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Note

Effect of chemical properties on drug release from hydrophobic matrices

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Abstract

The drug release of modified release matrix systems is often governed by erosion as well as by diffusion through the matrix. The purpose of the present work was to study the release kinetic parameters of inorganic and organic water soluble drugs from hydrophobic wax matrix systems, produced by melt coating. The drug release process was investigated both experimentally and by means of mathematical models. Different models (first order, cube root, square root, two-third root) and the Weibull distribution were applied for the evaluation of the drug release data. On the basis of our results, it can be concluded that not only the ratio but the chemical characteristic of the drug and the matrix base material as well determine the rate of drug release. © 1998 Elsevier Science B.V.

Keywords: Sustained release; Wax matrix; Water soluble salts; Release kinetics; Mathematical models

A well-designed dosage form is able to improve the efficiency and safety of drug administration. The mean plasma elimination half-lives of most highly water soluble drugs are relatively short (2–4.5 h), which necessitates several applications a day (Khan, 1995). Long-acting sustained and controlled release preparations make a once-a-day dose treatment possible. Waxy-type excipients were successfully applied as release-controlling agents (Huang et al., 1994; Giannola et al., 1995).

Potassium Chloride ($M_w = 74.6$), Ephedrine Hydrochloride ($M_w = 201.7$) and Procaine Hydrochloride ($M_w = 272.8$) of USP 23 grade were selected as highly water soluble model drugs. The chosen matrix base material was white beeswax (melting range of 62–65°C) purchased from the Fluka (Buchs, Switzerland).

The thermosoftening matrix material in all cases was heated in a double jacketed vessel mixer (Erweka SG 3/W, Erweka, and Stephan UMC-5,

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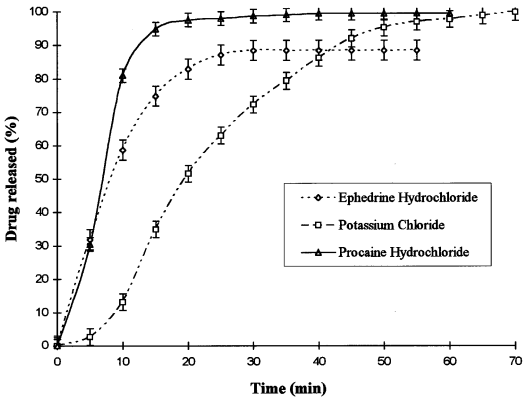

Fig. 1. Dissolution profiles of examined salts embedded into hydrophobic matrix (9/1 drug/excipient ratio; S.E.: ±2.8; $n = 6$).

Stephan und Söhne, Germany) to 70°C (±1°C). The crystals of the model drugs were mixed into the molten mass. Constant stirring was applied (30 rpm with Erweka mixer for 15 min and 300 rpm with Stephan mixer for 5 min) until the wax was completely molten. To prevent the sedimentation of the higher density component, 5% glycerol monostearate was added to increase the viscosity.

The diffusion reflectance was measured by Hitachi U-2501 UV/VIS/NIR spectrophotometer (Hitachi, Japan) equipped with integrating sphere ($d = 60$ mm) and PbS detector. The reflectance of samples was detected in the 200–2500 nm wavelength range using 5 mm layered cell.

For the determination of dissolution profiles of the samples the rotating paddle method of USP 23 at 100 rpm was used (PTW2 dissolution test apparatus, Pharmatest Apparatebau, Hainburg). The study was conducted in 500 ml of pH = 1.2 simulated gastric fluid, prepared with 0.1 N HNO_3 instead of HCl. The dissolution of Potassium Chloride was monitored continuously using a digital pH-meter (Radelkis OP 211/1, Budapest), equipped with chloride-selective electrode. The dissolved Procaine Hydrochloride and Ephedrine Hydrochloride were measured spectrophotometrically at their absorbance maximum (227 nm and 208 nm) using ATI UNICAM UV/VIS spectrophotometer with Vision 2.0 UNICAM Software.

Fig. 1 illustrates the differences in the dissolution profiles, according to the type of the embedded salts. The drug/excipient ratio was 9/1 for each of the examined samples. To describe the release patterns of the non-disintegrating lipophilic matrices (Su et al., 1994; Dredán et al., 1996) the following mathematical models were

Table 1
Dissolution rate constants determined applying different kinetic functions

	Fick	First order	Higuchi	Baker–Lonsdale
Ephedrine hydrochloride	1.32×10^{-1} (0.9922)	1.12×10^{-1} (0.9954)	2.03×10^{-1} (0.9916)	2.13×10^{-2} (0.9572)
Potassium chloride	9.37×10^{-3} (0.9688)	4.07×10^{-2} (0.9867)	1.25×10^{-1} (0.9669)	6.59×10^{-3} (0.9388)
Procaine hydrochloride	8.53×10^{-2} (0.9402)	1.34×10^{-1} (0.9800)	1.80×10^{-1} (0.9188)	1.39×10^{-2} (0.9571)

Correlation coefficients in parentheses.

Table 2
Characteristic parameter values of Weibull distribution function

	τ_d (min)	β	t_{lag} (min)	t_∞ (min)	M_∞ (%)
Ephedrine hydrochloride	8.9	1.199	0.00	25	97.4
Potassium chloride	23.0	1.254	0.12	70	99.8
Procaine hydrochloride	5.9	1.179	1.12	40	98.4

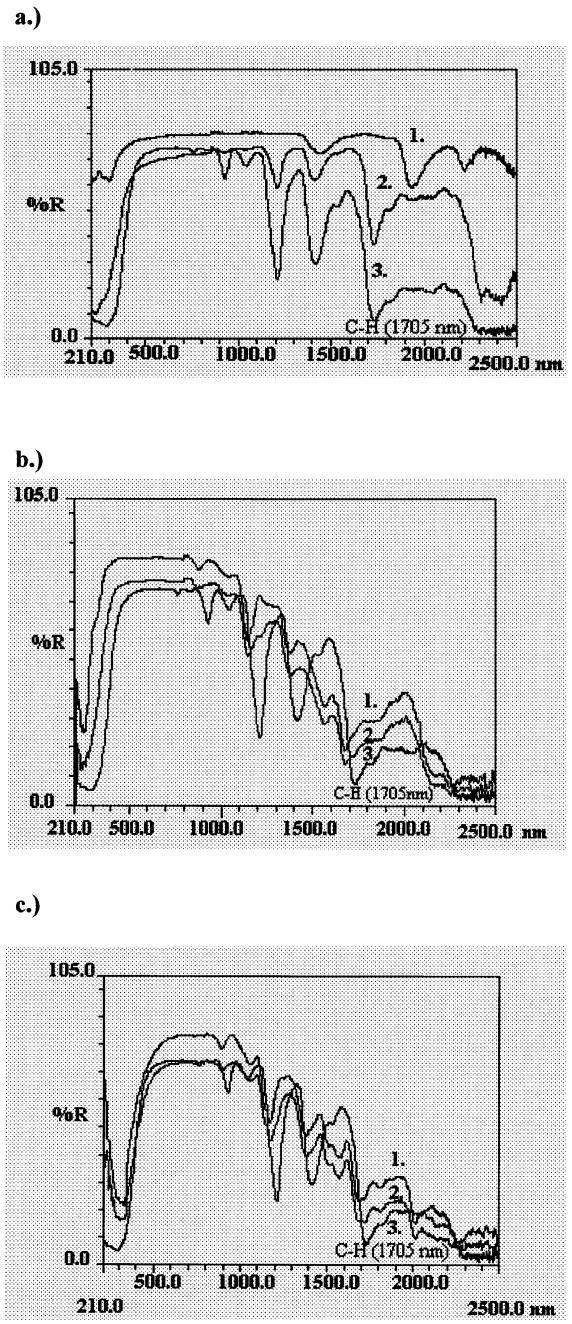

Fig. 2. Diffuse reflectance spectra of various salts embedded into white beeswax (9/1 drug/excipient ratio: 1, salt; 2, embedded salt; 3, white beeswax). (a) Potassium Chloride, (b) Ephedrine Hydrochloride, (c) Procaine Hydrochloride.

used. The computer package Microsoft Excel 5.0, solver function was applied for the nonlinear parameter estimation to minimize the squares of residuals.

Fickian diffusion based release model (Peppas, 1985)

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t amount of drug released at time t; M_∞ the maximal amount of the released drug at infinite time; k is the rate constant of drug release; n is the release exponent.

Higuchi square-root time model

$$\frac{M_t}{M_\infty} = kt^{1/2} \tag{2}$$

First-order model

$$\frac{M_t}{M_\infty} = 1 - \exp(-kt) \tag{3}$$

Baker and Lonsdale (two-thirds root) model

$$\frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{2/3}\right] \frac{M_t}{M_\infty} = k_t \tag{4}$$

Weibull distribution (Langenbucher, 1976; Carstensen, 1977)

$$\frac{M_t}{M_\infty} = 1 - \exp\left\{-\left[\frac{(t - t_0)}{\tau_d}\right]^\beta\right\} \tag{5}$$

where t_0 is the lag time of the drug dissolution; τ is the time, when 63.2% of M_∞ has been released; β shape parameter of the dissolution curve.

Table 1 summarizes the release rate constants calculated by the above mentioned kinetic functions and the correlation coefficients of the observed release data and the simulated profiles. The results show that the values of the rate constants are significantly smaller in the case of Potassium Chloride. For each of the examined samples the best correlation was achieved with the application of Weibull distribution. Correlation coefficients were over 0.9940 in each cases.

Table 2 summarizes the dissolution kinetic parameters of Weibull distribution. The results indicate that the dissolution process was faster (smaller τ_d values) when organic salts were embedded into the wax system. Due to the structural similarities, the organic salts are more soluble in

the matrix base, thus facilitates their diffusion. The strong electrolites, like the inorganic Potassium Chloride, completely dissociate in aqueous solution. The organic salts, containing hydrophobic molecular parts, diffuse through the hydrophobic matrix easier than hydrophillic materials, consequently their release rate—based on the matrix diffusion—is faster compared to that of the strong electrolite Potassium Chloride.

As the calculated M_∞ values indicate in Table 2 there was some drug retained in each of the embedded salt samples. The results of the infinite time ($t_\infty = 360$ min) measurements are good compliance with the calculated M_∞ values. The possible 'ghost' formation (Giannola et al., 1995; Moroni and Ghebre-Sellassie, 1995) between the organic salts and the wax matrix resulted in a higher residual drug content, mainly in the case of Ephedrine Hydrochloride. Concerning the Procaine Hydrochloride, the secondary protonation in acidic medium increased the difference in the solubility (The Merck Index, 1989) of the two organic salts therefore 'ghost' formation is not so expressed.

Fig. 2 demonstrates the diffuse reflectance spectra of various matrix samples. The C–H peaks which can be seen in Fig. 2a indicate the presence of the organic matrix base (C–H stretch first overtone at 1705 nm and second overtone at 1215 nm). In the case of Procaine and Ephedrine Hydrochloride it is clear that the structural elements of the matrix base material and of the embedded salts are similar to each other (peaks at 1705 and 1215 nm).

To sum up, our results demonstrate both of the ratio and the chemical characteristic of the drug and matrix material determine the rate of drug release.

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