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The effect of the physicochemical properties of a drug on its release from chitosonium malate matrix tablets

Julide Akbuğa

University of Marmara, Faculty of Pharmacy, Haydarpaşa 81010, Istanbul (Turkey)

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Summary

The effect of the physico-chemical properties of an active compound (such as solubility and molecular size) on its release characteristics from chitosonium malate matrix tablets has been investigated. For this purpose, the release of 11 drugs of various solubilities (1 in < 1 to 1 in 10000) and molecular weights (138–375) through chitosonium malate matrix tablets was studied. It may be concluded that, in addition to the solubility, the molecular size of drug is of importance in the drug release characteristics from the chitosonium malate matrix. When the release data (< 60%) were fitted to the simple power law equation, the mode of drug release from the chitosonium malate matrix was generally non-Fickian and Super Case II type. These drugs (timolol maleate, ephedrine, propranolol hydrochloride, acetylsalicylic acid, naproxen, sulphadiazine, indomethacin and pindolol) can be released at a nearly zero-order rate through the matrix.

Among the various polymers, chitosan may be preferred for sustained-release formulations, since it is a biodegradable and biocompatible natural polymer.

Previously, a salt of chitosan (chitosonium malate) was investigated as a matrix for sustained-release tablets and successful results were obtained (Akbuğa, 1993). Chitosonium malate has many more advantages than chitosan such as showing sustained-release properties even at low concentrations.

On the other hand, the aqueous solubility of a drug affects the release mechanism from polymer matrices (Higuchi, 1963; Lapidus and Lordi, 1968). The release of several drugs, having widely different molecular weights, through different matrices was studied, and the results revealed that, as the molecular size of the solute increases, the release rate decreases (Korsmeyer et al., 1983; Rango Rao et al., 1990).

The objective of this study was to determine the influence of aqueous solubility and molecular size of drugs on their release through chitosonium malate matrix tablets.

Chitosonium malate (chitosonium salt of malic acid) (20 mPa s viscosity grade, Protan A/S, Drammen, Norway), timolol maleate, naproxen (Bilim Pharm. Co., Turkey), propranolol hydrochloride atenolol, piroxicam, sulphadiazine (Doğu Pharm. Co., Turkey), indomethacin (Sigma, St.

Correspondence to: J. Akbuğa, University of Marmara, Faculty of Pharmacy, Haydarpaşa 81010, Istanbul, Turkey.

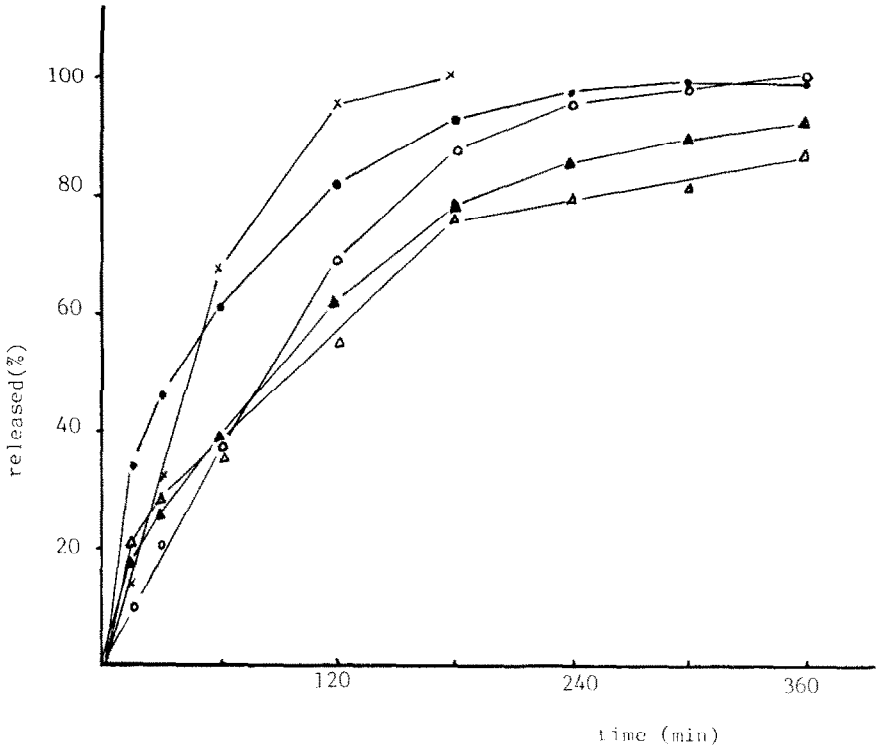

Fig. 1. Release profiles of timolol maleate (○), atenolol (●), ephedrine (△), propranolol hydrochloride (▲), and acetylsalicylic acid (×) from tablets.

Louis, MO, U.S.A.), acetylsalicylic acid (Bayer, Turkey), pindolol (Sandoz, Turkey) methyl prednisolone (Hoechst, Turkey) and ephedrine (E. Merck, Germany) were used. The list of drugs, their molecular weights and approximate aqueous solubilities according to the USP XXII are given in Table 1.

Active substance was manually mixed with chitosonium malate (1 : 1) and compressed into flat-faced tablets (400 mg, 13.06 mm diameter) using a hydraulic press (Specac, U.K.) at 5000 kg/cm^2 for 30 s. The amount of drug present in each tablet was 200 mg.

The USP XXII paddle method was employed at a rotation speed of 100 rpm. 900 ml of phosphate buffer (pH 7.4 ± 0.05) were used as the dissolution medium and maintained at 37 ± 0.2°C. Samples were periodically removed and analyzed spectrophotometrically (Shimadzu 2100 S Spectrophotometer, Japan). The means of six determinations are given. Corrections were made for any absorption due to matrix material.

The release profiles of drugs from chitosonium malate matrix tablets are given in Figs 1 and 2. The release rates of drugs from tablets were calculated by subjecting the dissolution data of ≥ 60% to least-squares linear fitting.

TABLE 1

Molecular weight, solubility and pK_a values of active compounds

Active compounds	Mol. Wt	Approximate solubility	pK_a
Timolol maleate	432.49	< 1	9.00
Atenolol	266.30	< 1	9.60
Ephedrine	165.23	20	9.63
Propranolol hydrochloride	259.34	20	9.45
Acetylsalicylic acid	180.15	300	3.50
Naproxen	230.26	1000–10000	4.15
Piroxicam	331.35	1000–10000	6.30
Indomethacin	359.79	10000	4.50
Methylprednisolone	374.46	10000	2.60, 6.00
Pindolol	248.32	> 10000	8.8
Sulphadiazine	250.28	13000	6.5

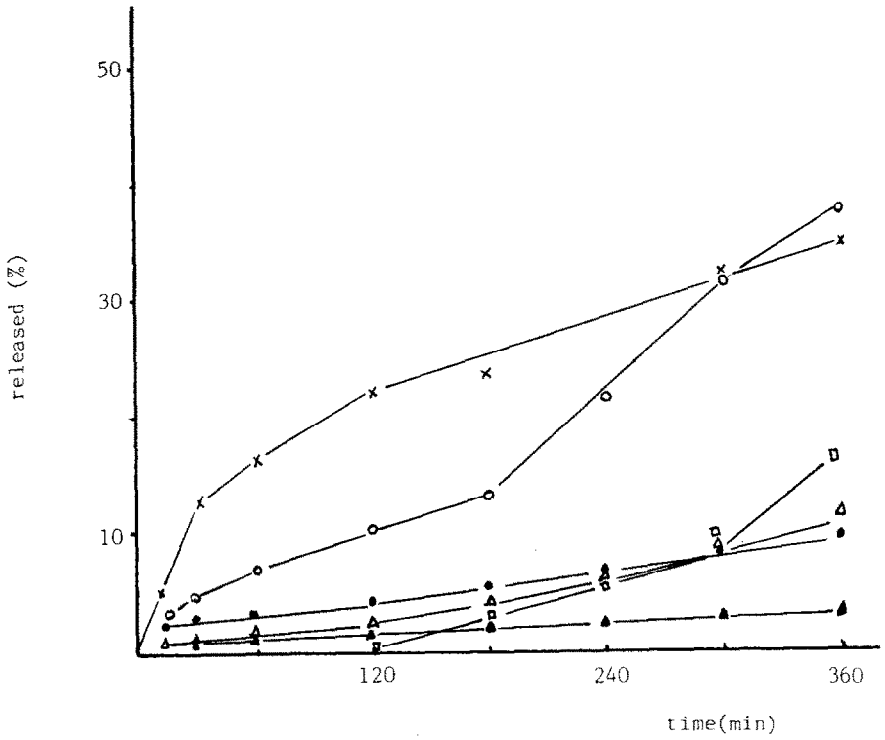

Fig. 2. Release profiles of naproxen (○), piroxicam (●), indomethacin (△), methylprednisolone (▲), pindolol (×) and sulphadiazine (□) from tablets.

The release parameters of drugs through chitosonium malate matrix tablets are listed in Table 2. As demonstrated in Figs 1 and 2 and Table 2, very soluble drugs such as timolol maleate and atenolol and soluble drugs, namely, ephedrine and propranolol hydrochloride, show sustained-release properties, however, their release rates are greater than the others. No disintegration of tablet matrices was observed during the test.

TABLE 2

Coefficient of correlation (r) and release parameters of drugs through chitosonium malate tablets

Drugs	r	Intercept	Slope (h^{-1})
Timolol maleate	0.998	2.67	0.550
Atenolol	0.992	25.65	0.597
Ephedrine	0.949	25.66	0.680
Propranolol hydrochloride	0.998	12.00	0.420
Acetylsalicylic acid	0.997	−4.97	1.220
Naproxen	0.975	0.73	0.090
Piroxicam	0.994	184	0.019
Indomethacin	0.986	−0.53	0.031
Methylprednisolone	0.962	1.22	3.88×10^{-3}
Pindolol	0.521	3.32	0.055
Sulphadiazine	0.314	24.33	0.063

Another parameter which determines drug solubility, the degree of ionization of the drugs is also important for release from the chitosonium malate matrix. A marked decrease was observed with drugs having pK_a values between 4.0 and 8.8.

On the other hand, chitosan is a cationic polymer, and anionic drug such as indomethacin and naproxen were released more slowly. This may be due to complex formation between anionic drugs and chitosonium malate and the complex might diffuse from the swollen gel at a much slower rate. Similar observations were reported for NaCMC, an ionic polymer (Feely and Davis, 1988; Ranga Rao et al., 1990).

In order to understand the mode of release of drug from the chitosonium malate matrix, the

TABLE 3

Coefficients and exponents of drug release functions according to $M_t/M_\infty = Kt^n$ for chitosonium malate matrix tablets

Active compounds	r^2	n	K
Timolol maleate	0.914	0.587	0.529
Atenolol	0.984	0.372	1.105
Ephedrine	0.984	0.492	0.727
Propranolol hydrochloride	0.992	0.578	0.558
Acetylsalicylic acid	0.974	0.918	0.121
Naproxen	0.961	0.728	−0.425
Piroxicam	0.920	0.428	−0.209
Sulphadiazine	0.974	2.870	−6.099
Pindolol	0.814	0.751	−0.252
Indomethacin	0.958	0.900	−1.365
Methylprednisolone	0.939	0.222	−0.202

r^2, coefficient of determination; n, release exponent in above equation; K, coefficient in above equation.

dissolution data ($\geq 60\%$) were fitted to the following power law equation (Ritger and Peppas, 1987):

$$M_t/M_\infty = Kt^n$$

where M_t/M_∞ is the fraction of drug released up to time t, K denotes a constant incorporating the structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of release.

The value of n for a cylinder is ≥ 0.45 for Fickian release, > 0.45 and < 0.89 for non-Fickian release (anomalous transport), 0.89 for Case II release and > 0.89 for Super Case II type release. The values of K, n and the coefficient of determination (r^2) are listed in Table 3. As observed in Table 3, Fickian diffusion ($t^{1/2}$ dependence) predominates in atenolol, piroxicam and methylprednisolone release from tablets. For timolol maleate, sparingly soluble drugs, such as ephedrine and propranolol hydrochloride, and slightly and very slightly soluble drugs, the mode of drug release from tablets was non-Fickian, Case II and super Case II types. These drugs can be released at a nearly zero-order rate through matrix.

As noted by Ritger and Peppas (1987), Case I and Case II solute release behavior in swelling-controlled systems is unique in that each can be described in terms of a single parameter. Case I transport is described by a diffusion coefficient while Case II transport is described by a characteristic relaxation constant.

On the other hand, for soluble and slightly soluble drugs, as the molecular weight (a parameter that may be indirectly related to the molecular size) of the drugs decreased, drug release increased. Although the solubility of ephedrine (Mol. Wt 165.23) and propranolol hydrochloride (Mol. Wt 259.34) is the same, greater drug release was obtained with ephedrine tablets (Tables 1 and 2). The same finding was made with acetylsalicylic acid (ASA). As seen in Table 2, rapid release was observed with ASA tablets (Mol. wt 180.15).

In previous studies, Miyazaki et al. (1981) and Sawayanagi et al. (1982) reported the usefulness of chitosan as a vehicle for water-insoluble and soluble drugs, both groups noting that chitosan showed excellent sustained-release properties in acidic media and at high concentration (at least 80%). The importance of the addition of an acidifying agent to chitosan was also reported by Nigalaye et al. (1990).

As reported for chitosan, chitosonium malate is a suitable matrix for water-soluble and insoluble drugs. In addition, the molecular size of drug is also an important factor for the control of drug release.

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