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Note

The effect of water-soluble polymers on aqueous solubility of drugs

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Abstract

The effect of three water-soluble polymers, i.e., hydroxypropyl methylcellulose and polyvinylpyrrolidone, on the aqueous solubility of drugs was investigated. Addition of a small amount, i.e., 0.10–0.25% (w/v), of the polymers results in significant enhancement of the aqueous solubility. The solubility studies indicate that a large fraction, e.g., 30–50%, of drug molecules in dilute aqueous polymer solutions is bound to the polymers. This polymer drug binding will affect the physicochemical properties and the availability of drugs in aqueous drug formulations containing water-soluble polymers.

Keywords: Complexation; Drugs; Polymer; Solubility; Aqueous solution; Incompatibility

Water-soluble polymers have been used in pharmaceutical formulations for many years and although the polymers are usually considered to be chemically inert, they are known to form complexes with small molecules in aqueous solutions. Almost 40 years ago Takeru Higuchi and co-workers investigated interactions of various drugs with a number of water-soluble polymers, i.e., polyethylene glycols, polypropylene glycols, polyvinylpyrrolidone and carboxymethylcellulose (Riley et al., 1991). In aqueous solutions, they frequently observed notable increase in the drug solubility due to formation of water-soluble drug-polymer complexes but sometimes phase separation was observed which was characterised in pharmaceutical systems as rather embarrassing incompatibilities (Riley et al., 1991; Marcus, 1956; Rácz, 1989). We have observed that addition of a very small amount of polymer can increase cyclodextrin complexation of drugs in aqueous solutions (Loftsson et al., 1994; Loftsson and Sigurðardóttir, 1994). Other investigators have shown that polymers interact with micelles in aqueous solutions (Attwood and Florence, 1983; Myers, 1988). In both cases the polymers have synergistic effect on the solubilising power of cyclodextrins and surfactants, respectively. In our work with cyclodextrins and polymers we have observed that polymers can be used to solubilize

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water-insoluble drugs, or drugs with limited aqueous solubility. In this paper we show that small amounts of polymers commonly used in various drug formulations, such as eye drops and nasal sprays, enhance aqueous solubility of many drugs through complex formation. The polymers can interact with drug molecules via electrostatic bonds (i.e., ion-to-ion, ion-to-dipole and dipole-to-dipole bonds) but other types of forces, such as van der Waals' forces and hydrogen bridges, may frequently participate in the complex formation (Rácz, 1989).

Acetazolamide was obtained from Agrar (Italy), hydrocortisone from Sigma Chemical Co. (USA), prazepam from Fabbrica Italiana sintetia (Italy) and sulfamethoxazole from Icelandic Pharmaceuticals (Iceland). Polyvinylpyrrolidone (PVP) of molecular weight (Mol. Wt) 40 000 and hydroxypropyl methylcellulose 4000 (HPMC) were obtained from Mecobenzone (Denmark), and PVP Mol. Wt 360 000 from Sigma. All other chemicals used were commercially available products of special reagent grade.

Solubilities were determined by adding an excess amount of the drug to be tested to aqueous buffered or unbuffered solution containing no polymer, 0.01–0.70% (w/v) PVP of Mol. Wt 40 000 or 360 000, or 0.01–0.30% (w/v) HPMC. The suspension formed was heated in an autoclave (M7 Speed Clave from Midmark Corporation, USA) in a sealed container to 120°C for 20 min (under 1 atm pressure). After equilibration at room temperature (23°C) for at least 3 days, the suspension was filtered through a 0.45-μm membrane filter (Millex-HV filter units from Millipore, USA), diluted with a mixture of methanol and water (7:3 v/v) and analysed by an HPLC method. Significant excess of the drug was always used in these studies and, thus, solid drug particles were always present in the aqueous solution during the whole equilibration period. The 3-day equilibration was considered sufficient since further equilibration of selected drug suspensions for up to 10 days did not result in any further drug precipitation. The drug solubility was determined at least three times under each condition and the results reported as the mean $\pm$ standard deviation (S.D.) of the mean. The following buffers were used: hydrochloric acid (pH 1), 0.11 M acetate (pH about 3.5 and about 5.5), 0.20 M acetate (pH about 4.5), buffer (phosphate) solution pH 6–7 (Ph. Eur., 2nd Edn., VII.1.3) and sodium hydroxide (pH 12). The exact pH of the final solution was determined at room temperature after the heating process and the mean pH and S.D. calculated for each buffer solution.

Quantitative determinations of the individual drugs were performed on a reversed-phase high-performance liquid chromatographic (HPLC) component system consisting of a Milton Roy ConstaMetric 3200 solvent delivery system operated at 1.50 ml/min, a Rheodyne 7125 injector, a Spectro Monitor 3200 uv/vis variable wavelength detector, operated at 263 (acetazolamide), 242 (hydrocortisone), 228 (prazepam) or 269 nm (sulfamethoxazole), and a Waters ODS 3.9 × 150 mm 4-μm (acetazolamide) or Beckman ODS 4.5 × 150 mm 4-μm (hydrocortisone, prazepam and sulfamethoxazole) column. For acetazolamide the mobile phase consisted of acetonitrile, acetic acid and water (10:2:88) containing 0.015% (w/v) 1-octanesulfonate and the retention time was 1.7 min. For hydrocortisone the mobile phase consisted of acetonitrile, tetrahydrofuran, acetic acid and water (35:1:1:63) and the retention time was 2.3 min. For prazepam the mobile phase consisted of methanol, tetrahydrofuran and water (85:1:14) and the retention time was 1.7 min. For sulfamethoxazole the mobile phase consisted of acetonitrile, acetic acid and water (30:1:69) and the retention time was 3.0 min. The HPLC methods were used to monitor the stability of the drugs. No or insignificant drug degradation was observed during the previously described heating process.

The effect of PVP and HPMC concentration on the aqueous solubility of hydrocortisone is shown in Fig. 1. Initially the aqueous solubility of hydrocortisone increases upon increasing polymer concentration but then the solubility levels off or decreases somewhat. When their concentration increases the polymer molecules tend to form electrostatic bonds between themselves which decreases their ability to form drug complexes. Also, brief heating in an autoclave and cooling to room temperature appeared to enhance the drug-poly-

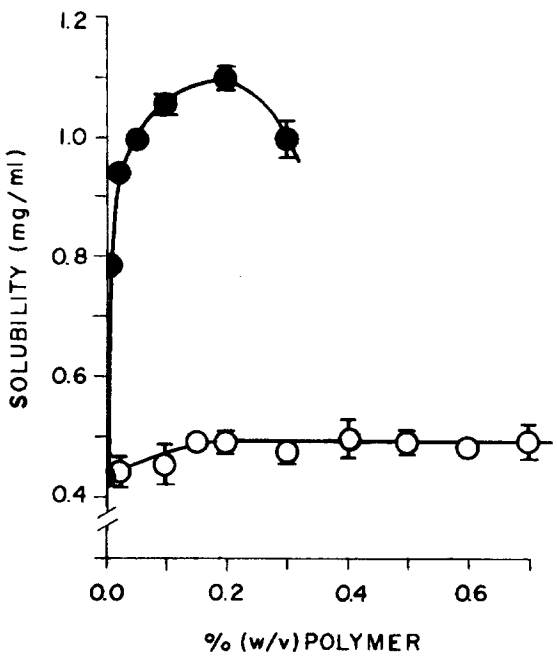

Fig. 1. The effect of increasing concentration of PVP Mol. Wt 360,000 (○) and HPMC (○) on the solubility of hydrocortisone in water at 22°C.

mer complex formation. HPMC has a much greater solubilising effect than PVP. Addition of 0.2% HPMC results in about 2.5-fold increase in the aqueous solubility of hydrocortisone which indicates that, under these conditions, at least 60% of the drug is bound to the polymer. The effect of the polymers on the aqueous solubility of acetazolamide, prazepam and sulfamethoxazole is shown in Tables 1, 2 and 3, respectively. The aqueous solubility of both the un-ionised and the ionised forms of the drugs is influenced by the polymers. For example, at pH 3.57–5.88 addition of 0.25% PVP about doubles the aqueous solubility of the un-ionised form of acetazolamide while at pH 7.25, where acetazolamide exists partly as the anion, the same amount of PVP results in about 33% solubility increase. Prazepam is a benzodiazepine possessing a protonable nitrogen group with pK_a of about 3.0 (Dox et al., 1978). At pH 1.13, where the drug is in a cationic form, addition of 0.10% HPMC results in about 25% increase in the solubility but at pH 5.52 and 12.2, where the drug is on the un-ionised form, the same amount of HPMC results in 30–35% increase (Table 2). Finally, Table 3 shows that the aqueous solubility of the cationic form (dominating at pH below 1.5) and the un-ionised form (dominating at pH between 2 and 6) of sulfamethoxazole is improved by addition of the polymers. Previously, we have shown that addition of 0.25% (w/v) PVP Mol. Wt 40 000 to water results in an average of 64% increase in the aqueous solubility of nine different drugs and addition of 0.25% (w/v) carboxymethylcellulose results in an average of 53% increase in the aqueous solubility of 16 different drugs (Loftsson et al., 1994). The solubility studies indicate that a large fraction, e.g., 30–50%, of drug molecules in aqueous polymer solutions are bound to the polymers. This will not only affect the aqueous solubility of the drugs but also various other physicochemical properties of drugs and their availability in aqueous drug formulations. Thus, in aqueous eye drop formulations polymer complexation of drug molecules will not only affect

Table 1
Effects of hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP) Mol. Wt 40,000 on solubility of acetazolamide in aqueous buffer solutions at 23°C

pH ± S.D.	Solubility (mg/ml) ± S.D.			
	No polymer	0.10% HPMC	0.10% PVP	0.25% PVP
1.17 ± 0.02	0.63 ± 0.00	1.1 ± 0.0	0.76 ± 0.03	0.91 ± 0.00
3.57 ± 0.21	0.53 ± 0.00	0.93 ± 0.02	0.67 ± 0.02	1.0 ± 0.0
4.47 ± 0.12	0.52 ± 0.00	0.78 ± 0.02	0.76 ± 0.02	1.0 ± 0.0
5.34 ± 0.12	0.57 ± 0.01	0.86 ± 0.04	0.78 ± 0.03	0.86 ± 0.00
5.88 ± 0.13	0.57 ± 0.01	0.90 ± 0.02	0.74 ± 0.03	1.0 ± 0.0
7.25 ± 0.18	0.99 ± 0.00	1.2 ± 0.0	1.4 ± 0.1	1.5 ± 0.0

Table 2
Effects of hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP) Mol. Wt 40,000 on solubility of prazepam in aqueous buffer solutions at 23°C

pH ± S.D.	Solubility (mg/ml) ± S.D.			
	No polymer	0.10% HPMC	0.10% PVP	0.25% PVP
1.13 ± 0.04	670 ± 70	840 ± 50	650 ± 20	940 ± 10
3.50 ± 0.07	9.5 ± 2.3	11 ± 0	20 ± 0	11 ± 0
4.49 ± 0.09	5.8 ± 0.0	7.1 ± 0.3	6.4 ± 0.1	5.6 ± 0.0
5.52 ± 0.08	4.9 ± 0.1	6.8 ± 0.1	5.9 ± 0.0	3.7 ± 0.0
12.2 ± 0.2	3.3 ± 0.5	4.3 ± 0.1	3.9 ± 0.5	6.9 ± 0.0

Table 3
Effects of hydroxypropyl methylcellulose (HPMC) and polyvinylpyrrolidone (PVP) Mol. Wt 40,000 on solubility of sulfamethoxazole in aqueous buffer solutions at 23°C

pH ± S.D.	Solubility (mg/ml) ± S.D.			
	No polymer	0.10%	0.10% PVP	0.25% PVP
1.18 ± 0.04	3.2 ± 0.5	4.4 ± 0.8	4.1 ± 0.6	6.3 ± 0.3
3.65 ± 0.13	0.35 ± 0.01	0.38 ± 0.01	0.42 ± 0.00	0.38 ± 0.16
4.57 ± 0.05	0.35 ± 0.00	0.39 ± 0.00	0.39 ± 0.00	0.39 ± 0.01
5.51 ± 0.02	0.47 ± 0.00	0.55 ± 0.00	0.55 ± 0.00	0.53 ± 0.00
6.06 ± 0.20	0.75 ± 0.00	0.78 ± 0.01	0.80 ± 0.01	0.80 ± 0.01
6.99 ± 0.35	7.5 ± 2.0	5.7 ± 0.2	6.5 ± 0.3	5.9 ± 0.2

the drug flux into the eye but also the rate of drug drainage from the surface of the eye.

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References

Attwood, D. and Florence, A.T., *Surfactant Systems. Their Chemistry, Pharmacy and Biology*, Chapman and Hall, London, 1983, pp. 361–365.

Dox, T. et al. *Iyakirkin Kenkyn*, 9 (1978) 205 (through Chem. Abstr. 88: 141601a, 1978).

Loftsson, T., Friðriksdóttir, H., Sigurðardóttir, A.M. and Ueda, H., The effect of water-soluble polymers on drug-cyclodextrin complexation. *Int. J. Pharm.*, 10 (1994) 169–177.

Loftsson, T. and Sigurðardóttir, A.M., The effect of polyvinylpyrrolidone and hydroxypropyl methylcellulose on HPbCD complexation of hydrocortisone and its permeability through hairless mouse skin. *Eur. J. Pharm. Sci.*, 2 (1994) 297–301.

Marcus, A.D., Complexation incompatibilities. *Drug Cosmet. Ind.*, 79 (1956) 456– 457, 554, 560–561 and 564.

Myers, D., *Surfactant Science and Technology*, VCH Publishers, New York, 1988, pp. 142–145.

Rácz, I. *Drug Formulation*, John Wiley and Sons, Budapest, 1989, pp. 212–242.

Riley, C.M., Rytting, J.H. and Kral, M.A. (Eds.), *Takeru Higuchi, a Memorial Tribute, Volume 3. Equilibria and Thermodynamics*. Allen Press, Lawrence (Kansas), 1991, pp. 220–272.