International Journal of Pharmaceutics, 85 (1992) R1–R4

IJP 10051

Rapid communication

Release kinetics of flurbiprofen from hydrophobic heterogeneous matrices containing surfactants

M. Efentakis

University of Athens, Department of Pharmacy, Division of Pharmaceutical Technology, Panepistimioupolis 157 71, Athens (Greece)

(Received 12 July 1992)
(Accepted 25 July 1992)

Key words: Eudragit RL100; Indragit RS100; Flurbiprofen; Dissolution; Solubilization; Surfactant; Controlled release

Summary

The action of surfactants on the release rate of flurbiprofen formulated with acrylic resins was studied. The dissolution data indicate that the release profiles of flurbiprofen are affected by the amount of surfactant incorporated in the matrix. The incorporation of large amounts of surfactants shows a biphasic release profile of the drug.

In earlier studies (Efentakis et al., 1990, 1991; Buckton et al., 1991) we have examined the influence of additives (especially surfactants) and formulation factors on drug release from acrylic hydrophobic matrix tablets containing flurbiprofen. Flurbiprofen is a well known non-steroidal antiflammatory agent very slightly soluble in water (Martindale, 1982). For this reason it seems reasonable to study the effect of surfactants on the drug release from directly compressed tablets. Dissolution profiles and release rates were derived for flurbiprofen. The results indicated zero-order drug release from Eudragit RS matrices when the dissolution data were regressed vs time. The mechanism of drug release naturally is influenced by the presence and the location of drug and surfactant molecules in the tablet. The possible sites of location of the surfactant molecules could be either on the surface of the tablet, within the tablet matrix isolated from the interior environment or within the tablet but connected with its outer surface by means of channels. A similar model was proposed by Cupta et al. (1986) in their work concerning the release of adriamycin from albumin microspheres.

Thus, the rate of release of the drug from one site will differ from the other sites and will depend on several factors. In particular, the release of the drug from the surface of the tablet will depend on drug solubility, its physical state, its affinity for the excipients and the ability of the surfactant to facilitate wetting, while the release of incorporated drug is mainly due to diffusion of the drug through the existing or created channels. The release rate is further affected on dissolution

Correspondence to: M. Efentakis, University of Athens, Department of Pharmacy, Division of Pharmaceutical Technology, Panepistimioupolis 157 71, Athens, Greece.

medium penetration and the wetting effect of the surfactant. Consequently, the release of the drug appears rather complex and differs from location to location.

The purpose of this study was to re-examine previously published data and to attempt to explore further the release kinetics of an insoluble drug (flurbiprofen) from hydrophobic inert matrices.

The acrylic resins Eudragit RS 100 and RL 100 obtained from Rhom Pharma (Darmstadt, Germany) were powdered in a ball mill and sieved through a 300 mm sieve. The powder was then blended with flurbiprofen (provided by Boots) and the other additives, i.e., sorbitol (Merck), or dextrose (Megglie), sodium taurocholate (Fluka), sodium lauryl sulphate (BDH) and magnesium stearate (BDH) for 5 min in a blender. The formulations prepared contained vary amounts of materials in the proportions shown in Table 1. The tablets (500 mg) were compressed using the direct compression technique on an instrumented single-punch tablet machine (Korch-Erweka). The ratio between the diameter and the thickness of the cylindrical tablets was between 0.7 and 0.9. The hardness level was 8–9 kg as measured in the Erweka hardness tester. The dissolution measurements were carried out in a USP dissolution apparatus (paddle method), using 1000 ml of phosphate buffer pH 7.2 at 37.7°C (USP), rotated at 100 rpm. Flurbiprofen samples were taken over an 8 h period and immediately replaced with an equal volume of test medium. The samples were analyzed spectrophotometrically at 248 nm using a Perkin Elmer spectrophotometer. Each data point represents the mean of measurements from three tablets.

In previous papers (Efentakis et al., 1990; Buckton et al., 1991) the dissolution profiles of flurbiprofen were obtained and were found to be linear when the percentage of drug released was regressed vs time showing zero-order drug release. In this study, these results and others have been replotted as the undissolved amount of drug vs time. The release profiles for the formulations without surfactant or with 1% surfactant (sodium taurocholate or sodium lauryl sulphate) incorporated were found to be linear as before. However, when the amount of surfactant incorporated was increased to 1.5% the release profile appeared to be biphasic and the phenomenon was more profound when the concentration was further increased to 1.7%. In all cases, increasing the amount of surfactant results in enhanced release rates of the drug, and sodium taurocholate exhibited a better dissolution profile than that of sodium lauryl sulphate (Efentakis et al., 1990).

Figs. 1–3 show the release profiles obtained and in Table 2 the release rate constants for each formulation are listed. The plots clearly show that when the concentration exceeds 1% the release profile becomes biphasic, i.e., it consists of two phases, an initial rather fast release phase and a terminal slower release phase. From Figs. 1–3 it is obvious that the initial phase lasts 210 min for RS mixtures (Figs. 1 and 2) while for the RL/RS mixtures it is of 180 min duration (Fig. 3). This is probably due to different permeability of RL and

TABLE 1

The formulations used in the study

	Percentage (% w/w)												
	A1	A2	A3	A4	A5	B1	B2	B3	B4	C1	C2	C3	C4
Flurbiprofen	49	49	49	49	49	49	49	49	49	49	49	49	49
Eudragit RS100	25	25	25	25	25	25	25	25	25	5	5	5	5
Eudragit RL100	–	–	–	–	–	–	–	–	–	5	5	5	5
Dextrose	–	–	–	–	–	25	24	23.5	23.3	40	39	39.5	39.3
Sorbitol	25	24	24	23.5	23.5	–	–	–	–	–	–	–	–
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1	1
Sodium taurocholate	–	–	1	–	1.5	–	1	1.5	1.7	–	–	–	–
Sodium lauryl sulphate	–	1	–	1.5	–	–	–	–	–	–	1	1.5	1.7

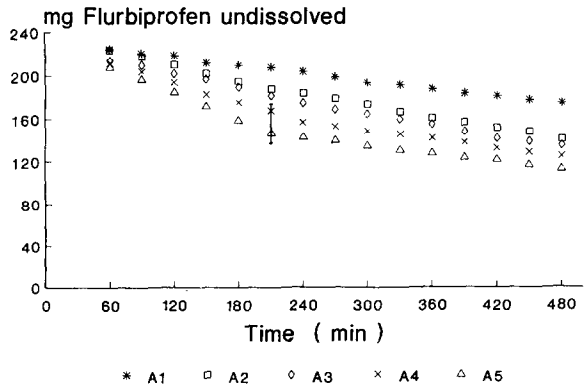

Fig. 1. Release profiles of formulations A1–A5.

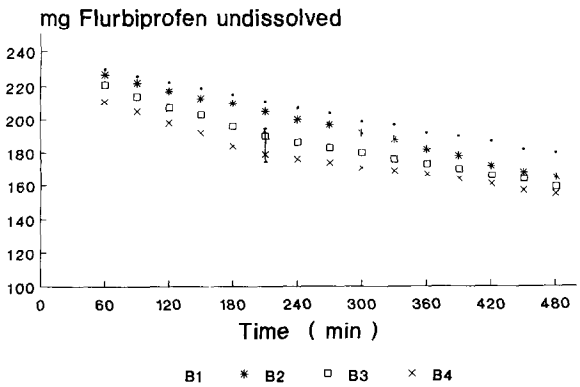

Fig. 2. Release profiles of formulations B1–B4.

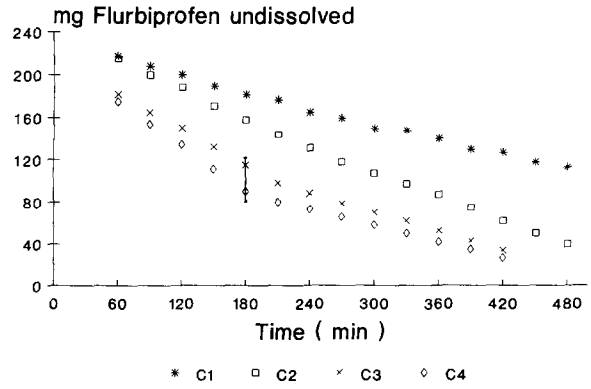

Fig. 3. Release profiles of formulations C1–C4.

RS (less permeable); therefore, RS matrices are permeated at a slower rate by the dissolution medium than the RL/RS matrices. The initial phase is faster in all cases as can be seen from the slopes (Table 2) and it is the combined effect of drug released from the surface of the matrix increased due to better wetting caused by the presence of surfactant and of the change of the matrix structure, i.e., the start of disintegration of the tablet resulting in a rapid increase in dissolution area. The slower terminal phase describes the dissolution of the amount of the drug entrapped in the interior of the matrix.

TABLE 2

Release rates of flurbiprofen (mg min $^{-1}$) using zero-order model

Formulation	Total release rate constant (±SD)	r^2	Initial release rate constant (±SD)	r^2	Terminal release rate constant (±SD)	r^2
A1	−0.120 ± 0.031	0.998				
A2	−0.193 ± 0.340	0.995				
A3	−0.194 ± 0.300	0.997				
B1	−0.122 ± 0.275	0.998				
B2	−0.149 ± 0.300	0.998				
C1	−0.247 ± 0.250	0.997				
C2	−0.410 ± 0.290	0.996				
			(0–210 min)		(240–480 min)	
A4	−0.202 ± 0.370	0.976	−0.300 ± 0.250	0.998	−0.133 ± 0.318	0.999
A5	−0.212 ± 0.340	0.960	−0.411 ± 0.203	0.999	−0.123 ± 0.305	0.997
B3	−0.140 ± 0.350	0.986	−0.207 ± 0.310	0.997	−0.110 ± 0.295	0.997
B4	−0.125 ± 0.390	0.975	−0.213 ± 0.285	0.998	−0.090 ± 0.250	0.997
			(0–180 min)		(210–420 min)	
C3	−0.404 ± 0.380	0.989	−0.556 ± 0.221	0.999	−0.313 ± 0.380	0.999
C4	−0.383 ± 0.390	0.970	−0.693 ± 0.291	0.999	−0.254 ± 0.270	0.999

The biphasic profile at concentrations higher than 1% might be attributed to increased drug release caused by the greater amount of surfactant incorporated, which results in greater wetting and solubilization of the drug (Schott et al., 1982). The results indicate that surface-active agents may produce more channels available for the dissolution fluid to leach out the drug at concentrations over 1%. At such high concentrations both surfactants are above their CMC (Efentakis et al., 1991) and the solubilization effect could enhance further the release of the drug, since when surfactant is present at concentrations above CMC dissolution may also be favoured by the increased solubility resulting from micellar solubilization (Hajratwala and Taylor, 1976; Wells and Parrott, 1992).

It can be concluded that the difference of dissolution mode, i.e., linear at low surfactant concentrations and biphasic at higher concentrations, can be attributed to the fact that at concentrations above the CMC the release of the insoluble drug is due to better wetting and solubilization and therefore the drug is released more rapidly while at levels below or around the CMC the release may be explained by better wetting only.

References

Buckton, G., Efentakis, M., Al-Hmoud, H. and Rajan, Z. The influence of surfactants on drug release from acrylic matrices. *Int. J. Pharm.*, 74 (1991) 169–174.

Cupta, P.K., Hung, C.T. and Perrier, P.G., Albumin microspheres. Release characteristics of adriamycin. *Int. J. Pharm.*, 33 (1986) 137–146.

Efentakis, M., Al-Hmoud, H. and Choulis, N.H., Effects of additives on flurbiprofen control led release preparation. *Acta Pharm. Technol.*, 36 (1990) 237–239.

Efentakis, M., Al-Hmoud, H., Buckton, G. and Rajan, Z., The influence of surfactants on drug release from hydrophobic matrix. *Int. J. Pharm.*, 70 (1991) 153–158.

Hajratwala, B.R. and Taylor, H., Effect of non-ionic surfactants on the dissolution and solubility of hydrocortisone. *J. Pharm. Pharmacol.*, 28 (1976) 934–935.

Martindale, *The Extra Pharamcopoeia*, 28th Edn The Pharmaceutical Press, London, 1982.

Schott, H., Kwan, L.C. and Feldman, S., The role of surfactants in the release of very slightly soluble drugs from tablets. *J. Pharm. Sci.*, 71 (1982) 1038–1045.

Wells, M.L. and Parrott, E.L., Effect of anionic surfactants on the release of chlorpheniramine maleate from an inert, heterogeneous matrix. *Drug Dev. Ind. Pharm.*, 18 (1992) 175–186.