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Dissolution kinetics and physical characterization of three-layered tablet with poly(ethylene oxide) core matrix capped by Carbopol

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Abstract

We have prepared poly(ethylene oxide) (PEO) tablets which have three-layered structure by direct compression. Carbopol (CP) was coated on both sides of the central PEO matrix which contains solid-dispersed nifedipine (NP) in PEG4000. For comparison, physical mixture of PEO with poly(ethylene glycol 4000) (PEG4000) solid dispersion was also prepared. The differential scanning calorimetry (DSC) thermogram and X-ray diffraction (XRD) pattern obtained after 4 weeks of storage indicated that the crystallinity of PEG4000 in solid dispersion only slightly increased upon aging during this storage period. The formation of crystalline domain of NP, PEO or sodium dodecyl sulfate (SDS) was not observed. CP layers decreased the surface area exposed to dissolution medium, and after swelling, they also covered the exposed side area of the tablet. It seems that swelling and morphological change of CP layers minimize the erosional release for rapidly erodible PEO200K (Mw 200,000) and change the NP release to a diffusion-controlled process. For PEO900K (Mw 900,000), initial release rate was slower than that of PEO200K, possibly due to the slower swelling and erosional release from the side of the tablet. Diffusional release seemed to be the dominating mechanism for the release of NP from PEO7000K (Mw 7,000,000) tablet. Physical mixture of PEO and CP delayed the release of NP remarkably. The increase in pH, ionic strength and buffer concentration of the dissolution medium decreased the release rate. The data obtained for capped and blended tablets were fitted using the power law equation to understand the release mechanism. These results provided some useful information on parameters which can be modulated in the design of a controlled release dosage form for NP.

Keywords: Nifedipine; Carbopol; Three-layered tablet; Controlled release; Swelling

1. Introduction

Modifying the rate and duration of drug release from dosage form may profoundly affect the clinical performance of the drug. Various methods have been designed and tested to achieve controlled release kinetics, such as film coating, multi-layering and using different polymer materials (Conte et al., 1993; Siepmann and Peppas, 2001; Kim and Fassihi, 2000). Using a hydrophilic polymer matrix to control the release of an active ingredient is one of the simple ways of formulating dosage form, and has been widely studied for various drug molecules with different hydrophilicity/hydrophobicity (Siepmann and Peppas, 2000; Tang et al., 2003; Maqqi et al., 2002). Variables such as physicochemical properties of drug and polymer such as solubility and molecular weight, relative ratio of polymer and drug content, morphology of the dosage form, degree of coating and incorporation of excipients have been evaluated on their effect on the release kinetics of the drug molecules (Huang et al., 2006; Wen et al., 2006; Tarvainen et al., 2004).

In this study, we have prepared a new type of tablet which has three-layered structure, using PEO and CP, and evaluated the feasibility as a controlled release system. CP was used as coating material on both sides of the central PEO matrix which contains solid-dispersed NP. Our design of the tablet was based on the expectation that CP can act as the viscous barrier material on the surface of the tablet and impede the diffusion of the water molecules into the central PEO matrix and the diffusion of NP out of the matrix. The slower swelling and dissolution of the PEO may retard the release of the NP, and sustained or controlled release could be obtained. Various factors such as the molecular weight of PEO, pH of the dissolution medium, ionic strength and buffer concentration were investigated for their effect on dissolution rate. The dissolution of NP from CP capped tablet was compared with that from physically blended tablet. The

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physical change of the solid dispersion (SD) with time was also studied by thermal analysis and X-ray powder diffraction.

As a model drug for the evaluation of the system, we have used NP, a calcium channel blocker which antagonises influx of calcium through cell membrane. It has poor water solubility, and often results in low and irregular bioavailability (Zajc et al., 2005). Sustained release formulations of the NP have been studied and shown to be effective in the treatment of mild to moderate hypertension and both stable and variant angina pectoris (Mehta et al., 2002; Chung et al., 1987). As once-daily formulation, osmotic pump system (gastrointestinal therapeutic system (GITS)) have been developed and used effectively in the treatment of stable angina pectoris. It is reported that the bioavailability of NP from this controlled release dosage form is higher about 20% than the conventional dosage form given three times daily (Grundy and Foster, 1996).

In this work, NP was incorporated into the central PEO matrix as a SD form. SD in PEG4000 was prepared by melting method, and the granules were made by grinding and sieving before incorporation into the PEO matrix. PEGs are widely used because of their hydrophilicity, low melting point and low toxicity (Ford, 1986). SD systems have been used widely in various formulations to increase dissolution rate and bioavailability of poorly water-soluble drugs (Bu and Erajuddin, 2000). It has been shown that water-soluble carriers can play an important role in dissolution characteristics of NP solid dispersions. SD with PEGs, poloxamer 407 and hydroxypropyl–beta-cyclodextrin in various mixing ratios were prepared by melting, solvent, and kneading methods in order to improve the dissolution of NP (Chutimaworapan et al., 2000). SD of NP in other hydrophilic carriers such as poly(vinyl pyrrolidone)–microcrystalline cellulose (MC), hydroxypropyl cellulose (HPC)–MC, HPMCP and HPMC markedly enhanced the dissolution rate and efficiency of NP (Chowdary and Ramesh, 1994; Yan et al., 2000). The nature and solid-state properties of a SD system of NP in a polymer matrix were characterized using X-ray diffractometry (XRD), differential scanning calorimetry (DSC) and diffuse reflectance infrared Fourier transform spectroscopy (Vippagunta et al., 2002).

We chose PEO as the central hydrophilic matrix material containing drug molecules. PEO resins are non-ionic, high molecular weight and water-soluble polymers with no toxicity or irritancy (Dhawan et al., 2005a,b). The PEOs have a molecular range from $\sim 1 \times 10^5$ to 7×10^6 and the average number of oxyethylene groups is ~2000 to more than 100,000. PEOs are completely soluble in cold and warm water. The viscosity of aqueous solution of PEO resin depends on the molecular weight, concentration and temperature. The well-known properties of PEO and its regulatory acceptability have helped extend this polymer's application to various drug delivery systems (Dhawan et al., 2005a,b). They have been extensively studied as a polymer material for controlled release and several oral drug delivery systems are already in the market (Sawada et al., 2004; Luber and Bunick, 2003). PEO hydrogels also have been applied to biomaterials because of their good biocompatibility (Alexandre, 2003).

CP was used as the coating material on both sides of the central PEO matrix to provide gel layer which may act as the rate controlling membrane. CP polymers are poly(acrylic acid)s cross-linked with polyalkenyl ethers or divinyl glycol. They swell in water up to 1000 times their original volume to form a gel when exposed to a neutral pH environment, due to the ionization of carboxyl group (the pK_a is less than 6.0). CP polymers have been used in a wide range of pharmaceutical applications including controlled release, bioadhesion in biomembrane and thickening in topical formulations (Khan and Jaibai, 1998). Many oral formulations of CP exhibited zero-order and near zero-order release kinetics (Lehr et al., 1990). CP polymers are effective at low concentrations (less than 10%) and show rapid gelation characteristics (Perez-Marcos et al., 1991).

2. Materials and methods

2.1. Materials

NP was purchased from Sigma Chemical Co. (St. Louis, MS, U.S.A.). CP 971P-NF and 934P-NF were provided by BF Goodrich Co. (Cleveland, OH, U.S.A.) and PEOs (200 K, 900 K, and 7000 K) were provided by Union Carbide Co. (Danbury, CT, U.S.A.). Materials for the dissolution medium ($NaH_2PO_4 \cdot 2H_2O$, KH_2PO_4 and NaCl), sodium dodecyl sulfate (SDS) and polyethylene glycol (PEG) 4000 for the preparation of solid dispersion were purchased from Duksan Pure Chemical (Seoul, Korea). Single use syringe filter (RC membrane, 0.45 μm) was purchased from Sartorius (Goettingen, Germany). Stainless steel punch and die tool for tablet compression were made by the shop in KRICT (Daejeon, Korea).

2.2. Preparation of solid dispersion of NP

In order to increase the dissolution rate and possibly the bioavailability, SD of NP was made by melt methods, using PEG4000 as the carrier material. After PEG4000 was melted in oil bath at 100–120 °C, NP and small amount of SDS were added to this melt with continuous stirring. This mixture was quickly cooled by placing in an ice bath for 2 h. SDS was added to increase the wettability of NP in the dissolution medium, and to increase the dissolution rate. After solidification, the solid dispersion was dried in desiccator at room temperature for 24 h. Solid dispersion was then pulverized using mortar and pestle, sieved by 355 μm sieve and stored in desiccator until use. The ratio between PEG4000, NP and SDS was 25:1:3. Because NP is a highly photosensitive drug that requires restricted protection from light during manufacturing, storage and handling of its dosage forms, all experiments including the preparation of the tablet were performed in dark condition (Bayomi et al., 2002).

2.3. Preparation of CP capped three-layered NP-PEO matrix tablet

NP-PEO matrix tablet was prepared by direct compressing method using stainless steel punch and die tool (Fig. 1). Solid

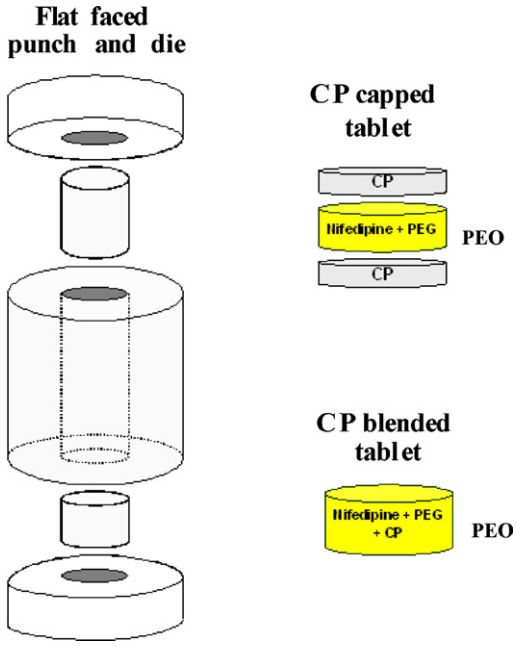

Fig. 1. Schematic diagram of punch and die used for the preparation of tablet.

dispersion particles containing 10 mg of NP was mixed with 100 mg of PEO (PEO 200 K, 900 K or 7000 K) and compressed into tablet at the pressure of 40 Mpa/cm^2. CP layer formation on both sides of the tablet was accomplished by filling the die with tablet and measured amount of CP on top of it manually and compressing at the same pressure. To compare the in vitro release characteristics, physical mixture of CP with PEO and solid dispersion (CP blended tablet) was also prepared by mixing CP with solid dispersion particles containing 10 mg of NP and PEO, and compressing using the same tool. Composition of the PEO matrix tablet is shown in Table 1.

2.4. Analysis

The determination of NP concentration in sample solution was made using a HPLC system (Shimadzu, Kyoto, Japan) and UV/vis spectrophotometer (Pharmacia U-400, Sweden) at 340 nm. The column used was LiChroCART.RTM. 125-4, 4 mm × 125 mm, 5 μm (Merck, Darmstadt, Germany). The mobile phase contained 0.1 M KH_2 PO_4 (pH 4.0):CH_3CN = 48:52 (v/v) and the flow rate was 1.0 ml/min.

Table 1
Composition of the PEO tablets (T1, T2 and T3), tablets capped with CP on both sides of the core PEO matrix (C1, C2 and C3) and blended tablets (physical mixture of PEO and CP) (B1, B2 and B3)

Tablet	Poly(ethylene oxide)			Carbopol	
	200 K	900 K	7000 K	Capping	Blending
T1	100 mg				
C1	100 mg			20 × 2 mg	
B1	100 mg				40 mg
T2		100 mg			
C2		100 mg		20 × 2 mg	
B2		100 mg			40 mg
T3			100 mg		
C3			100 mg	20 × 2 mg	
B3			100 mg		40 mg

2.5. Differential scanning calorimetry study (DSC) and X-ray diffraction (XRD)

The formation of crystalline domain in the SD with time was investigated using DSC and XRD. The drug (NP), the carrier (PEG4000), tablet (SD dispersed PEO), PEO and SDS were subjected to DSC study using a differential scanning calorimeter (TA Instruments, DSC2910, Dupont, U.S.A.) at a scanning speed of 10 °C/min in the temperature range of 40–200 °C under nitrogen gas flow. The crystallinity of the same samples used for DSC was investigated for their X-ray diffraction patterns, using a diffractometer (D8advance, Bruker Axs Gmbh, Karlsruhe, Germany) under ambient conditions over the 2θ range of 3–40°. Tablet was pulverized before measurement, using mortar and pestle, and sieved by 355 μm sieve.

2.6. Solubility of NP

Solubility measurement of NP in various solutions was made by placing excess amount of NP in solvent at 37 °C with stirring. After 48 h, 1 ml of solution was taken and filtered using a 0.45 μm membrane filter. After dilution, the concentration of the solution was determined. Solubility in distilled water, 0.01 M NaCl solution and 0.1 M NaCl solution was measured.

2.7. Dissolution study

Dissolution study was carried out using an USP XXIII dissolution apparatus II (DST-600A, Fine Inst., Ansan, Korea) with 900 ml of dissolution medium at 37.5 ± 0.1 °C and 100 rpm. Both the prepared three-layered tablet and the physical mixtures (blended) were evaluated for their dissolution characteristics in various mediums. At predetermined time intervals, 1 ml of sample was withdrawn and replaced with 1 ml of dissolution medium.

2.8. Dissolution medium

Simulated gastric fluid (pH 1.2) was prepared by dissolving HCl (7 ml) and NaCl (2 g) in 1 l of distilled water. Simulated intestinal fluid (pH 6.8) was prepared by adding 0.2N NaOH solution (118 ml) into 0.2 M KH_2PO_4 solution (250 ml) and make the final volume to be 1 l by the addition of distilled water. In order to study the effect of pH on dissolution, pH 11 phosphate buffer solution was also evaluated. The effect of ionic strength on dissolution was also evaluated using 0.01, 0.1 and 0.5 M NaCl solutions, which were made by dissolving NaCl in distilled water. The effect of buffer concentration on dissolution was carried out in pH 6.8 phosphate buffer solution at three buffer concentrations (0.01, 0.1 and 0.3 M).

3. Results and discussion

The successful formulation of a poorly soluble drug is very challenging in dosage form design. Poorly water-soluble drugs usually show low oral bioavailability due to poor dissolution profile in the GI fluid (Bu and Erajuddin, 2000). In this work, we have tried to modify the release profile of NP from hydrophilic matrix, PEO, containing solid dispersed NP, by restricting the drug releasing surface area. The restriction is achieved by applying polymeric barrier layers on both sides of the tablet using a viscous hydrophilic polymer, CP. In general, the release of drug molecules from hydrophilic, swellable matrices is governed by polymer chain relaxation by invading water and drug diffusion through the swollen matrix. Both of these phenomena are dependent upon the rate of water imbibition into the matrix. The tablets studied had thick CP polymer layers on both sides, and these CP layers could form viscous layer quickly upon hydration. We expect these CP layers not only reduce the surface area through which drug is released, but also lower both water hydration rate and drug diffusion rate out of the matrix. We chose CP as the release barrier, because it form very viscous layer upon hydration and it adheres to the surface of core tablet after hydration throughout the time period of drug release.

3.1. Solubility measurement

Table 2 shows the solubility of NP and solid dispersed NP in distilled water and NaCl solutions (0.01 M and 0.1 M). SD using PEG 4000 as the carrier increased the solubility of NP in distilled water from 12.7 μg/ml (drug itself) to 19.4 μg/ml. The mechanisms involved in the increase in solubility are thought to be the increased solubilization due to the change in crystallinity from crystalline form to amorphous form and to the decrease in crystal size and improved wetting of NP in PEG rich microenvironment formed at the surface of drug (due to the decreased surface tension) after the dissolution of the PEG4000 molecules (Verheyen et al., 2002). Small amount of SDS is also thought to contribute to the increase in the wetting of NP by water molecules. Addition of NaCl into the water decreased the solubility of NP. In 0.01 M NaCl solution, solubility was 18.3 μg/ml and, in 0.1 M NaCl solution, it decreased further to 16.4 μg/ml. It seems that the addition of salt deprives water molecules from wetting the NP molecules.

3.2. DSC and XRD study

The change in crystallinity with time after the preparation of SD can significantly affect the release pattern of NP from dosage form. In this work, we studied the change in crystallinity with time using DSC and XRD. NP was incorporated into the PEO tablet as a SD in PEG4000. The DSC thermograms and XRD diffractograms of NP, PEG4000, PEO, SDS and pulverized SD tablets are shown in Figs. 2 and 3. NP, PEG4000 and PEO900K each showed an endothermic peak at 173, 59.1 and 69.2 °C, respectively, corresponding to their melting point. The thermogram of the SD of NP-PEG4000 immediately after preparation gave only one endotherm peak at 56.7 °C, which is close to the PEG4000 melting temperature. The thermogram obtained after 48 weeks of storage also showed only one endotherm peak at the same temperature with a slightly larger size, indicating that the crystallinity of PEG4000 in solid dispersions only slightly increased upon aging during this storage period. Similar results were reported for SD of NP in PEG4000 (Verheyen et al., 2004). The formation of crystalline domain of NP, PEO or SDS was not observed. The XRD patterns were consistent with these results from DSC thermograms that only the recrystallization of PEG4000 occurred and the NP, PEO and SDS existed in the amorphous state until 48 weeks after preparation. The tablet prepared in this work contains PEO (PEO:PEG = 1.2:1.0), which makes envelope around the SD of PEG. It seems that PEO together with PEG increased the physical stability of NP

Table 2
Solubility of NP in different dissolution medium at 36.5 °C

Medium	Type of nifedipine	Solubility (μg/ml)
Water	Pure nifedipine	12.7
Water	Solid dispersion of nifedipine	19.4
0.01 M NaCl solution	Solid dispersion of nifedipine	18.3
0.1 M NaCl solution	Solid dispersion of nifedipine	16.4

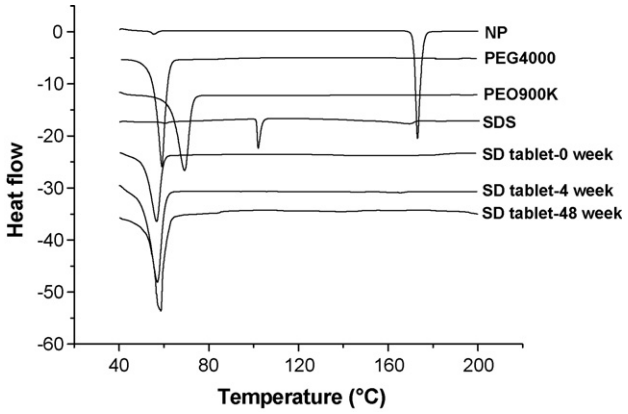

Fig. 2. DSC curves of NP, PEG4000, PEO900K, SDS and the mixture of them (T2).

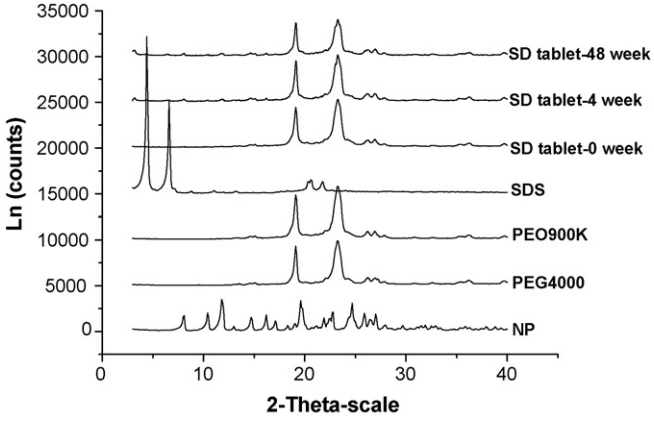

Fig. 3. X-ray powder diffraction pattern of NP, PEG4000, PEO900K, SDS and the mixture of them (T2).

by delaying or blocking the recrystallization of the dispersed NP. The storage condition of the SD (in a desiccator at room temperature) also seemed to contribute to the stability of NP. Investigation of drug–polymer interaction in SD prepared by melt extrusion showed that NP can make hydrogen bonding with the carrier polymer, poly(vinyl pyrrolidone), and stays stable as amorphous form in the SD during the period of 8 weeks at low humidity (<10%RH). However, at high humidity (75%RH), they observed crystal formation in SD after 4 weeks and suggested that it was probably due to the plasticizing effect of the imbibed water in the glassy SD which lowers the glass-transition temperature of the polymer (Foster et al., 2001).

3.3. Effect of PEO molecular weight

In our previous work (Hong et al., 2000), we have studied the effect of molecular weight of PEO and release medium on the release of NP from PEO tablets, and analyzed the data to get some mechanistic insights into the release of NP. The molecular weights of PEOs used were 200 K, 900 K, 2000 K and 7000 K and the release kinetics were studied for 24 h in aqueous ethanol solution, using a dissolution tester. The data showed that drug release rate increased, as the concentration of ethanol in the dissolution medium increased, probably due to the increased solubility and faster swelling of the matrix. On the other hand, the increase in molecular weight of PEO decreased the release rate, possibly due to the slower swelling and dissolution of PEO. The power values obtained by fitting data to the power law expression ($M_t/M_\infty = kt^n$) indicated that, at low ethanol concentration, the release of NP is governed by anomalous diffusion. However, as the ethanol concentration increased, diffusional release becomes to prevail over anomalous or zero-order release. These results prompted us to investigate further on the release kinetics in an aqueous environment, which is closer to the actual release medium in the body than the ethanol solution itself. Because the solubility of NP is too low in aqueous medium to properly study the release kinetics, we incorporated the NP as a solid dispersion form in PEG4000, knowing that solid dispersion systems have been used widely in various formulations to increase dissolution rate and bioavailability of poorly water-soluble drugs (Vippagunta et al., 2002). The solubility data in Table 2 shows that SD increased the solubility of NP in distilled water from 12.7 μg/ml (drug itself) to 19.4 μg/ml.

The tablets prepared in this work have CP layers on both sides, hoping that these CP layers can form viscous domain quickly upon hydration. These CP layers may not only reduce the surface area through which drug is released, but also lower both water hydration and drug diffusion rate out of the matrix. We also prepared CP blended tablets, which are physical mixture of CP with PEO, together with the PEG4000 SD particles, in order to compare the NP release profile with time. The release of NP from CP-capped and CP-blended tablet is shown in Fig. 4 together with the result from tablet without capping or blending. PEO200K was used as the hydrophilic matrix material. Release of NP from tablet without capping or blending showed a rapid initial increase. Nearly 80% of the NP incorporated in the tablet is released in an hour, and then slowly reached a plateau

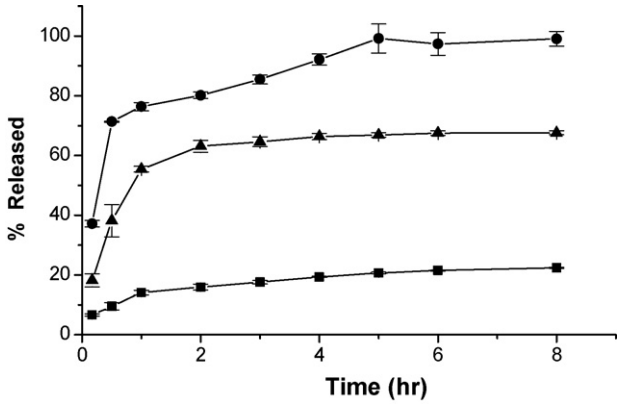

Fig. 4. Release profile of NP from T1 (●), C1 (▲) and B1 (■) tablets into distilled water.

value. After 5 h, nearly 100% of NP was released. When the PEO200K tablet was capped on both sides by CP, initial release rate decreased and only about 60% was released after 2 h. After that, the release was minimal and only 5% increase in released amount was observed for the next 6 h. No complete release of the incorporated NP was achieved for 8 h. CP-blending decreased the release rate remarkably, and only 22% of the incorporated NP was released after 8 h.

In order to have a better understanding on the reason for the slower and incomplete release for the CP capped tablet, we have carefully observed the morphological change of the tablet with time (Fig. 5). The CP layer was gradually swollen by water with time and, after 2 h, it almost covered the whole tablet surface. The diameter of the tablet increased to 25 mm from 8 mm after 2 h. During this time, PEO200K layer (core matrix) was also swollen gradually but it began eroding from the surface which is in contact with the water. Usually, drug release from the rapidly erodible polymers such as HPMC and HPC is governed by erosion of the polymer while both polymer erosion and drug diffusion play the major role for the release of drug molecules from the slowly erodible polymers (Kim, 1999). PEO200K is a fast swelling polymer and it seems that diffusion of NP and the erosion of the PEO200K from the side of the tablet are the main reasons for the rapid initial release up to 60% for the first 2 h. Drug release is occurring mainly from the side area of the tablet, because the diffusional release through CP layers are much slower process. Swollen CP layers on both sides

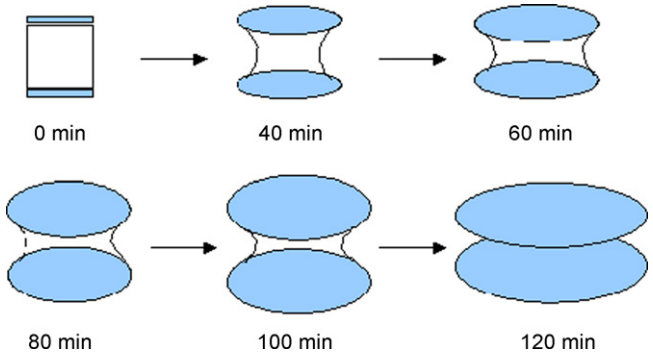

Fig. 5. Morphological change of C1 tablet with time in distilled water.

of the tablet begin to cover the side surface of the tablet after about 2 h, and this is why the release rate suddenly decreased to a minimal value. It seems that, from this point on, diffusional release through this CP layer becomes the main mechanism for the NP release. The rate of initial release was smaller than that from tablet without capping, and this can be explained by the decreased surface area, which is in contact with the water due to the CP capping. The effect of CP blending on delaying NP release was remarkable, and this is probably due to the slower diffusion of water and NP molecules into and out of the CP swollen PEO matrix. It seems that CP acts as a binder, so that it prevents the erosion of PEO200K and slows the diffusion of NP molecules through the swollen matrix.

The solubility of NP in dissolution medium is not the reason for the incomplete release, because the solubility of NP is larger than 10 μg/ml, which can be achieved when all the NP molecules in the tablet are dissolved. The incomplete release from the CP capped and CP blended tablets for the time period we studied is probably due to the very slow diffusional release through the CP hydrogel. After the side of the tablet is closed by the swollen CP, only diffusional release can occur, and this is much slower process than erosion. The viscosity of CP hydrogel significantly increases with increasing pH values up to pH 6.0, and after that it gradually reaches a plateau value (Liu et al., 2007). Hence, a significant decrease in the diffusion coefficient of NP through the CP hydrogel can occur at the pH we studied (pH ~5.8). The negative charges on the polymer chain of CP may significantly affect the release of basic drug like lidocaine by ion complexing effect. The pK_a of CP and lidocaine is about 6.0 and 7.9, and they are mostly charged at neutral pH. They can form ionic complex, and this decreases the diffusion of lidocaine inside the CP hydrogel (Liu et al., 2007). In case of NP, the pK_a is about 1.0 and we do not expect that there are any diffusional delay effect by ionic complexation between CP and NP.

Maintaining sink condition is important during the dissolution experiment for consistent and accurate measurement of the dissolution rate. According to the United States Pharmacopeia (USPC, 2005), sink condition is established when the saturation solubility is at least three times more than the drug concentration in the dissolution medium. In order to ensure sink condition, various techniques (e.g., addition of organic solvents to aqueous medium, use of large dissolution volume, removal of dissolved drug, pH changes and addition of surfactants) have been employed (Jinno et al., 2000; Pillay and Fassihi, 1998). In this work, sink condition was maintained only in some of the experimental conditions, where the amount of NP released was less than 50%. However, we have tried to facilitate the dissolution and release of NP by incorporating SDS in the amount of three times of NP directly into the tablet. We might have established a high concentration gradient across the diffusion layer, because the solubility of NP inside the tablet could be much higher than that without SDS. Released SDS from the tablet can also increase the solubility of NP in the bulk solution to help the establishment of sink condition.

Fig. 6 shows the release of NP from CP-capped and CP-blended tablet prepared from PEO900K. When the tablet was not capped or blended, rapid initial release of 59% was observed for an hour, and after that, the release was small and only about 6% increase in released amount was observed for the next 7 h. Initial release rate was slower than that observed in Fig. 4. PEO900K is a slowly swelling polymer than PEO200K, and this results in slower erosion and diffusion. After rapid initial release of NP near the surface, the release was very slow. This is also attributed to the same reason as described above, that is, very slow swelling of the inside of the matrix and thus very slow erosion and diffusion. The decrease in concentration gradient across the swollen matrix also could be a reason for the slower release. CP capping decreased initial release rate and only about 16% was released for an hours. Due to the decreased surface area exposed and the slower swelling, only 32% increase in the amount of NP released was observed for the next 7 h. CP-blending decreased the release rate further, and only 23% of the incorporated NP was released for 8 h. Slower swelling and diffusion without erosion could be the possible explanation for this.

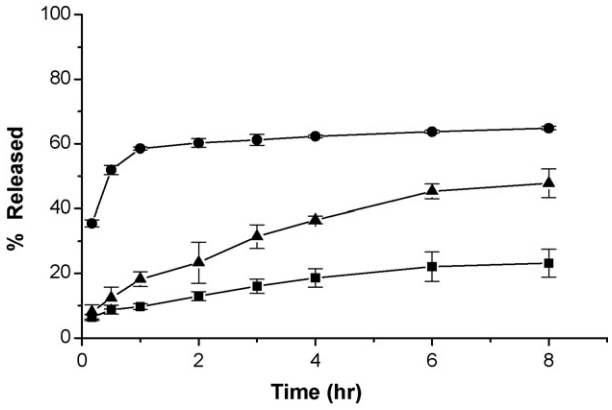

Fig. 6. Release profile of NP from T2 (●), C2 (▲) and B2 (■) tablets into distilled water.

Fig. 7 shows the release results from tablets of PEO7000K. When the tablet was not capped or blended, the initial release rate was much slower than that observed for PEO900K, and increased gradually for 6 h, and after that, the release was insignificant and only 53% was released for 8 h. CP capping decreased the release rate markedly and CP-blending decreased

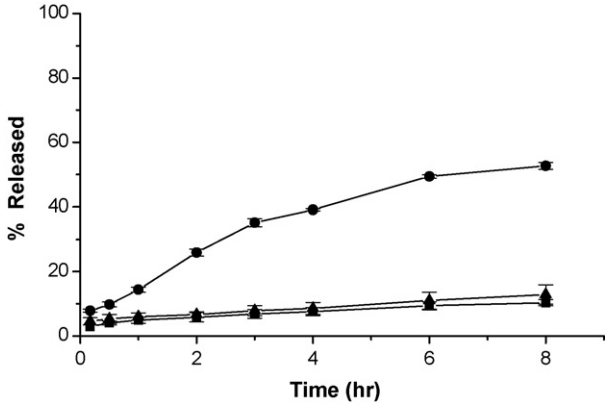

Fig. 7. Release profile of NP from T3 (●), C3 (▲) and B3 (■) tablets into distilled water.

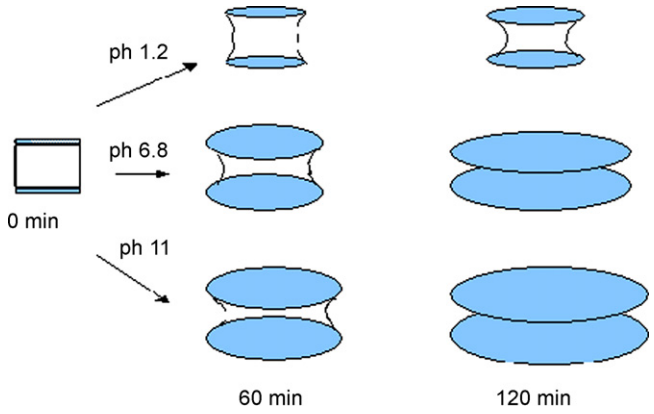

Fig. 8. The effect of pH on the morphological change of C1 tablets with time.

it even further. Only 10% of the incorporated NP was released for 8 h. For high molecular weight PEOs (>2 MDa), the release of drug molecules are controlled by swelling, whereas for low molecular weight PEOs (<0.9 MDa), the release is controlled by swelling and erosion (Pinto et al., 2004). Slower swelling and diffusion seem to be the much slower release of NP from PEO7000K tablets. In case of CP capping, only 13% was released after 8 h. Decreased surface area in contact with the medium by CP capping and the slower diffusion of NP molecules through the PEO and CP hydrogel seem to work together.

3.4. Effect of pH of the dissolution medium

The effect of pH of the dissolution medium on NP release was investigated using CP capped tablet at three pH values. PEO used for this study was PEO200K. Swelling rate of the CP layer increased as the pH increases, and when the pH was 11, CP layers on both sides of the tablet fully covered the side the tablet only after 1.3 h. It took about 2 h for the pH 6.8 medium. For pH 1.2 medium, swelling was much slower, and even after 2 h, the side of the tablet was not covered by swollen CP layers (Fig. 8). This swelling behavior is reflected in the release results of NP. After 2 h, 65% of NP was released into the pH 1.2 dissolution medium, whereas only 48% was released into the pH 11 medium (Fig. 9). After 8 h, 86% was released into the

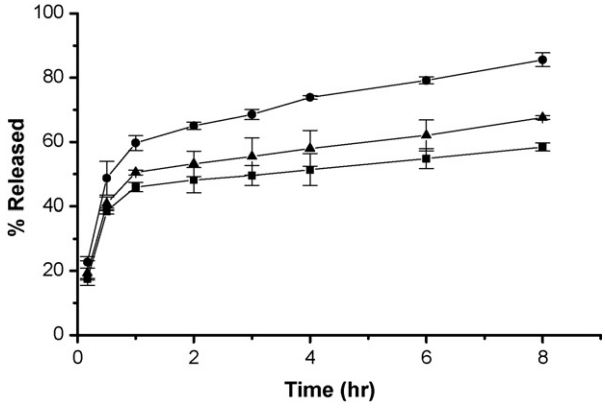

Fig. 9. Influence of pH on release rate of NP from C1 tablet into pH 1.2 (●), 6.8 (▲) and 11 (■) phosphate buffer solution (0.1 M).

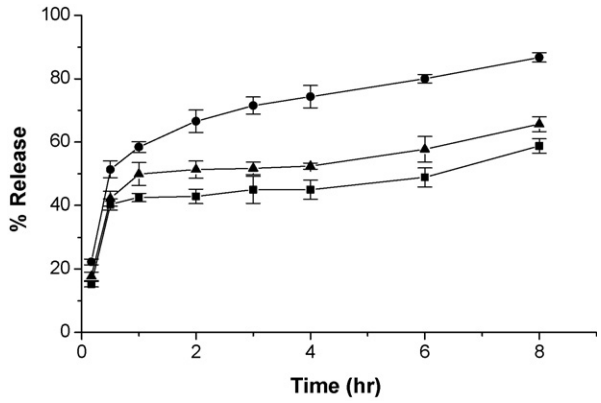

Fig. 10. Influence of ionic strength on release rate from C1 tablet into 0.01 M (●), 0.1 M (▲) and 0.5 M (■) NaCl aqueous solution.

pH 1.2 medium, whereas 68% and 58% was released into pH 6.8 and 11 dissolution medium, respectively. The pK_a of CP is 6.0 ± 0.5, and thus faster swelling should occur at pH 11, due to the complete ionization of the carboxyl groups on the CP. The faster release of NP into pH 1.2 medium seems to be related not only to the slower swelling, but also to the increased solubility of NP. The pK_a of NP is about 1.0, and the aqueous solubility of NP is higher than that at higher pHs.

3.5. Effect of ionic strength of the dissolution medium

The effect of ionic strength of the dissolution medium on NP release was studied using CP capped tablet at three different ionic strengths of the dissolution medium. NP release results from PEO200K tablet are shown in Fig. 10. As the ionic strength of the medium increased, release rate of NP decreased, and only 59% was released after 8 h into the 0.5 M NaCl aqueous solution. These results are probably due to the decreased solubility of NP in solution with high ionic strength. The solubility of NP in water was 19.4 μg/ml. Addition of NaCl into water decreased the solubility of NP (Table 2). In 0.01 M NaCl solution, solubility was 18.3 μg/ml and, in 0.1 M NaCl solution, it decreased further to 16.4 μg/ml. Slower swelling of the PEO core also seems to attribute to the slower release, because less water molecules are available for the swelling due to the hydration of Na^+ and Cl^- ions.

3.6. Effect of buffer concentration

Because the rate of release is related to the ionic strength of the dissolution medium, it should also be related to the concentration of the buffer solution used as the dissolution medium. We have studied the effect of buffer concentration at pH 6.8 at three different buffer concentrations and the results are shown in Fig. 11. PEO200K was used for this study. Initial release rate of NP was faster at low buffer concentration, possibly due to the faster swelling and erosion from the side of the tablet. Total amount of NP released after 8 h showed large difference between 0.01 M and 0.3 M buffer solution. In the 0.01 M buffer solution, 72% of NP was released, whereas only 41% of NP was released in the 0.3 M buffer solution.

Table 3
The *n* value obtained by fitting the release data to power law equation for CP capped and CP blended tablets in distilled water and other mediums

Capped											Blended	
	DW[a]	pH of buffer solution			NaCl concentration (M)[b]			Buffer concentration (M)[c]				DW
		1.2[d]	6.8[e]	11	0.01	0.1	0.5	0.01	0.1	0.3		
C1	0.52	0.55	0.55	0.56	0.56	0.60	0.61	0.57	0.56	0.52	B1	0.33
C2	0.49	–	–	–	–	–	–	–	–	–	B2	0.35
C3	0.15	–	–	–	–	–	–	–	–	–	B3	0.33

[a] Distilled water.
[b] Aqueous solution of NaCl in distilled water.
[c] The pH of the buffer was 6.8.
[d] Simulated gastric fluid.
[e] Simulated intestinal fluid.

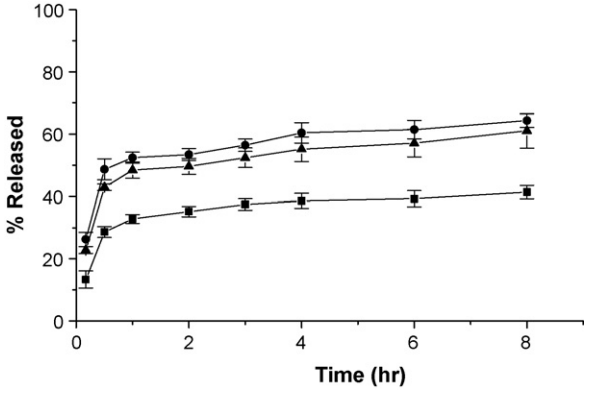

Fig. 11. Influence of buffer concentration on release rate from C1 tablet into 0.01 M (●), 0.1 M (▲) and 0.3 M (■) phosphate buffer solution (pH 6.8).

3.7. Characterization of release profile

In order to understand the release profiles, the data obtained for capped and blended tablets were fitted using the power law equation (Peppas and Sahlin, 1989). There are many kinetic models that can be fitted to elucidate the release mechanism, such as Higuchi model, cube root law model, zero order model, power law model and other theoretical models. Release of NP from high molecular weight PEO tablet occurs by the swelling of the PEO matrix, followed by the dissolution and diffusion of the NP molecules. For low molecular weight PEO tablet, erosion along with the diffusion may contribute to the release after swelling. Because of this complex nature of NP release, we chose the power law model for the characterization of the release profile. In power law equation, the n value of 0.5 or 1.0 indicates Fickian or Case II (zero order) transport. The value in between 0.5 and 1.0 indicates a non-Fickian (anomalous) transport. For cylindrical systems like tablets, the *n* values of 0.45 and 0.89 indicate pure diffusional or erosional release, respectively (Ritger and Peppas, 1987). The *n* values obtained for capped and blended tablets are listed in Table 3. For capped tablets, we used only the data from initial part of the release (up to 2 h) for the fit to the power law, because after 2 h, swollen CP layer begins to cover the side surface of the tablet and the release mechanism changes from diffusion/erosion to mainly diffusion with a continuously changing diffusion coefficient with time. Thus the *n* value obtained should be interpreted as a rough estimation of the release mechanism for the initial phase of the release. For C1, the *n* values between 0.52–0.6 were obtained in various mediums, indicating that the release of NP is governed by mainly diffusion and some erosion of the matrix from the side of the tablet. For C2, the *n* value obtained was 0.49, indicating that Fickian diffusion is determining the rate of NP release. In case of C3, the *n* value obtained was very small. This is probably due to the error involved in using very small values for the fitting to the power law equation. Only 6.6% was released for 2 h. For blended tablets (B1, B2 and B3), all data points were used for the fit. The *n* values obtained were very similar, irrespective of the molecular weight of the PEO. It seems that CP acts as a binder, so that it prevents the erosion of PEO matrix and decreases in diffusivity of water and NP molecules into and out of the PEO matrix.

4. Conclusion

Successful formulation of a poorly soluble drug is very challenging in dosage form design. We have prepared PEO tablet which has three-layered structure and evaluated their dissolution profile in various mediums. The DSC thermogram and X-ray diffraction results indicated that the formation of crystalline domain of NP, PEO or SDS was not detected. Swelling and morphological change of CP layer on both side of the tablet minimized the erosional release for rapidly swelling PEO200K, and thus changes the NP release to a diffusion-controlled process. For PEO900K, initial release rate was slower than that of PEO200K, possibly due to the slower swelling and erosional release from the side of the tablet. For PEO7000K tablet capped with CP, much slower release was observed. Decreased surface area in contact with the medium by CP capping and the slower diffusion of NP molecules through the PEO and CP hydrogel seem to work together. Physical mixture of PEO and CP delayed the release of NP remarkably. The increase in pH, ionic strength and buffer concentration of the dissolution medium decreased the release rate. These results provided some useful information on parameters which can be modulated in the formulation of a controlled release dosage form for NP.

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