Polyethylene Glycol

1 Nonproprietary Names

BP: Macrogols
JP: Macrogol 400
Macrogol 1500
Macrogol 4000
Macrogol 6000
Macrogol 20000
PhEur: Macrogola
USPNF: Polyethylene glycol

2 Synonyms

Carbowax; *Carbowax Sentry*; *Lipo*; *Lipoxol*; *Lutrol E*; PEG; *Pluriol E*; polyoxyethylene glycol.

3 Chemical Name and CAS Registry Number

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

4 Empirical Formula Molecular Weight

$HOCH_2(CH_2OCH_2)_mCH_2OH$ where m represents the average number of oxyethylene groups.

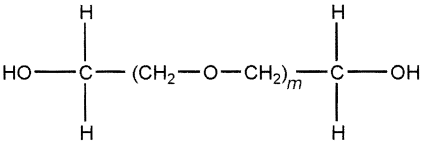
Alternatively, the general formula $H(OCH_2CH_2)_nOH$ may be used to represent polyethylene glycol, where n is a number m in the previous formula + 1.

See Table I for the average molecular weights of typical polyethylene glycols. Note that the number that follows PEG indicates the average molecular weight of the polymer.

Table I: Structural formula and molecular weight of typical polyethylene glycol polymers.

Grade	*m*	Average molecular weight
PEG 200	4.2	190–210
PEG 300	6.4	285–315
PEG 400	8.7	380–420
PEG 540 (blend)	—	500–600
PEG 600	13.2	570–613
PEG 900	15.3	855–900
PEG 1000	22.3	950–1 050
PEG 1450	32.5	1 300–1 600
PEG 1540	28.0–36.0	1 300–1 600
PEG 2000	40.0–50.0	1 800–2 200
PEG 3000	60.0–75.0	2 700–3 300
PEG 3350	75.7	3 000–3 700
PEG 4000	69.0–84.0	3 000–4 800
PEG 4600	104.1	4 400–4 800
PEG 8000	181.4	7 000–9 000

5 Structural Formula



6 Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

7 Applications in Pharmaceutical Formulation or Technology

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations.

Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin; *see* Section 14. They do not readily penetrate the skin, although the polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.[1] Solid grades are generally employed in topical ointments, with the consistency of the base being adjusted by the addition of liquid grades of polyethylene glycol.

Mixtures of polyethylene glycols can be used as suppository bases,[2] for which they have many advantages over fats. For example, the melting point of the suppository can be made higher to withstand exposure to warmer climates; release of the drug is not dependent upon melting point; the physical stability on storage is better; and suppositories are readily miscible with rectal fluids. Polyethylene glycols have the following disadvantages: they are chemically more reactive than fats; greater care is needed in processing to avoid inelegant contraction holes in the suppositories; the rate of release of water-soluble medications decreases with the increasing molecular weight of the polyethylene glycol; and polyethylene glycols tend to be more irritating to mucous membranes than fats.

Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as emulsion stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. However, they may cause hardening of the capsule shell by preferential absorption of moisture from gelatin in the shell.

In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.

In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules.[3] However, they have only limited binding action when used alone, and can

prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations,[4–6] a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75°C. The mass becomes pastelike and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.[7] Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers.[8] The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets. The lubricant action is not as good as that of magnesium stearate, and stickiness may develop if the material becomes too warm during compression. An antiadherent effect is also exerted, again subject to the avoidance of overheating.

In addition, polyethylene glycols have been used in the preparation of urethane hydrogels, which are used as controlled-release agents.

8 Description

The USPNF 20 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

9 Pharmacopeial Specifications

See Table II.

10 Typical Properties

Density:
1.11–1.14 g/cm^3 at 25°C for liquid PEGs
1.15–1.21 g/cm^3 at 25°C for solid PEGs

Flash point:
182°C for PEG 200
213°C for PEG 300
238°C for PEG 400
250°C for PEG 600

Freezing point:
< −65°C PEG 200 sets to a glass
−15 to −8°C for PEG 300
4–8°C for PEG 400
15–25°C for PEG 600

Melting point:
37–40°C for PEG 1000
44–48°C for PEG 1500
40–48°C for PEG 1540
45–50°C for PEG 2000
48–54°C for PEG 3000
50–58°C for PEG 4000
55–63°C for PEG 6000
60–63°C for PEG 8000
60–63°C for PEG 20000

Moisture content: liquid polyethylene glycols are very hygroscopic, although hygroscopicity decreases with increasing molecular weight. Solid grades, e.g., PEG 4000 and above, are not hygroscopic. *See* Figures 1–3.

Particle size distribution: *see* Figures 4 and 5.

Refractive index:
n_D^{25} = 1.459 for PEG 200
n_D^{25} = 1.463 for PEG 300
n_D^{25} = 1.465 for PEG 400
n_D^{25} = 1.467 for PEG 600

Table II: Pharmacopeial specifications for polyethylene glycol.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	—
Characters	—	+	—
Appearance of solution	—	+	+
Density	—	*See* Table IV	—
Freezing point	*See* Table III	*See* Table IV	—
Viscosity	—	*See* Table IV	*See* Table V
Average molecular weight	*See* Table III	—	*See* Table V
pH (5% w/v solution)	*See* Table III	—	4.5–7.5
Hydroxyl value	—	*See* Table IV	—
Reducing substances	—	+	—
Residue on ignition	*See* Table III	—	⩽0.1%
Sulfated ash	—	⩽0.2%	—
Limit of ethylene glycol and diethylene glycol	⩽0.25%	⩽0.4%	⩽0.25%
Ethylene oxide	—	⩽1 ppm	⩽10 ppm
1,4-Dioxane	—	⩽10 ppm	⩽10 ppm
Heavy metals	—	⩽20 ppm	⩽5 ppm
Organic volatile impurities	—	—	+
Water	⩽1.0%	⩽2.0%	—
Formaldehyde	—	⩽15 ppm	—

Table III: Specifications from JP 2001.

Type of PEG	Average molecular weight	Freezing point (°C)	pH (5% w/v solution)	Residue on ignition
400	380–420	4–8	4.0–7.0	⩽0.1%
1500	—	37–41	4.0–7.0	⩽0.1%
4000	2 600–3 800	53–57	4.0–7.5	⩽0.25%
6000	7 300–9 300	56–61	4.5–7.5	⩽0.25%
20000	15 000–25 000	56–64	4.5–7.5	⩽0.25%

Table IV: Specifications from PhEur 2002.

Type of PEG	Density (g/cm^3)	Freezing point (°C)	Hydroxyl value	Viscosity (dynamic) [mPa s (cP)]	Viscosity (kinematic) [mm^2/s (cSt)]
300	1.120	–	340–394	80–105	71–94
400	1.120	–	264–300	105–130	94–116
600	1.080	15–25	178–197	15–20	13.9–18.5
1000	1.080	35–40	107–118	22–30	20.4–27.7
1500	1.080	42–48	70–80	34–50	31–46
3000	1.080	50–56	34–42	75–100	69–93
3350	1.080	53–57	30–38	83–120	76–110
4000	1.080	53–59	25–32	110–170	102–158
6000	1.080	55–61	16–22	200–270	185–250
8000	1.080	55–62	12–16	260–510	240–472
20000	1.080	⩾57	–	2700–3500	2500–3200
35000	1.080	⩾57	–	11000–14000	10000–13000

Solubility: all grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol, and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Surface tension: approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

Viscosity (kinematic): *see* Tables IV, V, and VI.

11 Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.

Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.[9] Sterilization of solid grades by dry heat at 150°C for 1 hour may induce oxidation, darkening, and the formation of acidic degradation products. Ideally, sterilization should be carried out in an inert atmosphere. Oxidation of polyethylene glycols may also be inhibited by the inclusion of a suitable antioxidant.

If heated tanks are used to maintain normally solid polyethylene glycols in a molten state, care must be taken to avoid contamination with iron, which can lead to discoloration. The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 50°C. However, storage under nitrogen reduces the possibility of oxidation.

Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

12 Incompatibilities

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation.

Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents.

The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases, particularly that of penicillin and bacitracin. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.

Physical effects caused by polyethylene glycol bases include softening and liquefaction in mixtures with phenol, tannic acid, and salicylic acid. Discoloration of sulfonamides and dithranol can also occur and sorbitol may be precipitated from mixtures. Plastics, such as polyethylene, phenolformaldehyde, polyvinyl chloride, and cellulose-ester membranes (in filters) may be softened or dissolved by polyethylene glycols. Migration of polyethylene glycol can occur from tablet film coatings, leading to interaction with core components.

13 Method of Manufacture

Polyethylene glycols are condensation polymers formed by the reaction of ethylene oxide and water under pressure in the presence of a catalyst.

14 Safety

Polyethylene glycols are widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.[10–12]

Adverse reactions to polyethylene glycols have been reported, the greatest toxicity being with glycols of low molecular weight. However, the toxicity of glycols are relatively low.

Polyethylene glycols administered topically may cause stinging, especially when applied to mucous membranes. Hypersensitivity reactions to polyethylene glycols applied topically have also been reported, including urticaria and delayed allergic reactions.[13]

The most serious adverse effects associated with polyethylene glycols are hyperosmolarity, metabolic acidosis, and renal failure following the topical use of polyethylene glycols in burn patients.[14] Topical preparations containing polyethylene glycols should therefore be used cautiously in patients with renal failure, extensive burns, or open wounds.

Oral administration of large quantities of polyethylene glycols can have a laxative effect. Therapeutically, up to 4 L of an aqueous mixture of electrolytes and high-molecular-weight polyethylene glycol is consumed by patients undergoing bowel cleansing.[15]

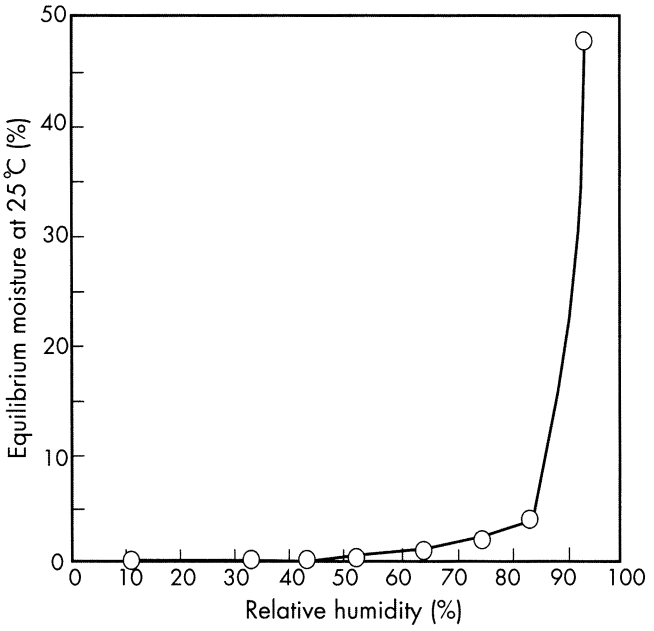


Figure 1: Equilibrium moisture content of PEG 4000 (McKesson, Lot No. B192–8209) at 25°C.

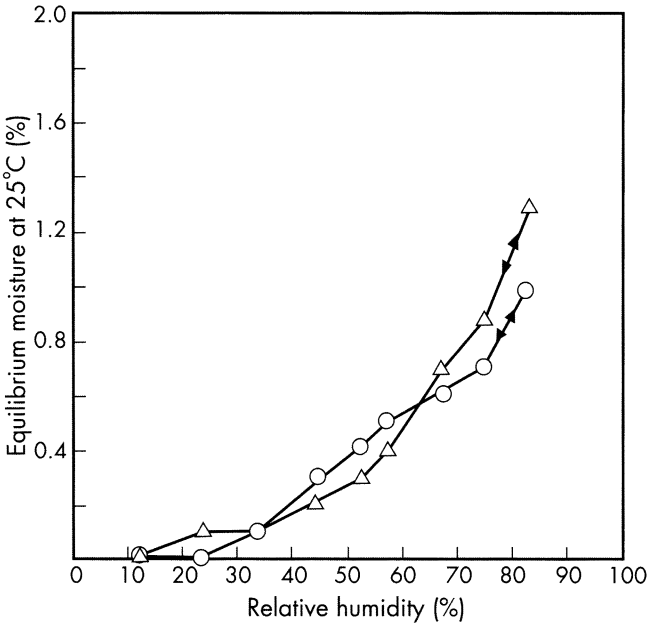


Figure 3: Equilibrium moisture content of PEG 6000 at 25°C.
○: PEG 6000 powder (Union Carbide Corp., Lot no. B–507)
△: PEG E–6000 (BASF, Lot no.WPNA–124B)

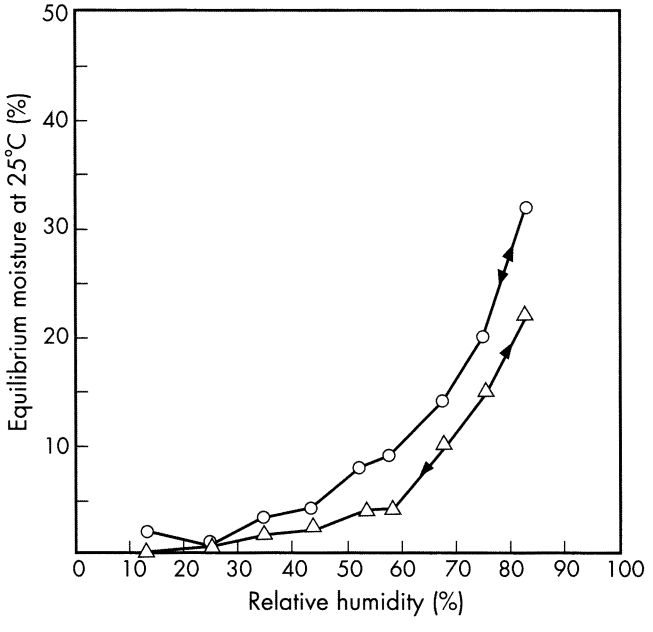


Figure 2: Equilibrium moisture content of PEG 4000 at 25°C.
○: PEG 4000 powder (Union Carbide Corp, Lot no. B-251)
△: PEG E–4000 (BASF, Lot no. WPYA–575B)

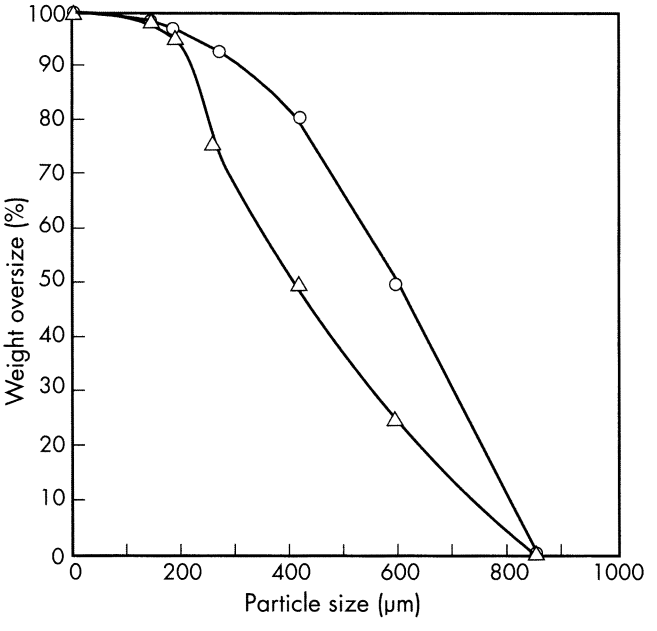


Figure 4: Particle size distribution of PEG 4000 and PEG 6000 flakes.
○: PEG 4000 flakes
△: PEG 6000 flakes

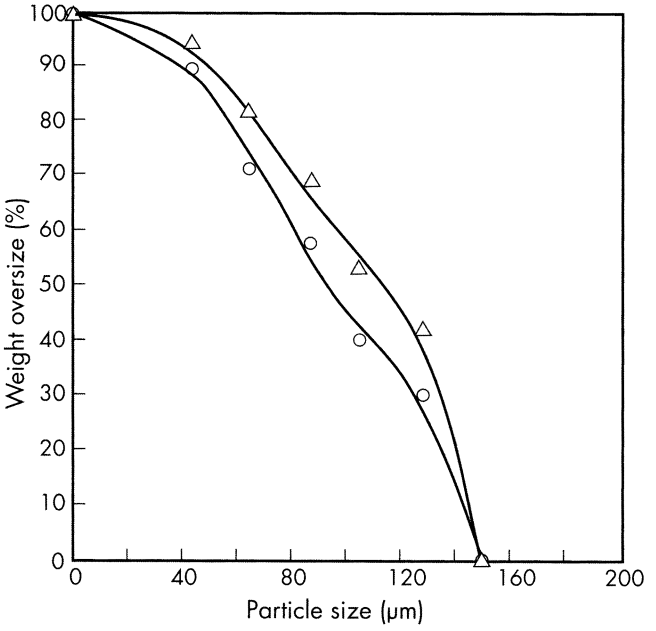


Figure 5: Particle size distribution of PEG 4000 and PEG 6000 powder.
○: PEG 4000 powder
△: PEG 6000 powder

Liquid polyethylene glycols may be absorbed when taken orally, but the higher-molecular-weight polyethylene glycols are not significantly absorbed from the gastrointestinal tract. Absorbed polyethylene glycol is excreted largely unchanged in the urine, although polyethylene glycols of low molecular weight may be partially metabolized.

The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg body-weight.[16]

In parenteral products, the maximum recommended concentration of PEG 300 is approximately 30% v/v as hemolytic effects have been observed at concentrations greater than about 40% v/v.

For animal toxicity data, *see* Table VII.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations; IM and IV injections; ophthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Polyoxyethylene alkyl ethers; polyoxyethylene sorbitan fatty acid esters; suppository bases.

18 Comments

—

Table V: Specification for viscosity of polyethylene glycol of the given nominal molecular weight at 98.9°C ± 0.3°C from the USPNF 20.

Type of PEG (nominal average molecular weight)	Viscosity (kinematic) [mm^2/s (cSt)]
200	3.9–4.8
300	5.4–6.4
400	6.8–8.0
500	8.3–9.6
600	9.9–11.3
700	11.5–13.0
800	12.5–14.5
900	15.0–17.0
1000	16.0–19.0
1100	18.0–22.0
1200	20.0–24.5
1300	22.0–27.5
1400	24–30
1450	25–32
1500	26–33
1600	28–36
1700	31–39
1800	33–42
1900	35–45
2000	38–49
2100	40–53
2200	43–56
2300	46–60
2400	49–65
2500	51–70
2600	54–74
2700	57–78
2800	60–83
2900	64–88
3000	67–93
3250	73–105
3350	76–110
3500	87–123
3750	99–140
4000	110–158
4250	123–177
4500	140–200
4750	155–228
5000	170–250
5500	206–315
6000	250–390
6500	295–480
7000	350–590
7500	405–735
8000	470–900

Table VI: Viscosity of selected polyethylene glycols at 25°C and 99°C.

Type of PEG	Viscosity [mm^2/s (cSt)]	
	25°C	99°C
PEG 200	39.9	4.4
PEG 300	68.8	5.9
PEG 400	90.0	7.4
PEG 600	131	11.0
PEG 1000 solid	19.5	—
PEG 2000 solid	47	—
PEG 4000 solid	180	—
PEG 6000 solid	580	—
PEG 20000 solid	6900	—

Table VII: Animal toxicity data (LD_{50}) for various grades of polyethylene glycol.[17]

PEG grade	LD_{50} (g/kg)								
	Guinea pig (oral)	Mouse (IP)	Mouse (IV)	Mouse (oral)	Rabbit (oral)	Rabbit (IV)	Rat (IP)	Rat (IV)	Rat (oral)
PEG 200	–	7.5	–	34	19.9	–	–	–	28.0
PEG 300	19.6	–	–	–	17.3	–	–	–	27.5
PEG 400	15.7	10.0	8.6	28.9	26.8	–	9.7	7.3	–
PEG 600	–	–	–	47	–	–	–	–	38.1
PEG 1000	–	20	–	–	–	–	15.6	–	32
PEG 1500	28.9	–	–	–	28.9	8	17.7	–	44.2
PEG 4000	50.9	–	16	–	76	–	11.6	–	50
PEG 6000	50	–	–	–	–	–	6.8	–	–

19 Specific References

1 Hadia IA, Ugriné HE, Farouk AM, Shayoub M. Formulation of polyethylene glycol ointment bases suitable for tropical and subtropical climates I. *Acta Pharm Hung* 1989; **59**: 137–142.
2 Kellaway IW, Marriott C. Correlations between physical and drug release characteristics of polyethylene glycol suppositories. *J Pharm Sci* 1975; **64**: 1162–1166.
3 Wells JI, Bhatt DA, Khan KA. Improved wet massed tableting using plasticized binder. *J Pharm Pharmacol* 1982; **34**(Suppl.): 46P.
4 Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *J Pharm Sci* 1971; **60**: 1281–1302.
5 Ford JL, Rubinstein MH. Formulation and ageing of tablets prepared from indomethacin–polyethylene glycol 6000 solid dispersions. *Pharm Acta Helv* 1980; **55**: 1–7.
6 Vila-Jato JL, Blanco J, Alonso MJ. The effect of the molecular weight of polyethylene glycol on the bioavailability of paracetamol–polyethylene glycol solid dispersions. *J Pharm Pharmacol* 1986; **38**: 126–128.
7 Miralles MJ, McGinity JW, Martin A. Combined water-soluble carriers for coprecipitates of tolbutamide. *J Pharm Sci* 1982; **71**: 302–304.
8 Okhamafe AO, York P. Moisture permeation mechanism of some aqueous-based film coats. *J Pharm Pharmacol* 1982; **34**(Suppl.): 53P.
9 Bhalla HL, Menon MR, Gopal NGS. Radiation sterilization of polyethylene glycols. *Int J Pharm* 1983; **17**: 351–355.
10 Smyth HF, Carpenter CP, Weil CS. The toxicology of the polyethylene glycols. *J Am Pharm Assoc (Sci)* 1950; **39**: 349–354.
11 Tusing TW, Elsea JR, Sauveur AB. The chronic dermal toxicity of a series of polyethylene glycols. *J Am Pharm Assoc (Sci)* 1954; **43**: 489–490.
12 Smyth HF, Carpenter CP, Weil CS. The chronic oral toxicology of the polyethylene glycols. *J Am Pharm Assoc (Sci)* 1955; **44**: 27–30.
13 Fisher AA. Immediate and delayed allergic contact reactions to polyethylene glycol. *Contact Dermatitis* 1978; **4**: 135–138.
14 Anonymous. Topical PEG in burn ointments. *FDA Drug Bull* 1982; **12**: 25–26.
15 Sweetman SC, ed. *Martindale: The Complete Drug Reference*, 33rd edn. London: Pharmaceutical Press, 2002: 1630–1631.
16 FAO/WHO. Evaluation of certain food additives. Twenty-third report of the joint FAO/WHO expert committee on food additives. *World Health Organ Tech Rep Ser* 1980; No. 648.
17 Lewis RJ, ed. *Sax's Dangerous Properties of Industrial Materials*, 10th edn. New York: Wiley, 2000: 2999–3001.

20 General References

Donovan MD, Flynn GL, Amidon GL. Absorption of polyethylene glycols 600 through 2000: molecular weight dependence of gastrointestinal and nasal absorption. *Pharm Res* 1990; **7**: 863–867.
Union Carbide Corporation. Technical literature: *Carbowax polyethylene glycols*, 1986.
Van Dam J, Daenens P. Molecular weight identification of polyethylene glycols in pharmaceutical preparations by gel permeation chromatography. *J Pharm Sci* 1993; **82**: 938–941.
Yamaoka T, Tabata Y, Ikada Y. Distribution and tissue uptake of poly(ethylene glycol) with different molecular weights after intravenous administration to mice. *J Pharm Sci* 1994; **83**: 601–606.

21 Author

JC Price.

22 Date of Revision

29 October 2002.