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A pharma-robust design method to investigate the effect of PEG and PEO on matrix tablets

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ABSTRACT

Even though polyethyleneoxide (PEO)–polyethyleneglycol (PEG) blends have been used widely for sustained release matrix tablets, evaluations of the effects of PEG or PEO on the matrix properties have been limited. In order to evaluate gelling behavior and drug release profiles of PEG, various contents of the polymers were investigated through a robust experimental design method. When exposed to an aqueous environment, the PEO–PEG matrix hydrated slowly and swelled, causing a thick gel layer to form on the surface, the thickness of which increased significantly depending on the PEG contents. Since polyacrylate plates were used for the study, the matrix was not completely hydrated and gelled even after 5 h. However, the results could be applied to the time-oriented responses RD (robust design) models to obtain optimal settings and responses for the observed times. The optimal settings of PEO and PEG were 94.26 and 140.04 mg, respectively (PEG rate of 148.57%). Moreover, as the amount of PEG increased, the release rate also increased. When the formulation contained more than 150% of PEG, most of the drug loaded in the tablet was released in about 12 h. When the amount of PEG was less than 100%, the drug release rate was sustained significantly. Based on the RD optimization model for drug release, the optimal settings were PEG and PEO of 124.3 and 110 mg, respectively (PEG rate of 88.50%). Therefore, PEG rate of about 90–150% is suggested for matrix tablet formulations, and the exact ratio could be formulated according to the resulting tablet's properties.

1. Introduction

Hydrophilic swellable polymers have been used widely in matrix tablet formulations to control the release rate of a drug (Alderman, 1984; Ford et al., 1991; Juarez et al., 2001; Rao et al., 1990; Dhawan et al., 2005). The main goal of the matrix system is to extend drug release with zero-order release kinetics to maintain a constant *in vivo* plasma drug concentration and a consistent pharmacological effect. To achieve a constant release rate, a number of matrix devices have been developed with various types of polymeric excipients, either alone or in a mixture, to modify tablet hydration and to change the release rate and mechanism (Ebube and Jones, 2004; Madhusudan et al., 2001; Neau et al., 1999; Nerurkar et al., 2005).

The matrix tablets are usually composed of active pharmaceutical ingredients and hydrophilic swellable polymers that form gels when exposed to an aqueous environment. Among the various types of polymers, hydroxypropyl methylcellulose (HPMC) is one of the most common because of its safety, application, and compatibility with many drugs (Conti et al., 2007a; Khurahashi et al., 1996; Reynolds et al., 1998). Moreover, blends of pharmaceutically approved polymeric materials have been used extensively, including systems of Na CMC (carboxymethylcellulose)–HPMC (Conti et al., 2007a,b), PEO (polyethylene oxide)–carbopol (carboxyvinyl polymer) (Hong and Oh, 2008), and PEO–PEG (polyethylene glycol) (Kojima et al., 2008; Sako et al., 1996).

When administered, the surface of the matrix tablets is hydrated upon exposure to the gastrointestinal (GI) fluid, forming a viscous-gel layer that may hinder water penetration. Therefore, water penetration may be the rate-controlling step during gel formation. It is both the formation of the gel layer and its physicochemical properties that can modify the drug release kinetics from the matrix system. Water penetration may be dependent on the polymers' chemical structure, concentration, and viscosity. If the gelling rate or swelling is too slow, *i.e.*, more than 5–6 h after administration (incomplete gelation while passing through stomach and small

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intestine), part of the tablet may not be fully wetted or hydrated, resulting in a 'dry core' and incomplete drug release. Moreover, the mechanical strength of the viscous-gel layer should be strong enough to maintain its integrity and release rate and mechanism. If too weak, most of the gel will disintegrate quickly without any significant sustained release effect.

Depending on the mechanical properties of the gel layer, drug release is controlled by different mechanisms with different kinetics (Conti et al., 2007a). In the case of low viscosity gelling agents, erosion of the swollen polymer is the major release factor that generally leads to zero-order release kinetics. If high viscosity polymers are used, a mechanically stable gel can be formed and polymer dissolution/disintegration will be minimal (Conti et al., 2007a). Therefore, the diffusion-controlled mechanism will be the major mechanism for drug release from the swollen matrix. Both mechanisms can be modulated by formulating different types of polymers.

Among the polymeric blends for the matrix tablet, combination of PEO and PEG showed significant sustained release of a drug throughout the GI tract, including the colon, where the amount of aqueous media is limited (Sako et al., 1996). In the blend, PEO was incorporated as a gel-forming polymer and PEG was used as a hydrophilic agent to facilitate water uptake into the tablet matrix. The tablet showed stable drug release in the GI tract without any significant burst effect (Kojima et al., 2008).

Even though the PEO–PEG blend can be used for matrix tablets, most previous studies investigated a fixed ratio between both excipients and the effects of different ratios of PEO and PEG on the matrix tablets have not been quantitatively evaluated. The present study investigates the properties of matrix systems containing various ratios of the two polymers to find a correlation and optimum ratio for a specific purpose. Among the tablet properties, gelling behavior and drug dissolution profiles are evaluated together with a robust experimental design method.

Robust design (RD) is an enhanced process/product design methodology to determine the best factor settings while minimizing process variability and bias (*i.e.*, the deviation from the target value of a product). The primary procedure in RD includes experimental design, estimation of model parameters, and optimization to obtain the optimal factor settings. By exploiting the information about the relationships between input factors and output responses from an experimental design, RD methods reveal robust solutions that are less sensitive to input variations. Given this fact, one of the main challenges is the optimal design of pharmaceutical formulations to identify better approaches to various unmet clinical needs. Traditional design methods have often been applied to situations in which the primary characteristics of interest are time-insensitive. However, in pharmaceutical processes, time-oriented characteristics, such as drug release and gelation kinetics, are often of interest. In this study, a new 'pharma-RD method' is proposed and this method aims to apply RD techniques to those time-oriented characteristics. In each experimental run, mean and variance values of drug release and gelation kinetics are measured over time. In this situation, both responses are functions of control factors and observed time since the tentative relationship can be analyzed according to both vertical and horizontal directions. The response surface methodology (RSM) is utilized for both analysis directions.

2. Materials and methods

2.1. Materials

The model drug, Terazosin HCl dihydrate (molecular weight 459.93, free base 387.43, log P 1.4), was purchased from Hanseo Chemical (Seoul, Korea), which is freely soluble in water. PEO (Polyox WSR-303) of average molecular weight 7.0×10^6 and viscosity 7,500–10,000 mPa (1% solution) was purchased from Dow Chemical (Midland, MI, USA). Polyethylene glycol 6000 (PEG 6000) was purchased from Sanyo Chemical Industries (Ibaraki, Japan). Magnesium stearate was purchased from Faci Asia (Jurong Island, Singapore). All other reagents used were of analytical grade.

2.2. Preparation of matrix tablets

The formulations of each tablet are shown in Table 1. All materials were passed through a sieve (#40 mesh) before mixing to remove any aggregates. The model drug (Terazosin HCl dihydrate) was mixed manually with PEO and PEG in a mortar and then blended with magnesium stearate. The resultant mixture was compressed on a single-punch hydraulic laboratory press using plane-face punches with a diameter of 9.0 mm. The compression force was kept constant at 8.0 MPa and the total weight of each tablet was around 241 mg. The thickness of the tablets was about 4.0 mm.

2.3. Evaluation of tablet gelation

Gelation index might be a useful tool to represent the portion of a tablet that has undergone gelation on time. Each tablet was inserted between two transparent polyacrylate plates (5 cm × 5 cm) and held tight with a rubber band. The polyacrylate plates and tablet were immersed in 900 mL of dissolution medium (pH 6.8) and stirred with a magnetic bar (180 rpm/min). Due to the size of the plates, gelation study was performed in a different condition compared to drug release test. Test tablets were removed from the medium at predetermined time intervals (30, 60, 90, 120, 180, 240, and 300 min) and the diameters of gelated tablets were measured with a caliper. After the gel layer was carefully peeled off, the diameter of the non-gelated core was also measured (D_{obs}). The gelation index was calculated using the following equation (Sako et al., 1996).

$$\text{gelation index}\,(G, \%) = \left\{ 1 - \frac{(D_{obs})^3}{(D_{ini})^3} \right\} \times 100$$

D_{obs} is the diameter of the portion not gelled after the test; D_{ini} is the diameter of the tablet before the test.

Table 1
Formulation compositions of the matrix tablets.

Components (mg)	PEG 10%	PEG 50%	PEG 100%	PEG 150%	PEG 300%	PEG 500%
Terazosin HCl, $2H_2O$	5.935	←	←	←	←	←
Polyox WSR 303 (PEO)	213.00	156.20	117.15	93.71	58.58	39.05
PEG 6000	21.30	78.10	117.15	140.57	175.73	195.23
Magnesium stearate	0.96	←	←	←	←	←
Total weight	241.2	←	←	←	←	←
Percentage of PEG to PEO	10%	50%	100%	150%	300%	500%