

# High Molecular Weight Poly(ethylene oxide)–Based Drug Delivery Systems

## Part I: Hydrogels and Hydrophilic Matrix Systems

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Polyethylene oxide resins are non-ionic, high molecular weight, water-soluble polymers with good hydrophilicity. Their use in controlled-release delivery systems has gained recent interest, and several oral drug delivery systems based on hydrophilic matrix and hydrogels have been successfully commercialized. The authors review the properties and use of PEO in hydrogels and hydrophilic matrix systems.

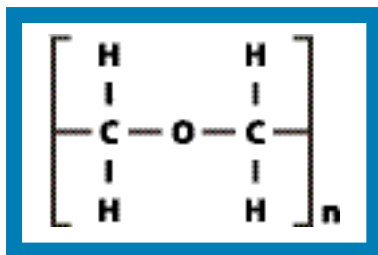


Figure 1: Structure of polyethylene oxide.

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Polyethylene oxide (PEO) resins are made commercially by the catalytic polymerization of ethylene oxide in the presence of metallic catalyst systems. They are available with average molecular weights from 200 to  $7 \times 10^6$ . Products with a molecular weight less than  $\sim 25,000$  are viscous liquids or waxy solids commonly referred to as poly(ethylene glycols) (1). The PEO resins described in this review have a molecular range from  $\sim 1 \times 10^5$  to  $7 \times 10^6$ . They are represented by the formula  $(\text{OCH}_2\text{CH}_2)_n$  in which  $n$  represents the average number of oxyethylene groups ( $\sim 2000$  to more than 100,000). As shown in Figure 1, the molecule between the brackets corresponds to the repeat unit of poly(ethylene oxide). The brackets indicate that this unit is repeated  $n$ -times to form the polymer.

Various grades of PEO are available that differ from one another depending on their molecular weight. All these grades find official status in *USP 23–NF 18* (see Table I).

### Physical properties of PEO

All the grades of PEO are white to off-white powder or granules with a mild ammoniacal odor. They have crystalline melting point range of  $62\text{--}67^\circ\text{C}$ , with autoignition temperatures of  $280\text{--}330^\circ\text{C}$  and thermal decomposition temperatures of  $423\text{--}425^\circ\text{C}$ . They form association complexes through hydrogen bonding with a number of monomeric and polymeric electron acceptors as well as certain inorganic electrolytes. Electrochemically, they are classified as non-ionic polymers. The decomposition products of PEO are carbon monoxide and carbon dioxide. They have a bulk density of  $\sim 500\text{ kg/m}^3$  and contain less than 3% of silicon dioxide and 1% of volatiles. PEOs are tough, crystalline polymers at room temperature, and their glass transition temperature decreases slightly with increasing molecular weight from  $-45$  to  $-53^\circ\text{C}$ . They are nontoxic, nonirritant, and do not generate residue, sediment, or vaporous elements (2). All these properties indicate that these polymer grades are stable to work with.

**Solution properties.** PEOs are completely soluble in water at temperatures as high as  $98^\circ\text{C}$  and completely soluble in certain organic solvents such as chlorinated hydrocarbons. Limited solubility exists in a wide variety of other organic solvents (e.g., acetone, anisole, butanol, butyl acetate, ethanol, isopropanol,

**Table I: PEO water-soluble resins (Union Carbide literature 377).**

Approximate molecular weight	Viscosity range (cP) at 25° C 5% solution	2% solution	1% solution
100,000	30–50		
200,000	55–90		
300,000	600–1200		
900,000	8800–17,600		
2,000,000		2000–4000	
4,000,000			1650–5500
5,000,000			5500–7500
7,000,000			7500–10,000

toluene, and xylene), but the resin in these solvents is soluble only at elevated temperatures, and the resin may precipitate from the solution at room temperature. Although PEOs are completely soluble in cold or warm water, they undergo an inverse solubility relationship near the boiling point of water (3). Thus at ~98 °C, the resin becomes insoluble in water and precipitates. In solution, PEOs give a pH from ~6.5 to 7.5.

**Viscosity.** The viscosity of the aqueous solutions of PEO resins depends on the molecular weight, concentration, temperature, and, because of their pseudoplastic character, the rate of shear applied during the viscosity measurement. The viscosity increases directly as either the molecular weight of the resin or its concentration in aqueous solution increases. The viscosity of 5% solution of PEOs with molecular weight 100,000, 200,000, 300,000 and 900,000 is 30–50, 55–90, 600–1200, and 8800–17,600 cP, respectively. The viscosity of 2% solution of PEO with molecular weight  $2 \times 10^6$  has been reported to be 2000–4000 cP. High molecular weight PEOs have high viscosity. For example, 1% solution of PEO with molecular weight  $4 \times 10^6$ ,  $5 \times 10^6$ , and  $7 \times 10^6$  has viscosity of 1650–3500, 5500–7500, and 7500–10,000 cP, respectively.

**Powder properties.** To prepare a solid dosage form containing one or more active ingredients (such as drugs), the material being compressed into the dosage form must possess certain physical characteristics that lend itself to processing in such a manner. Among other things, the material to be compressed must be free flowing, lubricated, and, most important, must possess sufficient cohesiveness to ensure that the solid dosage form remains intact after compression. Granular grades of PEO can be compressed because granules impart good flow properties. Yang *et al.* determined the powder properties, mechanical properties, rheological properties, and related parameters such as surface morphology, particle size, glass transition temperature, and degree of crystallinity of bulk PEO samples (4). The angle of repose was found to be ~35 for all the grades of PEO. The aerated bulk density of PEO varies from 0.39 to 0.53 and the packed density varies from 0.42 to 0.59. The true density values of PEOs are similar, and the degree of crystallinity does not seem to decrease as molecular weight increases (4).

High crystallinity and smooth symmetric chains make PEOs mechanically strong, although their glass transition tempera-

tures are well below 0 °C. The degree of crystallinity is likely to vary during material processing such as shearing and tableting. Yang *et al.* also reported that bulk WSR N-80H (molecular weight  $0.2 \times 10^6$ ) as received had a crystallinity of 85% (4). The crystallinity was reduced to 61.2%, however, when the material was compressed at 2000 lb, and its crystallinity was reduced to 50.6% when ground for 5 min with a pestle and mortar. This is probably a result of the structural irregularities in the crystal lattice by shearing, slip planes, and stressing. It also has been reported that because of the viscoelastic behavior and large axial expansion of PEO, tablets of relatively low tensile strength were produced. Hence, PEOs should be blended with highly compressible excipients to produce tablets on a high-speed production press.

## Applications

**Hydrogels.** The hydrogel drug delivery systems represent a significant interest to pharmaceutical practice because of their potentiality for drug release within large limits (5). These monolithic systems, under certain conditions, can release drugs at a constant rate, approximating a zero-order reaction kinetics as a result of case II transport. Graham studied the diffusion of uniformly dispersed caffeine in water-swollen PEO hydrogels by quantitating the release of solute from thin slabs into a finite volume of solution at 37 °C (6). Fractional release followed a time ( $t^{0.5}$ ) relation for thicknesses between 1 and 5 mm and various polymer compositions with equilibrium water uptake of 118–530 parts per 100 dry polymer. Values of the diffusion coefficient were calculated from the experimental results by assuming the hydrogel to be an infinite sheet and a rectangular parallelepiped. Both bound and free water were identified in differential calorimetry scans of the hydrogel. The diffusion coefficient for the various water contents obeyed the Davis relation, and this equation appeared to represent the diffusion characteristics of these PEO hydrogels quite accurately.

McNeill and Graham investigated the release of water-soluble solutes from PEO hydrogels (7). The hydrogels—which owe their hydrophilicity as a result of PEO content—swelled and absorbed as much as three times their dry weight in water. They had a glass transition temperature below body temperature. A range of diffusates was studied ranging from low water-soluble prostaglandin  $E_2$  to highly water-soluble lithium chloride. Device geometry was restricted to approximations to infinite slabs with more than 85% total surface area over the top and bottom surfaces so that release was predominantly one-dimensional and the controlling variable was thickness. The increase in surface area with time, drug-solubility in the water-swelling matrix, and the presence of crystallinity were important factors governing the profile and level of release rate with time. The diffusional exponent,  $n$ , ranged from 0.79 to 1; that is, good anomalous to zero-order release. This is a highly desirable range of values for controlled-release devices.

Transforming growth factor-beta 1 (TGF-beta 1) has beneficial effects on wound healing. However, the ideal method for its administration to the wound site remains unknown. Puolakkainen *et al.* incorporated TGF-beta 1 into a poloxamer gel, Duoderm hydroactive paste, and PEO hydrogel (8). The release

of  $^{125}\text{I}$ -labeled TGF- $\beta$  1 from the carriers was measured in full-thickness wounds in rats. The healing of the wounds was analyzed by histology and wound area measurements. Wound size measurements and the analysis on the amount of cellular influx, fibroplasia, and granulation tissue showed that a single dose (1  $\mu\text{g}/\text{wound}$ ) of locally administered TGF- $\beta$  1 significantly ( $p < 0.01$ ) enhanced the wound healing. Kofinas *et al.* also observed that hydrogels formed from poly(ethylene oxide) are of interest for biomedical applications, such as the transportation of growth factors (9).

McNeill and Graham investigated the diffusive release of proxiphylline from urethane cross-linked PEO hydrogels in water-swollen slabs, spheres, and cylinders (10). Contrary to general conventional wisdom, they found that cylinders and spheres, which have considerable potential advantages for oral delivery, could provide good anomalous rates for which the exponent of release into water from the dry xerogels was 0.8, compared with 1.0 for zero-order. An exponent of 0.94 was found for release into water from larger xerogel flat slabs, thereby confirming that these configurations can provide essentially constant delivery formulations from which the active agent cannot be dumped. The experimental release of proxiphylline was sustained from swollen spheres of these polymers.

Abraham *et al.* observed that hydrogels made from PEO provided an aqueous environment for unhindered diffusion of small polar molecules (11). These hydrogels also provided a suitable matrix for a large protein such as glucose oxidase and retain the enzyme in the active form. Although electron-beam irradiation can be detrimental to protein stability, it is possible to incorporate protein in such hydrogel matrices by keeping the irradiation to ultra-low doses. These hydrogels can be suitable platforms for drug delivery across the skin.

Lambov *et al.* studied the factors that can eventually influence the release of drugs from PEO hydrogels (12). They determined a difference in the swelling of wet and dried matrices. Generally, the release takes place as an anomalous diffusion (release exponent  $n = 0.53$  to  $0.86$ ). The rate and kinetics of release ( $t_{1/2}$  or zero-order prevailing) depended mostly on the drug content in the matrices and the irradiation dose.

Silverman *et al.* demonstrated that photopolymerizable PEO hydrogels can be used as a tissue adhesive and that such an adhesive significantly reduces seroma formation in the rat mastectomy model (13).

Savas and Guven synthesized PEO hydrogels by irradiation and then characterized them for their network structure, swelling properties in water, and the number average molecular weight between crosslinks (14). Salicylic acid, phthalic acid, and resorcinol were used as model substances for their controlled release from hydrogels. The active substance uptake capacity of hydrogels was lowest for phthalic acid and highest for resorcinol in the gel system. The release was lowest both in rate and in total amounts in hydrogels containing phthalic acid. The release was greater in samples with salicylic acid and highest in those with resorcinol.

PEO hydrogels were synthesized and used to produce coated wires and conduits for baboon blood compatibility studies.

Blood material interactions were studied both by SEM and  $^{111}\text{In}$ -labeled platelet deposition. The formulations containing PEO had low levels of platelet deposition (15).

Masuda and Nakanishi investigated the swelling behavior of PEO gel in solutions of various salts (16). The gel deswelled in solutions of sodium salts and swelled in solutions containing strongly hydrated cations. The degree of swelling of the gel was in the following order:  $\text{CsCl} < \text{KCl} < \text{NaCl} < \text{LiCl}$  and  $\text{BaCl}_2 < \text{SrCl}_2 < \text{CaCl}_2 < \text{MgCl}_2$ . These results were interpreted in terms of interactions between the polymer and the ions through the hydration layers of the cations.

The swelling behavior of radiochemically crosslinked PEO gels in aqueous sodium dodecyl sulfate (SDS) with and without NaCl was investigated (17). In the absence of NaCl, PEO gels with various degrees of crosslinking began to swell from a concentration lower than the critical micelle concentration of SDS, and then showed sigmoidal enhancements of swelling in a higher SDS concentration region until the degrees of swelling reached maximum values. When NaCl was present, the swelling behavior of PEO gel was different from that when NaCl was absent. The concentration where the swelling appears decreased with an increase in NaCl concentration.

Alexandre *et al.* prepared PEO macromonomer-based hydrogels for artificial organs (18). They observed that implanted PEO hydrogels are well tolerated by the host immune system. A biocompatibility test of the hydrogel showed that only a few fibroblasts were adsorbed on the hydrogel surface. Diffusion of glucose through PEO hydrogels was possible.

Hyung and Bae prepared various hydrogels, composed of short hydrophilic PEO and hydrophobic block, by polycondensation reaction (19). Poly(tetramethylene oxide) (PTMO) or poly(dimethyl siloxane) (PDMS) was chosen as a hydrophobic block because of their wide use as a biomaterial. Most hydrogels showed a comparable value of macrophage density to Pellethane (Dow), control polymer, whereas they did significantly lower foreign body giant cell density and coverage because of the presence of PEO. The more significant degradation was observed in the hydrogels with longer PEO block and PTMO as a hydrophobic block instead of PDMS.

In another study, two kinds of chitosan-based hydrogels, a crosslinked chitosan reference gel and a chitosan-PEO semi-interpenetrating network (semi-IPN), with potential pH-sensitive swelling and drug delivery properties were characterized (20). Swelling studies were performed on the two kinds of hydrogels by differential scanning calorimetry at pH 1.2 and by the gravimetric method at pH 1.2 and pH 7.2. The pH-dependent swelling properties were observed with both hydrogels, they were however improved for the semi-IPN. The results obtained by both techniques were in good agreement and indicated that the semi-IPN contained more bound water than the reference gel, probably because of the presence of the hydrophilic PEO chains. The semi-IPN displayed improved mechanical properties compared with those of the reference gel.

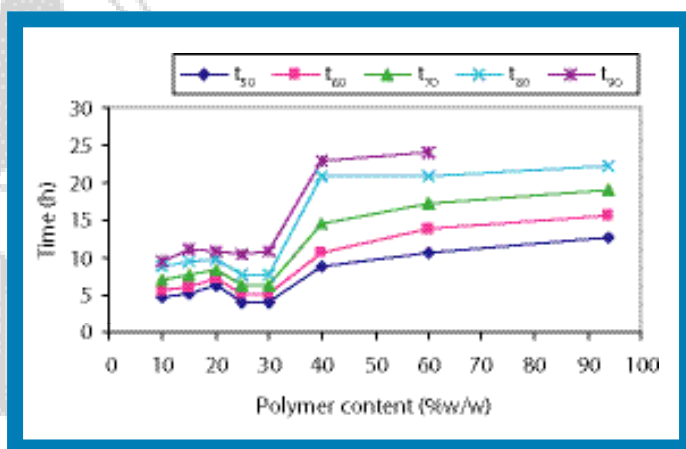
**Hydrophilic matrix system.** Hydrophilic matrix tablets are a common and commercially successful means for prolonged oral drug delivery. There are numerous applications of PEO in matrix systems. Sako *et al.* (21) investigated the effect of gelation



of two types of PEO matrices—slowgelling (SG) tablet and rapid gelling (RG) tablet containing PEG 6000—on the colonic release of acetaminophen in dogs. Slow gelling and rapid gelling showed similar drug-release behavior *in vitro*. In oral administration to dogs, the two formulations showed similar gastrointestinal transit, reaching the colon within 2–4 h after oral dosing. In contrast, however, the two tablets produced different plasma levels from 2 h postdosing, with plasma levels of RG tablets higher than those of SG tablets and with smaller individual variation. Directly observed colonic drug-release behavior of RG tablets was similar to *in vitro* drug release, whereas that from SG tablets was suppressed. The researchers concluded that colonic drug release was closely related to the gelation of hydrophilic matrix, and rapid gelation provided continuous *in vivo* drug release.

Dimitrov and Lambov investigated the release of verapamil hydrochloride from high molecular weight PEO tablets (22). The drug release proceeded as a controlled diffusion with the value of  $n$  ranging from 0.44 to 0.47. Zhang and McGinity investigated the release of chlorpheniramine maleate from matrix tablets prepared by hot-melt extrusion (23). During the hot-melt extrusion process, a dry powder blend of drug, polymer, and other adjuvants was fed into the extruder and melted inside the barrel of the machine. The molten mass was extruded through a rod-shaped die and then cut manually into 400-mg tablets. Chlorpheniramine maleate and PEO were stable under the processing conditions. The molecular weight of the PEO, the drug loading percentage, and the inclusion of poly(ethylene glycol) as a processing aid influenced the processing conditions and the drug release properties of the extruded tablets. Release of chlorpheniramine maleate from the matrix tablets was faster in acidic medium than in purified water and phosphate buffer (pH 7.4). Drug release from the matrix tablet was controlled by erosion of the PEO matrix and the diffusion of the drug through the swollen gel layer at the surface of the tablets. Chlorpheniramine maleate was dispersed at the molecular level in the PEO matrix at low drug-loading levels, and the researchers observed recrystallization of chlorpheniramine maleate at high drug-loading levels. Hot-melt extrusion was shown to be a viable novel method to prepare sustained-release tablets. PEO was a stable and suitable polymeric carrier for the hot-melt extrusion process.

Pillay and Fasshi described a novel monolithic drug delivery system for metoprolol tartrate (24). This system followed pH-independent zero-order kinetics over an extended period. PEO was used as a hydrophilic gel-based swellable polymeric material for this novel approach. The system used various electrolytes, namely, sodium carbonate and/or pentasodium triphosphate. Electrolytic conductivity measurements performed with the simultaneous analysis of matrix swelling showed that sodium carbonate formed a highly reactive matrix within the first 3 h of medium penetration. On the other hand, larger molecules such as pentasodium triphosphate maintained a constant conductivity level, which may be related to its lower solubility and diffusion in comparison with sodium carbonate. On the basis of model fitting and statistical analysis, the researchers showed that drug-release kinetics were zero



**Figure 2:** Effect of polyethylene oxide concentration on release  $t_{50}$ – $t_{90}$  values of glipizide from hydrophilic matrices. Upon wetting of the tablet, the polymer on the tablet surface hydrates to form a gel layer, which expands with time into the interior of the tablet, allowing diffusion of the drug from the tablet core. It is expected that the release kinetics are governed by the erosion–drug diffusion process after the swelling front meets at the core of the tablet.

order. This novel approach in formulation development could potentially be used for constant-rate delivery of highly soluble bioactive agents over an extended period for specific biopharmaceutical needs.

Pillay and Fasshi also worked to probe the mechanism associated with induced matrix stiffening *via* textural analysis as a consequence of *in situ* electrolyte interactions within hydroxypropyl methylcellulose (HPMC) and PEO matrices in relation to their role in controlling the release of highly soluble drugs such as diltiazem hydrochloride (25). The dynamics of HPMC and PEO matrix swelling during hydration in the presence of appropriate electrolytes intended to induce constant drug-release rates from simple monolithic systems were influenced by continuously shifting peripheral matrix stiffening toward the matrix core in a manner dependent on electrolyte content and hydration time. Matrix erosion for HPMC and PEO controls (*i.e.*, without electrolyte) follow linear dissolution kinetics, and formulations with electrolyte characteristically undergo a square-root-of-time decline in weight. The swelling potential of the electrolyte-containing matrices, influenced by the boundary infiltration process, reflected considerable suppression during the first 2 h of exposure to the medium, whereas subsequent events differed in both polymers.

Yi *et al.* used PEO as a sustained-release matrix system of cefatrizine propylene glycol, which is a new semisynthetic broad-spectrum and orally active cephalosporin (26). Five kinds of sustained-release matrix tablets were formulated with various content of PEO and other ingredients. On increasing the PEO content, the drug-release rate from matrix tablets decreased. After oral administration, Cefa-PG PEO matrix tablets were more bioavailable than general Cefa-PG capsules in beagle dogs. The area under the curve for the sustained-release PEO matrix tablet was higher than that of the general dosage form.

Maggi *et al.* evaluated the effect of UV light on the release

characteristics of extended-release matrix tablets containing HPMC or PEO as retarding polymers (27). Two drugs, nifedipine (insoluble and photolabile drug) and diltiazem (soluble and photostable drug) were used in the study. Photodecomposition of nifedipine was evaluated, and the formation of the photoproducts was followed during the dissolution process. Regarding the dissolution stability, the matrix tablets containing HPMC exposed to UV light did not show significant differences in drug-release profiles compared with the same non-irradiated formulation. The matrix tablets that contained PEO were exposed to the same conditions of UV light showed a remarkable increase of drug-release rate within the first minutes of the dissolution test (burst effect), which is particularly important because it can cause the loss of the desired therapeutic control.

Luber and Bunick described an invention related to an immediate-release tablet capable of being chewed or disintegrated in the oral cavity, which comprised a pharmaceutically active ingredient and a matrix composed of poly(ethylene oxide) having average molecular weight from  $\sim 500,000$  to  $\sim 10,000,000$  (28). The tablet possessed exceptionally good mouth feel and stability.

Berner and Louie described controlled-release oral dosage forms for the continuous, sustained administration of ciprofloxacin to the upper gastrointestinal tract of a patient in whom the fed mode was induced (29). The majority of the agent was delivered on an extended-release basis to the stomach, duodenum, and upper regions of the small intestine, with drug delivery in the lower gastrointestinal tract and colon substantially restricted. The dosage form comprised a matrix of a biocompatible, hydrophilic, erodible polymer PEO. The drug release rate was primarily controlled by erosion rate.

**Geomatrix system.** The Geomatrix technology is a versatile, well-known method to achieve extended release of drugs at a constant rate (see Figure 2). It consists of a hydrophilic matrix core, which contains the active ingredient, and one or two impermeable or semipermeable polymeric coatings (films or compressed barriers) applied on one or both bases of the core. Maggi *et al.* prepared four core formula-

tions containing a soluble drug (diltiazem) and, alternatively, PEO or HPMC of two different viscosity grades (30). These formulations had the same composition except for the polymer used. Results showed that slower release rates can be obtained from the plain matrices containing HPMC compared with those containing PEO.

**Swelling properties of PEO hydrophilic matrices.** To characterize properly the drug release

from the swelling and dissolving systems, Apicella *et al.* examined the solvent penetration, polymer swelling, and dissolution behavior of etophylline-containing PEO tablets (31). The authors reported the penetration depth evolution kinetics of tablets made of pure PEOs with average molecular weights of 600,000 and  $4 \times 10^6$  containing 10% etophylline. The PEO tablets of molecular weight of 600,000

showed an almost linear shape in the penetration depth curve as a function of time, which indicated that after a very short initial transient, the penetration front moved into the polymer at a constant rate. The tablet containing the PEO of higher molecular weight was characterized by an initial rapid water penetration rate. It was observed that a sharp front moved at a constant rate through the unpenetrated tablet core after a swelling time significantly larger than the time elapse detected for the PEO of lower molecular weight.

Kim observed the swollen gel thickness and outer diameter of a drug-free PEO tablet (32). It was observed that the constant gel thickness was obtainable with the PEO tablets of molecular weight 900,000 and  $2 \times 10^6$ , whereas the swollen gel thickness from the PEO tablet of  $4 \times 10^6$  kept increasing with time. Early in the swelling-erosion process, the overall size of the tablet along with the gel layer increased rapidly as a result of the immediate swelling of the PEO tablet. The swelling rate of the polymer equals the dissolution rate of the swollen polymer gel, resulting in the synchronization of the gel-layer thickness. With the low molecular weight PEO, the synchronization of the gel-layer thickness took place earlier compared with the PEO of high molecular weight. The constant gel-layer thickness occurred shortly after the outer diameter began to decrease. The higher the molecular weight, the later the synchronization took place. However, for a higher molecular weight ( $4 \times 10^6$ ) tablet, a synchronized gel layer was not obtained and the gel-layer thickness continued to increase. The researchers also concluded that with high molecular weight PEO and HPMC, the swelling of the polymer was the dominant step in controlling release kinetics over the erosion of the swollen polymer. With PEO of low molecular weight, the erosion was the rate-determining step for the release kinetics. However, the degree of swelling of PEO was higher than HPMC, therefore drug release from PEO matrices provided more favorable kinetics with  $n = 0.8$  as compared with  $n = 0.66$  for HPMC (32).

Maggi *et al.* evaluated the relative influence of drug diffusion and polymer erosion mechanisms of PEO in the drug delivery process (33). They studied the hydration behavior of matrix tablets containing a water-soluble drug and PEOs of two different molecular weights: Polyox WSRN 1105 (molecular weight  $0.9 \times 10^6$ ) and Polyox WSRN 301 (molecular weight  $4 \times 10^6$ ). Results showed that the PEO with the higher molecular weight swelled to a greater extent and formed, upon hydration, a stronger gel, which is therefore less liable to erosion than the PEO of lower molecular weight.

**Drug release from a hydrophilic matrix system.** A hydrophilic matrix tablet is a simple-to-formulate, yet effective, sustained-release drug delivery system, in which bioactive is uniformly distributed within a polymer matrix. Because PEO is non-ionic, no interaction between the drug and polymer is expected. Mensitieri *et al.* observed that the low-molecular weight PEO shows a zero-order release kinetic over the entire duration of the test (34). To increase mucoadhesion, however, it could be blended with higher-molecular weight fractions to increase gel elasticity and adhesion.

Kim *et al.* investigated the release of theophylline from PEO tablets and observed that the release of the drug was not influ-

enced by the pH variation of the dissolution medium (35). This result suggested that PEO may be a good candidate for oral drug delivery systems because oral dosage forms travel along the gastrointestinal tract in which the pH changes from an acidic environment in the stomach to a weak base.

Wu *et al.* developed a comprehensive mathematical model to describe the transport phenomena in controlled-release of a small-molecule drug from PEO cylindrical tablets (36). Several aspects in release kinetics were taken into account, including the swelling of the hydrophilic matrix and water penetration, three-dimensional and concentration-dependent diffusion of drug and water, and polymer dissolution. At low and moderate initial loadings, drug-release profiles using this model were predicted with an extremely good agreement with experimental data. At very high loadings, the model showed rather acceptable agreement between theoretical and experimental results. The overall release process was highly dependent on the matrix swelling, diffusion, and polymer dissolution.

**Effect of drug solubility on the release of drug from a matrix system.** Kim investigated the effects of drug solubility on zero-order release kinetics and elucidated the release mechanism of a drug from directly compressed tablets of PEO (35). Directly compressed tablets consisting of PEO (molecular weight 0.9, 2.0, and  $4.0 \times 10^6$ ) and drugs (solubility ranging from 290 to 25,000 mg/L) were formulated with or without a water-soluble excipient (lactose). The researchers observed that as the solubility of the drug decreased, the duration of drug release increased. The release of diclofenac sodium (2.5% solubility in water) was characterized as non-Fickian kinetics. In this case, drug diffusion through the swollen gel matrix was the governing step for the drug release. As drug solubility decreased below 1% (theophylline and salicylic acid), drug release slowed as a result of the longer dissolution time of the drug ion in the matrix. As the drug solubility decreased further below 1000 mg/L, the dissolution of the drug became a dominant process in controlling the drug release from PEO tablets. This accounted for a constant release with  $n = 0.96$  and  $n = 1.10$  for sulfathiazole and sufapyridine to as high as 85–90% release, respectively.

**Effect of polymer molecular weight and concentration on drug release.** Apicella *et al.* studied the release of  $\beta$ -hydroxyethyl theophylline from various molecular blends of PEO (31). They observed that the drug release from the high molecular weight PEO was strictly related to polymer swelling rather than dissolution, and drug release from the low molecular weight PEO was strictly dependent upon the polymer dissolution mechanism.

Kim investigated the effect of PEO molecular weight and drug loading on the release of drugs of varying solubility from directly compressed tablets (35). The drug release was controlled at a zero-order rate by the dissolution of the drug at high loading (39%) from tablets containing PEO of molecular weight  $4.0 \times 10^6$ . The release of water-insoluble drugs from high molecular weight ( $0.9 \times 10^6$ ) tablets was swelling-erosion controlled, resulting in zero-order release kinetics. At low loading (20%), drug diffusion through the swollen gel layer was the governing release mechanism. For a highly water-soluble drug (*e.g.*, diclofenac sodium), drug diffusion was the controlling mechanism regardless of the molecular weight of the PEO.



Migliani prepared hydrophilic matrices containing glipizide, PEO, dicalcium phosphate, and lubricants (37–39). At extremely low polymer content, the hydrophobic effect of dicalcium phosphate resulted in low-swelling tablets and the system behaved like an erosion system. Because of the hydrophobic nature of dicalcium phosphate, the entry of the penetrant into the matrix was relatively slower, thereby resulting in a low degree of swelling. However, at a particular concentration, the hydrophilic effect of the polymer was high enough to form a gel that acted as a diffusion barrier. After that concentration, the release of the drug decreased with an increase in polymer content (see Figure 3). But when lactose was used as a diluent, the release rate decreased with an increase in polymer content owing to the formation of an effective gel layer.

## Conclusion

Various grades of high molecular weight PEO are available that can be selected depending upon the nature of active pharmaceutical agent and delivery system required. PEO resins form association complexes with a wide variety of monomeric and polymeric organic compounds. The formation of an association complex with one of these compounds generally produces a product with properties and utility quite different from those of either component. PEO hydrogels have attracted interest for biomedical applications because of their generally favorable biocompatibility. Various therapeutic agents such as transforming growth factor beta 1, proxiphylline, and caffeine have been incorporated in the hydrogels. Chitosan-PEO semi-IPN showed pH-dependent swelling. Factors that influence the release of drugs from hydrogels also have been investigated. Generally, the release takes place as anomalous diffusion. Various hydrophilic as well as hydrophobic block polymers have been used with PEO for hydrogels. PEO has been used for controlled-release matrix systems of water-insoluble as well as water-soluble drugs. The drug-release mechanism is controlled by several variables in a dynamic process. During the release of drugs from hydrophilic matrices of PEO, two mechanistic phenomena take place: the swelling and the erosion of the polymer. The release kinetics of the drug from the tablet are dependent upon the relative magnitude of the rate of polymer swelling at the moving rubbery-glassy front and the rate of polymer erosion at the swollen polymer-dissolution medium front. It is preferable to attain the synchronization of the velocities of the swelling front and the erosion front to achieve zero-order release kinetics from PEO matrices. Water-soluble drugs are released by diffusion of the drug through swollen gel layer, and insoluble drugs are released by erosion of the polymer layer. The molecular weight of PEO, concentration of polymer, solubility of the drug, and the amount of the drug affect the release of the drug from the matrices.

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