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COMMUNICATION

Effect of Drug Properties on Physical and Release Characteristics of Eudragit Microspheres Prepared by Spherical Crystallization Technique

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ABSTRACT

Ten compounds having different solubilities and molecular weights were evaluated for incorporation into Eudragit microspheres using the spherical crystallization technique, and the effects of drug-related factors on the properties of Eudragit microspheres were investigated. The entrapment of the active compound within the microspheres was highly dependent on the acidic or basic characteristics of the drug. Structural changes were also observed on the microsphere surface prepared at different pH values. Microspheres prepared with slightly and very slightly soluble drugs such as salicylic acid, naproxen, piroxicam, indomethacin, and methylprednisolone indicated controlled-release properties. Generally, drug release from microspheres followed the Fickian diffusion model.

INTRODUCTION

A wide variety of methods exist for the formulation of polymeric microparticulate drug delivery systems. The choice of one particular method is governed to a great extent by the solubility characteristics of active compounds (1–3). The spherical crystallization (or quasi-emulsion solvent diffusion) method is a novel technique for the preparation of controlled-release microspheres (4–6). Compared with solvent evaporation technique, the solidification of the liquid droplets in the present process is much faster and has many advantages over the solvent evaporation method (5,6). Although, drug-related variables of the solvent evaporation technique have been extensively studied (7–9), there is no report about the role of drug characteristics in the physical and release properties of Eudragit microspheres prepared by the spherical crystallization technique.

The objectives of this investigation were to evaluate the suitability of this process to entrap active compounds

with different physicochemical properties and to study the in vitro release characteristics of the resulting microspheres.

EXPERIMENTAL

Materials

Eudragit RS (Rhöm Pharma GmbH, Darmstadt, Germany)
Timolol maleate, propranolol hydrochloride, piroxicam, salicyclic acid, and indomethacin (Sigma, USA)
Acetaminophen and naproxen (Aldrich, USA)
Acetylsalicylic acid (Bayer, Turkey)
Ephedrine and methylene chloride (E. Merck, Germany)

Preparation of Microspheres

Eudragit microspheres were prepared by the spherical crystallization technique (5). Weighed amounts of drug and Eudragit RS were dissolved in a mixture of methylene chloride:ethanol (1:1). The formed solution was poured into aqueous phase while stirring continuously with the aid of a propeller-type agitator (Ika-Werk Janke Kunkel, Germany). After 30 min the microspheres were collected by filtration, washed with water, and then dried in vacuo. All batches were prepared at least 3 times. During this study drug:polymer ratios were kept constant. Ten drugs with various solubilities and molecular weights were chosen as model compounds (Table 1).

In Vitro Release Studies

A weighed quantity of microspheres was suspended in phosphate buffer (pH 7.4 USP, 50 ml) contained in a 100-ml glass bottle. The dissolution medium was stirred at 100 rpm in a horizontal laboratory shaker and maintained at constant temperature (37°C ± 0.1) in a water bath. Samples were periodically removed and analyzed spectrophotometrically (Shimadzu Spectrophotometer 2100S, Japan). The means of six determinations are given. Corrections were made for any absorption due to Eudragit RS.

Determination of Drug Content in Microspheres

Drug content of microspheres was spectrophotometrically assayed. The means of three experiments are reported.

RESULTS AND DISCUSSION

Several drugs with different solubility characteristics and molecular weights were chosen as model compounds (Table 1). All of them were completely soluble in ethanol–methylene chloride mixtures. Table 2 indicates the drug loading capacity of Eudragit microspheres prepared by the spherical crystallization technique. Bodmeier and McGinity (7) reported that in the solvent evaporation technique, successful entrapment of the active compound within the microspheres was highly dependent on water solubility of drug. As seen in Table 2, very soluble drugs such as timolol maleate showed

Table 1

Molecular Weight, Solubility, and pK_a Values of Active Compounds

Active Compound	MW	Approximate Solubility	pK_a
Timolol maleate	432.49	<1	9.00
Ephedrine	165.23	20	9.63
Propranolol HCl	259.34	20	9.45
Acetylsalicyclic acid	180.15	300	3.50
Salicylic acid	138.12	460	2.97 and 13.40
Acetaminophen	151.16	1,000–10,000	9.5
Naproxen	230.26	1,000–10,000	4.15
Piroxicam	331.35	1,000–10,000	6.30
Indomethacin	359.79	10,000	4.50
Methylprednisolone	374.46	10,000	2.60 and 6.00

Table 2

Drug Loading Capacity of Eudragit Microspheres Prepared with Distilled Water

Active Compound	Drug Loading Capacity (%)
Timolol maleate	1.84 ± 0.01
Ephedrine	33.52 ± 1.28
Propranolol HCl	2.00 ± 0.56
Acetylsalicylic acid	20.25 ± 4.80
Salicylic acid	15.20 ± 0.20
Acetaminophen	0.59 ± 0.01
Naproxen	34.32 ± 0.68
Piroxicam	29.30 ± 7.65
Indomethacin	98.36 ± 1.64
Methylprednisolone	11.57 ± 2.56

very low entrapment property while the very slightly soluble methylprednisolone was also entrapped in a very low percentage. Therefore one can conclude that, contrary to the solvent evaporation method, water solubility is not the main factor in drug loading capacity of Eudragit microspheres prepared by the spherical crystallization technique.

On the other hand, ionization degree of the drug is highly dependent on the pH. Drug entrapment in the Eudragit microspheres as a function of different pH values of aqueous phase is summarized in Table 3. As seen in this table the drug content of Eudragit

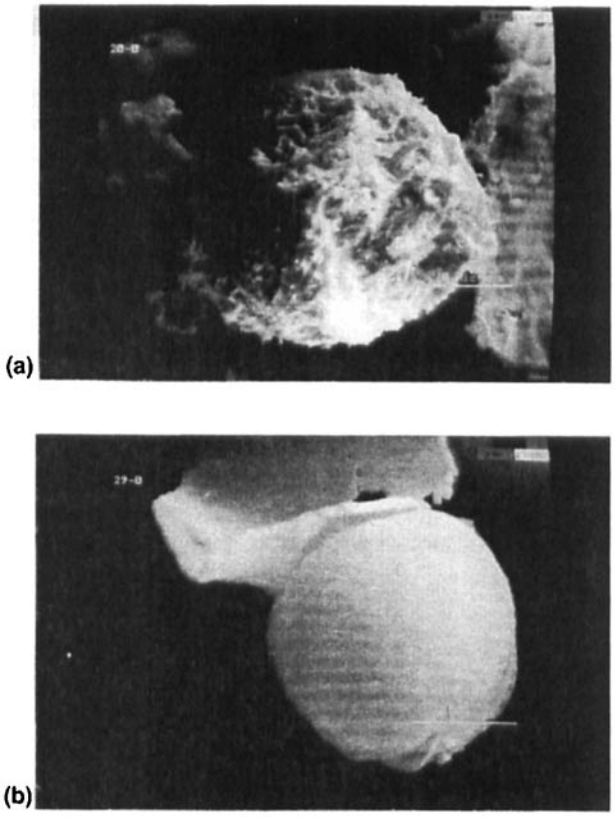

Figure 1. Scanning electron micrographs of microspheres prepared at different pH values. (a) Indomethacin microspheres (pH 1.2). (b) Indomethacin microspheres (pH 11).

Table 3

pH-Dependent Drug Loading Capacity of Eudragit Microspheres

	pH			
Active Compound	1.2	4.0	7.0	11.0
Timolol maleate	0	—[a]	—[a]	2.00 ± 0.10
Ephedrine	26.67 ± 7.57	47.20 ± 6.74	42.56 ± 5.64	31.64 ± 3.96
Propranolol HCl	2.06 ± 0.11	—[a]	—[a]	15.86 ± 4.16
Acetylsalcyclic acid	7.44 ± 4.87	5.48 ± 3.60	8.48 ± 0.83	15.12 ± 1.53
Salicyclic acid	8.58 ± 2.70	7.76 ± 3.47	9.60 ± 0.02	8.64 ± 0.13
Acetaminophen	0.75 ± 0.15	—[a]	—[a]	4.85 ± 0.71
Naproxen	35.42 ± 1.26	—[a]	—[a]	14.32 ± 0.33
Piroxicam	17.90 ± 6.04	62.00 ± 1.54	37.04 ± 0.89	28.00 ± 2.48
Indomethacin	99.00 ± 1.00	100.00 ± 0.20	63.12 ± 0.25	8.88 ± 1.47
Methylprednisolone	14.86 ± 0.46	—[a]	—[a]	16.72 ± 2.21

[a]Not tested at this pH.

microspheres changed with the pH values of the aqueous phase, and a remarkable decrease was observed in the drug content of indomethacin microspheres as the pH changed from 1.2 to 11.0. pK values of the drug are also important in entrapment. Weakly basic drugs such as acetaminophen and propranolol hydrochloride showed low entrapment capacities. Moreover, poor drug incorporation was observed with the drugs having lower pK_a and pK_b values such as acetylsalicyclic acid and piroxicam.

Increase in molecular weight of the active compound also increased the incorporation efficiency of very soluble drugs. However, no significant effect of drug molecular weight was observed on drug loading capacity. Distinct differences in the surface structure of the microspheres prepared at different pH values are seen in Fig. 1. The surface changed from a virtually smooth texture at low drug loadings to a honey-comb-like structure containing small holes at high loading at pH 1.2. Structural changes in the microsphere surface prepared at different pH values have been reported in the literature (8–10). No retardant property was obtained with Eudragit microspheres containing very soluble and soluble drugs such as propranolol hydrochloride and acetaminophen respectively. Microspheres prepared with salicyclic acid, naproxen, piroxicam, indomethacin, and methylprednisolone indicated controlled-release properties.

Release rates were determined by least squares linear regression analysis (Table 4). The main models which have been suggested to describe drug release kinetics from microspheres are zero-order, first-order, and matrix models. On the other hand, the equation proposed by Baker and Londsdale:

Table 4

Coefficients and Exponents of Drug Release Functions According to $Q(t) = at^n$ for Microspheres Prepared with Different Drugs

Coefficient or Exponent[a]	Drug				
	Naproxen	Salicylic Acid	Piroxicam	Indomethacin	Methylprednisolone
r	0.940	0.992	0.974	0.995	0.996
n	0.120	0.221	0.281	0.428	0.264
a	3.805	3.239	2.371	1.141	2.537

[a]*r*: correlation coefficient; *n*: release exponent; *a*: coefficient in the equation.

Table 5

Release Kinetics of Drug-Loaded Microspheres

Kinetics[a]	Drug				
	Naproxen	Salicylic Acid	Piroxicam	Indomethacin	Methylprednisolone
Zero order					
r	0.931	0.947	0.950	0.987	0.965
k	0.078	0.132	0.082	0.077	0.082
First-order					
r	0.899	0.986	0.951	0.991	0.979
k	-4.82×10^{-3}	-5.33×10^{-3}	-1.51×10^{-3}	-1.06×10^{-3}	-1.58×10^{-3}
Higuchi					
r	0.935	0.976	0.962	0.994	0.991
k	1.819	2.816	2.085	1.904	2.119
Baker and Lonsdale					
r	0.915	0.954	0.945	0.988	0.691
k	6.21×10^{-4}	7.22×10^{-4}	1.83×10^{-4}	8.48×10^{-5}	1.49×10^{-4}

[a]*r*: correlation coefficient; *k*: release rate constant.

$$3/2\ [1 - (1 - F)2/3] - F = KT$$

describes the drug release from spherical matrices: F is the fraction of drug released and K is a constant (11).

Results according to these models are given in Table 4. As seen in this table, to differentiate one possible mechanism is too difficult. Therefore a more stringent test was used to distinguish the mechanism of drug release. Release data were analyzed by the empirical equation

$$Q(t) = at^n$$

where $Q(t)$ is the fraction of drug released after time t and a is a coefficient (12,13). Values for the coefficient a and the exponent are given in Table 5. The values of n were in the range of 0.12–0.42; thus the release process is diffusion controlled.

In conclusion, the entrapment of drug within the microspheres prepared by spherical crystallization technique was highly dependent on the acidic or basic characteristics of the active compound. Adjustment of pH in aqueous phase to minimize drug solubility resulted in increased drug contents within the microspheres in the case of ionizable drugs.

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