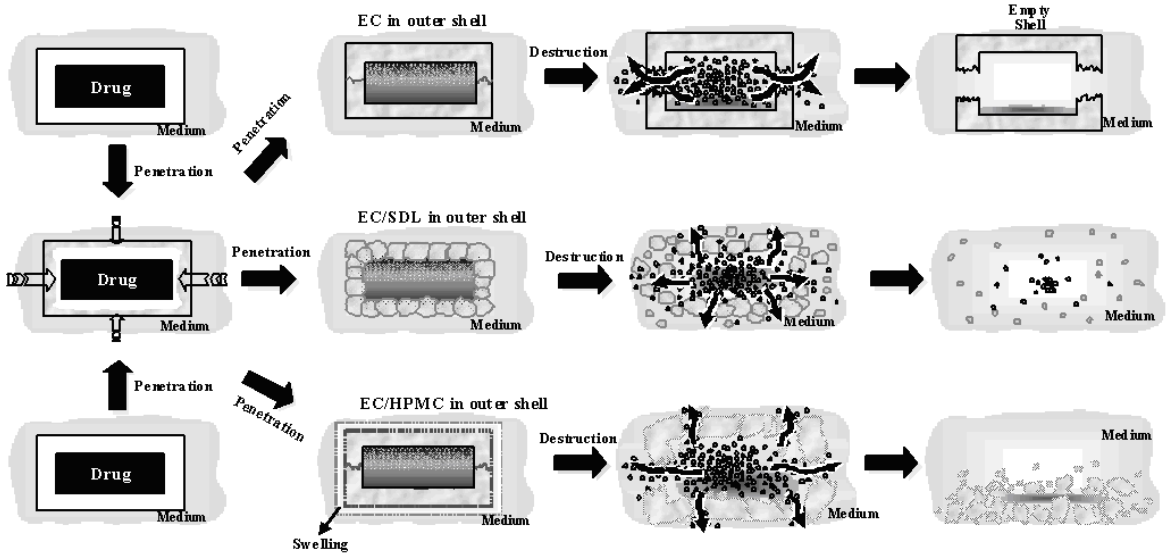

Figure 2. Possible scheme for drug release from the time-controlled disintegrating or rupturing press-coated tablet.

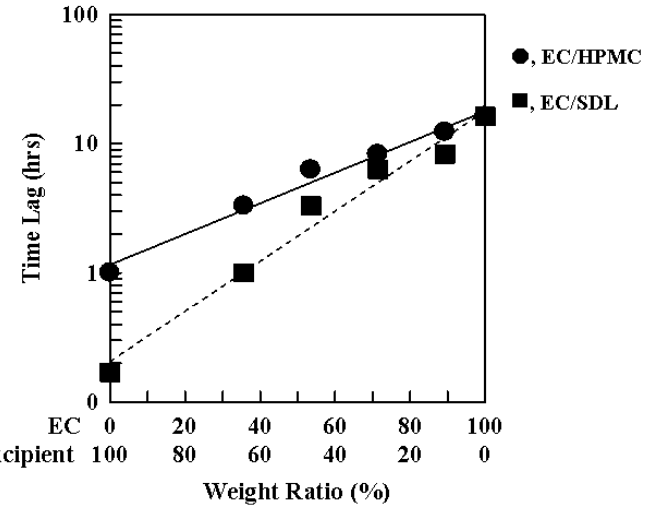

Figure 3. Relationship between the semilogarithm of the time lag of drug released from the press-coated tablet and the weight ratios of EC and SDL or EC and HPMC in the formulation of the outer shell.

Figure 1 also illustrates the release profiles of sodium diclofenac from the press-coated tablets prepared with different weight ratios of EC and HPMC in the outer shell. The dissolution profile was similar to that of the dissolution profile of EC/SDL, showing a distinctive induction lag followed by rapid drug release, which was consistent with other reports.[28,34] After the time lag, the outer shell of the press-coated tablet ruptured or broke into 2 halves to result in rapid drug release. The time lag was gradually shortened with the increase of HPMC in the formulation of the outer shell. It should be noted that another delay phase after the time lag was also found for the press-coated tablet containing a higher content of HPMC in the outer shell. This might be due to the time lag prior to drug release was controlled by the thickness and the viscosity of the gel layer of HPMC. After erosion or dissolution of the HPMC gelling layer, a distinct onset for drug release was observed. The viscous HPMC gel deposited within and on the surface of press-coated tablets might somewhat prolong the time lag, as compared with that of the press-coated tablet prepared with EC/SDL in the outer shell. Figure 2 also shows the possible scheme for drug release from the press-coated tablets prepared by using EC/HPMC in the outer shell. The eroded flocculates were observed in the dissolution medium after rupturing the press-coated tablet, suggesting that both erosion and destruction mechanisms might be responsible for the time-controlled release mechanism.[35] Moreover, the driving force of internal osmotic pressure caused by dissolving drug after medium penetration through the pore-forming agent of HPMC also plays an important role to rupture the whole gelled tablet.[31,36] The mean time lag of the press-coated tablets containing 10.7%, 26.8%, 46.4%, or 64.3% of HPMC was ~12.3, 8.3, 6.3, or 3.3 hours, respectively. However, the time lag for EC-free or HPMC-free press-coated tablets was ~1.0 or 16.3 hours, respectively. The time lag of the press-coated tablet was obviously influenced by the amount of HPMC used.

To achieve drug release at a specific targeting site or at a definite time point, the outer shell of the press-coated tablet should have reliable tolerance in the GI tract before it is disintegrated or destroyed. Therefore, the time lag for the tolerance of a press-coated tablet is a key factor.[34] After the lag phase, the drug should be released quickly. The mean value (n = 3) of time lag of a press-coated tablet plotting semilogarithmically against the weight ratio of the EC and excipient in the formulation of outer shell is shown in Figure 3. The lag time was quite reproducible, since the difference among the lag times for each formulation was smaller than 0.2 hour. A good linear relationship was obtained between the semilogarithm of in vitro time lag and the weight ratios of EC/SDL or EC/HPMC in the outer shell. The equations for the EC/SDL and EC/HPMC formulations were as follows: *ln* (time lag) = 0.0446 (weight ratio) – 1.575 (r = 0.976) and ln [time lag] = 0.0273 [weight ratio] + 0.148 (r = 0.982), respectively. With the increase of the amount of SDL or HPMC in the outer shell, the time lag was decreased. It is evident that the time lag of press-coated tablets containing HPMC in the formulation of outer shell was longer than that of SDL; the different physico-chemical property of SDL or HPMC might be responsible for this result. The quick dissolution of SDL might improve more porous structure in the outer shell for medium penetration, leading to quick rupturing the press-coated tablet and resulted in shorter time lag prior to drug release, whereas the viscous gel layer of HPMC swollen on the whole tablet might delay the medium penetration to cause the prolongation of the time lag before drug release. However, the water-soluble function of HPMC might also increase the permeability of medium and therefore reduce the lag time.[37] From the linear equation, the time lag of press-coated tablet could be modulated by choosing the types and amount of excipient used in the outer shell to achieve the time-controlled destruction according to the time required or the site required. However, it should be noticed that the micronized EC still played an important role to monitor this time-controlled disintegrating or rupturing press-coated tablet.

In conclusion, time lag was controllable by varying the composition of the outer coating layer. The present study indicates that the time lag of the press-coated tablet can be suitably modulated by formulating the outer shell with micronized EC powders and SDL or HPMC.

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