International Journal of Pharmaceutics, 14 (1983) 95–102
Elsevier Biomedical Press

Release of drugs from microcapsules of methacrylate polymers

A.M. Fouli, A.A. El-Sayed and A.A. Badawi *

Dept. of Pharmaceutics, Faculty of Pharmacy, Cairo University, Cairo (Egypt)

(Received June 1st, 1982)
(Accepted July 20th, 1982)

Summary

Microencapsulation of salicylic acid using methacrylate copolymers was devised utilizing coacervation by non-solvent addition. Release of salicylic acid as a model of an acid drug from such microcapsules was studied.

It was found that the release from individual microcapsules and tablets showed matrix-controlled mechanism. The cationic methacrylate copolymer was different because it reacts with the acidic drugs; the complex formed can form a coacervate which microencapsulates excess drug. Methacrylate copolymers can microencapsulate efficiently the drug in the ratio of 95 : 5 drug-to-polymer.

Introduction

The concept of microencapsulation originated a number of years ago and had recently received increasing attention as a means of formulating pharmaceuticals for controlled-release purposes. However, microencapsulation remained an art more than a science (Thies, 1975), and most of the literature only claimed that the release of drugs rom microcapsules depends on thei size and/or drug-to-polymer ratio (Gutcho 1976). The release of drugs from cellulose acetate phthalate microcapsules was described (Merkle and Speizer, 1973) to occur at its first step by inhibition of the solvent by the film. In the second step, the solvent diffuses into the free space within the capsule, then the dissolution of drug takes place and in the fourth step, the dissolved drug is released by diffusion through the coacervate film, whereas further drug is continually dissolved.

* To whom enquiries should be addressed.

With gelatin microcapsules containing glycerol, an induction period occurred for water to equilibrate with the capsule wall, then the water was transported into the capsules, where there was an enormous osmotic driving force resulting in stressing the capsule wall causing a change in release pattern of glycerol. Once the ultimate strength of the capsule wall was exceeded, rupture of capsule occurs with a discontinuity of the release curve (Thies, 1975).

The shape of the dissolution plot of sodium phenobarbitone from ethyl cellulose microcapsules made into tablets followed those from the corresponding microcapsules, but with the drug release time significantly increased, and Higuchi plots showed a straight-line relation (Jalsenjak et al., 1977).

This communication includes the study of the release mechanism of salicylic acid as a model for acid drugs from microcapsules made of cationic and anionic methacrylate copolymers, the first synthesized from dimethyl-amino-ethyl methacrylate and other from neutral methacrylic esters, while the second is a copolymer of methacrylate and methacrylic esters. The two polymers were chosen to investigate the possible effect of the charge on the polymer in its behaviour as microcapsulating agent for such an acidic drug. Release regimen from microcapsules were compared with solid dispersion of the drug and the polymer.

Materials and methods

Materials

Salicylic acid [1], cationic [2] and anionic [3] methacrylate polymers.

Preparation of microcapsules

An alcoholic solution of salicylic acid was mixed with an alcoholic solution of each of the methacrylate copolymers in order to give the required ratio. A saturated solution of salicylic acid in water was added dropwise with continuous stirring until complete phase separation occurred, and continued until equilibrium was well established. The microcapsules were separated by filtration, air-dried, and kept in a desiccator for at least 2 days before further processing. The product was used without sieving, being free-flowing and very fine.

Preparation of solid dispersion

Alcoholic solutions of salicylic acid and each of the two copolymers were mixed, the alcohol was evaporated on a boiling water bath with continuous trituration until complete dryness. The mass was pulverized in a mortar to pass through sieve no. 30 [4], and kept in a desiccator until used.

[1] B.P. 1973.
[2] Eudragit E granulate, Rohm Pharma GMBH, Darmstadt, F.R.G.
[3] Eudragit L_{30} granulate, Rohm Pharma GMBH, Darmstadt, F.R.G.
[4] B.P. 1968.

Preparation of physical mixture

A weighed sample (100 g) of each of the two copolymers used was pulverized in a small ball-mill to pass through sieve no. 30 [4]; salicylic acid was mixed in geometric dilution technique with the suitable amount of the powdered copolymers to form a physical mixture.

Preparation of tablets

The microcapsules, the solid dispersion and the physical mixture were made into tablets (Jalsenjak et al., 1977), using a single-stroke compression machine [5] to produce tablets weighing 220 mg ± 5%, 8 mm in diameter, 1.8 mm in thickness and of an average hardness 5–6 kg.

Dissolution studies

(a) From microcapsules and solid dispersion particles. Microcapsules (220 mg) and a solid dispersion (220 mg) of salicylic acid and each of the two copolymers containing 60% of the acid drug were placed into a 600 ml beaker (10 cm in diameter) along with 400 ml of distilled water. Constant stirring at 100 rpm was performed by a mechanical propeller stirrer [6] at 25 ± 1°C to ensure the non-aggregation of the particles and to attain hydrodynamic equilibrium in the dissolution medium. At each time interval an aliquot of 1 ml was withdrawn and assayed spectrophotometrically [7] at 297 nm for its salicylic acid content. Replacement of 1 ml of distilled water was done.

(b) From whole tablets. Tablets of microcapsules, solid dispersion and the physical mixture containing 60% of the drug, were placed in a beaker and dissolution test was performed as before, under the same conditions.

(c) From planar surface. This was to compare the dissolution rate from microcapsules made with each of the two copolymers containing different ratios of salicylic acid. Tablets were fixed into melted bees-wax on the top of test-tubes, each of 15 mm in diameter. Each tablet was placed at constant level 5 cm below the surface of 400 ml water which was stirred at constant speed of 100 rpm and the dissolution test was performed as before.

The results are shown in Figs. 1–4.

Results and discussion

Salicylic acid, as a model of acidic drugs, was chosen because it is fairly soluble in water, thus its dissolution within the microcapsules would not be the rate-determining step. The cationic and anionic methacrylate copolymers were chosen to show the possible effect of such charged polymers on the release of an acidic drug. Both polymers do not sorb water and hence the inhibition step (Merkle and Speizer, 1973)

[5] Diaf, Copenhagen, Denmark.
[6] Gallenkamp, U.K.
[7] Unicam Spectrophotometer Sp.500.

does not exist; the release of drugs will therefore be controlled by diffusion and interaction with the polymer. Although release of drugs from coating made of the chosen copolymers is described to be pH-dependent, water was used as the dissolution medium to eliminate the erosion of the polymer and limit the dissolution through diffusion. Although the film coats of the anionic copolymer was described (Lehmann, 1968) to be impermeable to water, yet the experiments showed that coacervated film made with non-solvent addition was permeable to water.

From the solid dispersions, salicylic acid was released with more or less the same regimen (Fig. 1). The release rate was initially very high followed by a plateau.

The amount of the drug released from microcapsules made with the two copolymers was a linear function of the square root of time indicating a diffusion or matrix-controlled mechanism as described (Sjauib et al., 1972; Goodhart et al., 1974). The linear curve was extrapolated to intercept the y-axis in order to deduce the amount of the drug existing in solution at zero time; that is, the free or non-microencapsulated drug. The free salicylic acid was 28 mg in the case of microcapsules made of the anionic copolymer, and only 3 mg in the case of microcapsules of the cationic type. This indicated the relatively complete microencapsulation of salicylic acid with the copolymer containing cationic sites. On the other hand, these microcapsules released the drug at a rate of 14.667 mg/100 ml/$min^{1/2}$, while the ones made with the anionic copolymer showed lower rate of 7.3 mg/100 ml/$min^{1/2}$.

By the aid of microscopical investigation, it was concluded that the copolymer interacts with salicylic acid and, on adding water, phase separation coacervation of the complex occurs with the formation of very tiny globules which coalesced to form

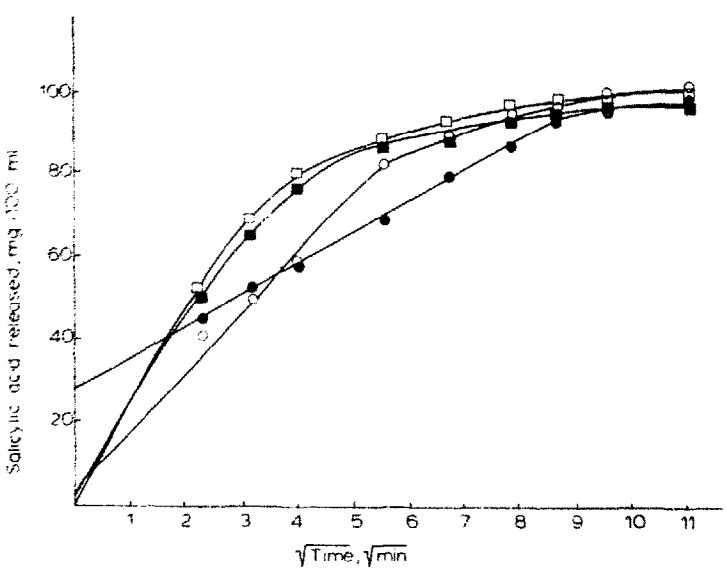

Fig. 1. Release of salicylic acid from its microcapsules and its solid dispersions of polymethacrylate copolymers. The cationic type (○) microcapsules and (□) solid dispersion; as well as the anionic type (●) microcapsules and (■) solid dispersion.

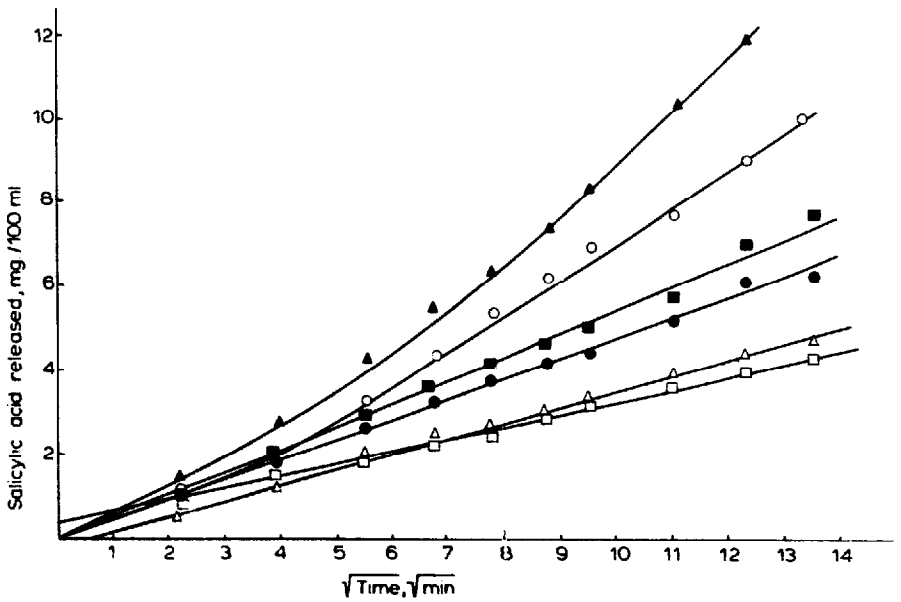

Fig. 2. Release of salicylic acid from its tablet matrix made of microcapsules, solid dispersion, and physical mixture with polymethacrylate copolymers. The cationic type (○) microcapsules, (□) solid dispersion and (△) physical mixture; as well as the anionic type (●) microcapsules. (■) solid dispersion, and (▲) physical mixture.

needle-shaped crystals characteristic of salicylic acid. In the presence of excess salicylic acid, the complex formed a coacervate which microencapsulated the crystals of excess precipitated salicylic acid.

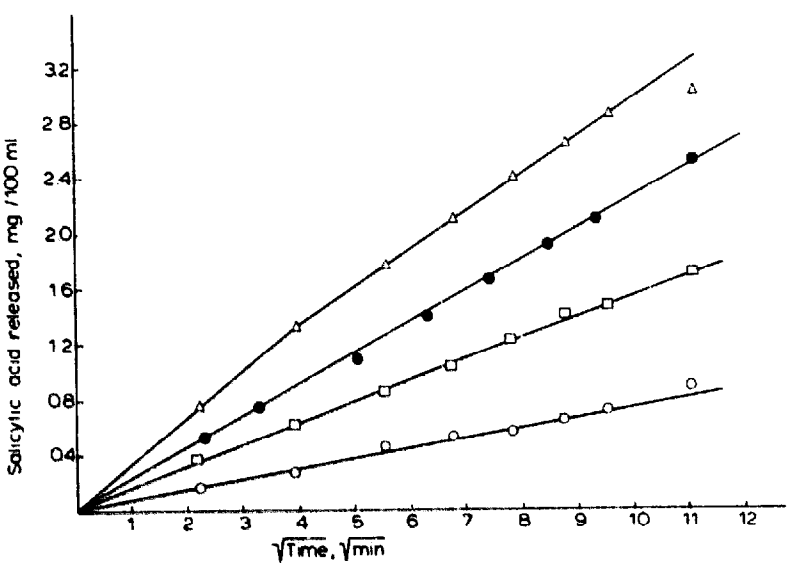

Fig. 3. Release of salicylic acid from its anionic polymethacrylate copolymer microcapsules. △, 95% salicylic acid; ●, 90% salicylic acid; □, 80% salicylic acid; and ○, 60% salicylic acid.

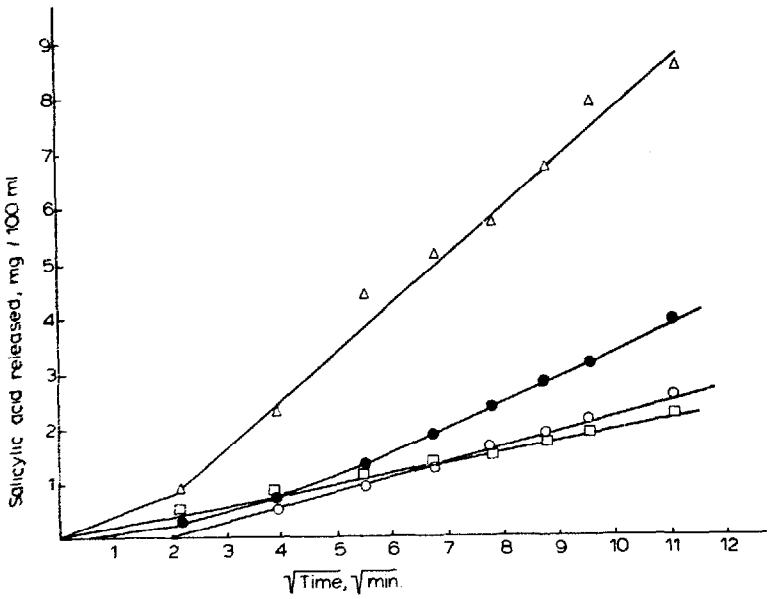

Fig. 4. Release of salicylic acid from its cationic polymethacrylate copolymer microcapsules. △, 95% salicylic acid; ●, 90% salicylic acid; □, 80% salicylic acid; and ○, 60% salicylic acid.

The tablets after release of the drug did not change in their dimensions indicating no or very slight swelling. Contrary to that claimed (Jalsenjak et al., 1977), the release of salicylic acid from methacrylate copolymers was very slow from tablets relative to that from individual microcapsules. Jalsenjak et al. (1977) explained their finding by the possible destruction of the ethylcellulose coat under the compression

TABLE I

PERCENTAGE FREQUENCY OF PARTICLE SIZE OF SOLID DISPERSION, MICROCAPSULES AND PHYSICAL MIXTURE OF SALICYLIC ACID AND METHACRYLATE COPOLYMERS

Screen limits	Average particle size (μm)	Average percentages of particles having the stated size in the system of:			
		Solid dispersion (%)	Microcapsules (%)	Physical mixture of:	
				Salicylic acid (%)	Polymer (%)
200/120	99.5	6.3	8.1	56.3	1.2
120/100	137.0	17.1	25.4	32.5	12.3
100/ 80	163.0	43.4	41.2	11.2	17.4
80/ 60	213.5	25.5	16.6	-	32.6
60/ 50	273.5	4.6	5.0	-	20.3
50/ 30	443.5	3.1	3.7	-	7.2

pressure and hence, methacrylate copolymers must have a high tensile and elasticity to withstand the compression. Moreover, the coat of methacrylate copolymer microcapsules may merge to form a thick bonding holding the drug within a sea of polymer.

Tablets made from the physical mixture of salicylic acid and the anionic methacrylate copolymer released the drug at a very high zero-order rate and this means that the polymer was unable to flow around the drug particles and the drug is released by a partitioning mechanism (Chien and Lambert, 1974). All other tablets showed a perfect Higuchi plot (Higuchi, 1963). This indicated that, in both cases, the polymer coated the particles of the drug, and on compression, the coat of adjacent particles merge together and form a matrix of the polymer enmeshing the drug particles. The slope of the curve in case of tablets made of solid dispersion was 0.56 mg/100 ml/min$^{1/2}$ relative to 0.50 mg/100 ml/min$^{1/2}$ with those made of microcapsules. This showed that porosity and tortuosity of the two matrices were different (Desai et al., 1965). and the deposition of the polymer onto the salicylic acid particles by microencapsulation gave a more controlled release of the drug.

From tablets made from the physical mixture of the drug with the cationic polymer, a slower rate than that of the previous two was noticed. This means that either the two materials react together under the action of the compression machine, or that upon the attack of the tablet surface by water, salicylic acid is first dissoluted and then it reacts with the polymer. The same pattern was seen with tablets made from the solid dispersion and the possible interaction in the alcohol solution is added.

One possible explanation would be the fact that the microcapsules are made of a core of salicylic acid particles and a coat made of copolymer chains along with a complex of the copolymer and salicylic acid. This complex would be more soluble and when the microcapsules are placed in water, the complex would dissolve first leaving a porous coat and thus allowing higher diffusion rate of the enclosed core particles.

From a planar surface, tablets made of microcapsules of salicylic acid with either the cationic and anionic copolymers obeyed Higuchi's equation for a matrix-controlled mechanism. The release rate was much higher in the case of the cationic copolymer and this conform with that of the whole tablet. It is noteworthy that the relative amounts dissoluted were nearly in the ratio of 1 : 2.5 from planar surface to the whole tablets corresponding to the relative surface areas and this ensures the uniform release of salicylic acid all over the tablet surface.

With the anionic copolymer, in the case of tablets containing 95% of the drug and 5% of the polymer, the initial rate was very slightly higher than in the terminal stage (0.35 relative to 0.28 mg/100 ml/min$^{1/2}$) and this may be due to some free drug escaping microencapsulation. But with drug content of 90, 80 and 60%, a linear plots with slopes (rates) of decreasing order were observed. With the cationic copolymer, complete microencapsulation was achieved when the salicylic acid content were 95, 90 and 80%. With those containing 60% a lag-time of 4 min was noted, indicating reduced access of the microencapsulated core particles.

References

Chien, Y.W. and Lambert, M.J., Controlled drug release from polymeric delivery devices II. Differentiation between partition-controlled and matrix-controlled drug release mechanisms. J. Pharm. Sci., 63 (1974) 515–519.

Desai, S., Singh, P., Simonelli, A.P. and Higuchi, W.I., Investigation of factors influencing release of solid drug dispersed in inert matrices, I. J. Pharm. Sci., 54 (1965) 1459–1464.

Goodhart, F.W., McCoy, R.H. and Ninger, F.C., Release of a water soluble drug from a wax matrix time release tablet. J. Pharm. Sci., 63 (1974) 1748–1751.

Gutcho, M., Microcapsules and Microencapsulation Technique, Chemical Technology, Review No. 73, Noyes Data Corporation, Park Ridge, NJ, 1976, pp. 236–253.

Higuchi, T., Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm Sci., 52 (1963) 1145–1149.

Jalsenjak, C., Nicolaidou, F. and Nixon, J.R., Dissolution from tablets prepared using ethyl cellulose microcapsules. J. Pharm. Pharmacol., 29 (1977) 169–172.

Lehmann, K., Acrylic Resin Coatings for Drugs. Drugs made in Germany, XI (1968) 34–41.

Merkle, H.P. and Speizer, P., Preparation and in vitro evaluation of cellulose acetate phthalate coacervate microcapsules. J. Pharm. Sci., 62 (1973) 1444–1448.

Sjauib, F., Simonelli, A.B. and Higuchi, W.I., Release rates of solid drug mixtures dispersed in inert matrices III. Binary mixture of acid drugs released into alkaline media. J. Pharm. Sci., 61 (1972) 1374–1380.

Thies, C., Physicochemical aspects of microencapsulation. Polym. Plast. Technol., 5 (1) (1975) 1–22.