International Journal of Pharmaceutics, 48 (1988) 217–222
Elsevier

IJP 01634

Effect of eluant properties on drug release from cellulose acetate butyrate-coated drug resin complexes

Omar L. Sprockel and Waruwan Prapaitrakul

Division of Pharmaceutics and Drug Delivery Systems, College of Pharmacy, University of Cincinnati, Cincinnati, OH 45267 (U.S.A.)

(Received 25 November 1987)
(Modified version received 14 April 1988)
(Accepted 15 June 1988)

Key words: Phenylpropanolamine; Drug–resin complex; Microcapsule; Eluant property; Drug release; Sustained release

Summary

Phenylpropanolamine adsorbed onto sulfonic acid cation-exchange resin particles was coated with cellulose acetate butyrate using an emulsion–solvent evaporation technique. Release of drug from such microcapsules required counter-ions in the eluting media, which permeated the coating and displaced the drug from its binding sites. The type of counter-ion had a significant influence on the rate of drug release; in the presence of hydrogen ions release was rapid, but if the eluant contained calcium ions release was slow. Eluants with low pH values caused a more rapid release of drug from the coated drug–resin complexes when compared to eluants of higher pH values, even though the ionic strength was maintained constant. An increase in ionic strength at selected pH values resulted in an enhancement of the drug release rate, with the increase being more noticeable at lower pH values.

Introduction

Microencapsulation has been a common method to sustain drug release from a dosage form in the gastrointestinal tract and, thereby, prolonging the pharmacological effect of the drug. Incorporation of microcapsules into solid dosage forms such as tablets raises the potential problem of fracture (Sayed and Price, 1986; Chemotob et al., 1986).

To prepare liquid sustained release dosage forms, Smith et al. (1960) adsorbed drug onto an ion-exchange resin. The kinetics of drug exchange were previously investigated (Boyd et al., 1947; Reichenberg, 1953; Chaudhry and Saunders, 1956). Several patents were obtained using this technology for sustained release of drugs (Hays, 1962; Keating, 1964). To further retard the release of drug adsorbed onto ion-exchange resins, the drug–resin complexes were microencapsulated (Motycka and Nairn, 1974; Motycka and Nairn, 1979; Sprockel and Price, 1984).

Development of techniques to microencapsulate drug adsorbed onto ion-exchange resins provided a means of suspending microcapsules in aqueous media (Raghunathan, 1980; Raghunathan et al., 1981). Sprockel and Price (1985, 1986) have shown that microencapsulated drug–resin complexes could be suspended in various aqueous

Correspondence: O.L. Sprockel, Division of Pharmaceutics and Drug Delivery Systems, College of Pharmacy, University of Cincinnati, Cincinnati, OH 45267, U.S.A.

vehicles for up to 28 weeks without any adverse effects on the drug release profiles.

Drug release from suspended microcapsules containing drug–resin complexes when placed in an eluting medium is preceded by an exchange of adsorbed drug for counter-ions which have permeated the microcapsule membrane. Factors which influence the counter-ion content of the medium or the rate of counter-ion permeation may affect the rate and the extent of drug release from the microcapsules. This may lead to in vivo variability due to differences in gastrointestinal content composition. Hence, it is important to determine the extent to which eluant properties modify drug release.

The purpose of this investigation was to study the influence of 3 eluant parameters on the rate of drug release from microencapsulated phenylpropanolamine–resin complexes. The parameters included counter-ion type, eluant ionic strength and eluant pH.

Materials and Methods

Materials

The following materials were used as received from the supplier without further purification: phenylpropanolamine-HCl, sulfonic acid cation-exchange resin (Amberlite IRP 69) (Aldrich Chemical Co., Milwaukee, WI); cellulose acetate butyrate (Scientific Polymer Products, Ontario, NY); acetone, liquid paraffin, and hexane (J.T. Baker, Phillipsburg, NJ); magnesium stearate (Fisher Scientific, Cincinnati, OH); and sorbitan sesquioleate (ICI, Wilmington, DE).

Method

The resin particles were suspended in a charging solution consisting of a concentrated solution of phenylpropanolamine-HCl in deionized water and stirred continuously for 12 h to form the drug–resin complexes. The drug–resin complexes were collected by filtration and washed with copious amounts of deionized water to remove free, uncomplexed drug, followed by drying at 50 °C.

An emulsion–solvent evaporation technique was used to microencapsulate the drug–resin complexes with cellulose acetate butyrate (CAB). The polymer was dissolved in acetone to form a 10% solution, into which the drug–resin complexes were dispersed with a polymer:complex ratio of 1 : 1, forming the internal phase. Magnesium stearate (1%) and sorbitan sesquioleate (1%) were added to liquid paraffin, the dispersing vehicle. The polymer solution containing the drug–resin complexes was emulsified in the liquid paraffin solution under constant agitation at 1500 rpm and stirring was continued until all the polymer solvent evaporated. The microcapsules were washed with hexane to remove the oily phase and were then dried under vacuum.

Microcapsules with a mean diameter of 303 μm were subjected to drug release studies using a Hanson Dissolution Apparatus at 100 rpm and 37 °C. The first release parameter studied was the counter-ion type. Drug release in media containing sodium chloride, hydrochloric acid or calcium chloride were compared at an ionic strength of 0.1. The influence of eluant pH on the rate of drug release was studied by adjusting the media pH at a constant ionic strength of 0.1 using various buffer systems: HCl/NaCl (pH 1), citric acid/Na_2HPO_4 (pH 3 and 5), and KH_2PO_4/NaOH (pH 7). The ionic strength of the pH 1 and the pH 7 media was varied from 0.01 to 0.20 to examine its effects on the rate of drug release from the microcapsules.

Results and Discussion

Drug–resin complex

The dissolved phenylpropanolamine-HCl exists primarily in the protonated state. The protonated drug species competes with and displaces the sodium counter-ion from the sulfonic acid functional groups on the resin particle. With time an equilibrium is reached between the resin-bound phenylpropanolamine and the unbound protonated drug. The equilibrium depends on the concentration of drug in the charging solution and the presence of counter-ions beyond those ions displaced from the resin.

The cation-exchange resin used had a maximum binding capacity of 4.3 meq./g of resin. The charging solution contained 5.3 meq. of phenyl-

propanolamine-HCl/g of resin. The resulting drug–resin complexes contained 2.6 meq. of drug/g of complex. Therefore, 0.41 meq. of drug/g of resin was lost during the preparation of the drug–resin complex.

When the drug–resin complexes are placed in an eluting medium containing counter-ions, the drug adsorption process is reversed. The counter-ions displace the drug from its binding site, causing drug to be released until an equilibrium is re-established.

Microencapsulation

Emulsification of the drug–resin complex suspension in the dispersing media produced polymer solution droplets containing drug–resin complex particles. The magnesium stearate and sorbitan sesquioleate in the external phase reduced aggregation between forming microcapsules and in conjunction with the optimum rate of agitation resulted in microcapsules of the desired size range upon complete evaporation of the polymer solvent. The microcapsules had a size distribution ranging from 66 to 500 μm and a geometric mean diameter of 283 ± 1.48 μm (see Fig. 1). Microcapsules falling in the size range 250–355 μm were selected for drug release studies.

To establish reproducibility for the microencapsulation process, 3 batches of microcapsules were prepared under identical conditions and evaluated. The coefficient of variance for particle size distribution between batches ranged from 6% (215 μm) to 29% (500 μm). The evaluations for drug content and drug release were repeated 3 times for each batch. The coefficient of variance for drug content within batch ranged from 1% to 10% and between batches was 14%. For the times required for 50% of the drug content to be released from the microcapsules, the coefficient of variance within batch ranged from 3% to 5% and between batch was 10%.

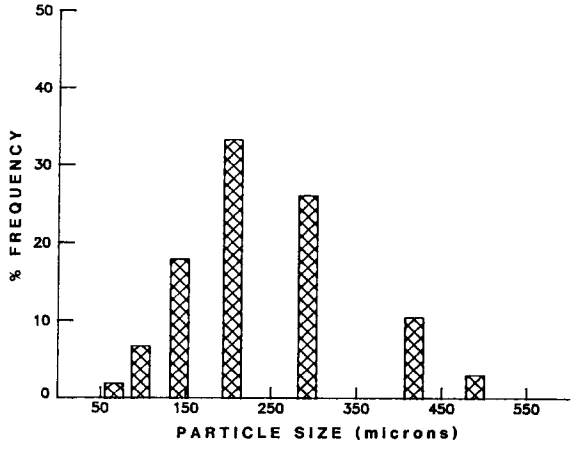

Fig. 1. Particle size distribution for complexes coated with cellulose acetate butyrate.

Drug release from microcapsules

Drug release from microencapsulated drug–resin complexes requires two processes: drug displacement and drug diffusion. When the microcapsules are placed in an aqueous environment containing positive counter-ions, the counter-ions permeate the microcapsule coating. The counter-ions compete with and displace the drug from the binding sites on the resin. The displaced drug then diffuses outward through the polymer membrane into the bulk of the solution. Over time an equilibrium is reached between the resin-bound form and the unbound form of the drug. The rate and extent of drug release depends on the composition of the eluting medium and the type of functional group on the resin particle. The rate of release also depends on the thickness and permeability of the microcapsule coating.

Effect of counter-ion type on drug release

In comparing different counter-ions, it was observed that the hydrogen ion caused the fastest release of drug followed by the sodium ion and the calcium ion (see Fig. 2). The times required for 50% of the drug content to be released from the microcapsules ($T_{50\%}$) range from 3.8 h for H^+ to 5.6 h for Na^+ and 7.5 h for Ca^{2+}.

The slower release of phenylpropanolamine from microcapsules placed in eluting media containing calcium ions or sodium ions may have two possible explanations. The calcium ions or sodiums ions may have a slower permeation rate through the microcapsule membrane, leading to a slower drug release. Alternatively, the lower affinity of the sulfonic acid functional groups for the calcium

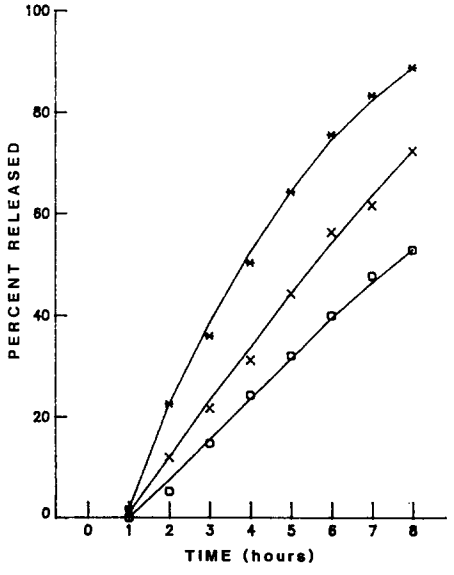

Fig. 2. Effect of counter ion type on drug release (ionic strength 0.1). Key: □, Ca^{2+}; × Na^{+}; *, H^{+}.

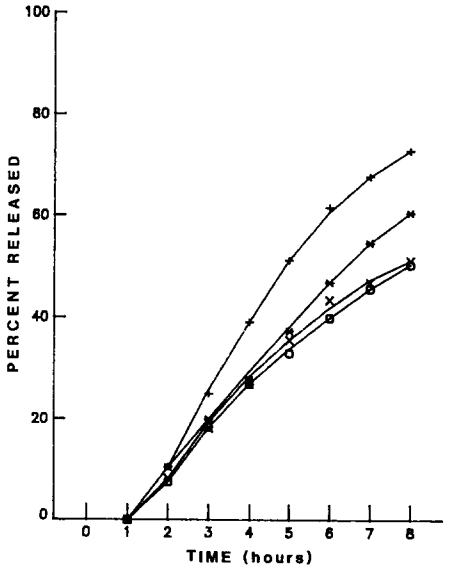

Fig. 3. Effect of media pH on drug release (ionic strength 0.1). Key: +, pH 1; *, pH 3; ×, pH 5; and □, pH 7.

and sodium ions may cause a slower drug release by retarding drug displacement from the binding sites.

To elucidate the relative contribution of each process to drug release further studies are required. These future studies should comprise two series of experiments to separate the influence of counter-ion type from the effects of the CAB coating. The first series of experiments should establish the difference in affinity of the uncoated drug–resin complex for the hydrogen, sodium, and calcium ions by contrasting the rate and extent of drug release from uncoated complexes in the presence of each counter-ion. The second series of experiments should compare the diffusion of the counter-ions through CAB films of known thickness. A simulation of drug release from coated complexes can be effected by conducting permeability studies through CAB films using diffusion cells in which the donor side contains solutions of counter-ions and the receptor side contains uncoated complexes in deionized water.

Effect of eluant pH on drug release

The influence of media pH at constant ionic strength ($\mu = 0.1$) on the rate of drug release was less dramatic than the effect of counter-ion type. The most rapid release of phenylpropanolamine was seen at lower pH values (see Fig. 3). The times required for 50% of the drug to be released ($T_{50\%}$) increased from 4.9 hours at a pH of 1 to 7.9 h at a pH of 7 (see Table 1). This change in release profile was less pronounced at higher pH values; there was a difference of 1.5 h in $T_{50\%}$ between pH 1 and pH 3, but only a difference of 0.4 h between pH 5 and pH 7 (see Table 1). Even though the ionic strength was kept constant at 0.1, the rate of drug release declined with an increase in eluant pH.

The buffers used have similar ionic strengths, but the relative concentrations of the different counter-ions in solution varied depending on the

TABLE 1

Effect of media pH on times required for 10%, 30% and 50% of drug to be released (ionic strength 0.1)

Media pH	$T_{10\%}$ (h)	$T_{30\%}$ (h)	$T_{50\%}$ (h)
1	1.9±0.24	3.3±0.25	4.9±0.21
3	2.0±0.26	4.0±0.35	6.4±0.10
5	2.1±0.35	4.3±0.15	7.5±0.22
7	2.2±0.10	4.5±0.08	7.9±0.32

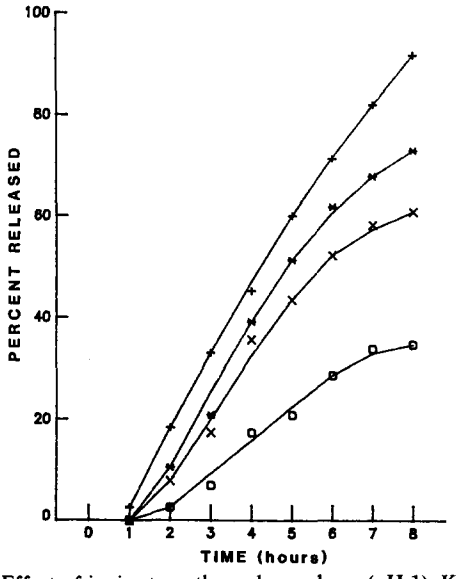

Fig. 4. Effect of ionic strength on drug release (pH 1). Key: □, 0.01; ×, 0.05; *, 0.10; and +, 0.20.

buffer and pH. Buffers with low pH values had a higher concentration of H^+, whereas buffers with high pH values had higher concentrations of Na^+. Since drug release was faster in the presence of H^+, it is not surprising that low pH buffers elicited a faster release than higher pH buffers.

Effect of eluant ionic strength on drug release

The ionic strength of the media was varied while maintaining the pH constant at pH 1 or pH 7. The rate at which phenylpropanolamine was released from the microcapsules increased dramatically at higher ionic strengths (see Fig. 4). The differences in release profile as a function of ionic strength were larger at lower ionic strengths. At pH 1, the $T_{50\%}$ decreased from more than 8 h at $\mu = 0.01$ to 4.2 h at $\mu = 0.2$, with a sharper decline in $T_{50\%}$ of lower ionic strengths (see Table 2).

The differences in release profile for phenylpropanolamine as a function of increased ionic strength at pH 7 are less than the differences observed at pH 1 (see Fig. 5). The times required for 30% of the drug content to be released decreased from 6.8 h at $\mu = 0.01$ to 3.8 h at $\mu = 0.2$ (see Table 3).

TABLE 2

Effect of ionic strength on times required for 10%, 30% and 50% of drug to be released (pH 1)

Ionic strength	$T_{10\%}$ (h)	$T_{30\%}$ (h)	$T_{50\%}$ (h)
0.01	3.1 ± 1.00	6.2 ± 0.80	> 8
0.05	2.2 ± 0.39	3.8 ± 0.13	5.8 ± 0.41
0.10	1.9 ± 0.24	3.3 ± 0.25	4.9 ± 0.21
0.20	1.5 ± 0.04	2.9 ± 0.04	4.2 ± 0.12

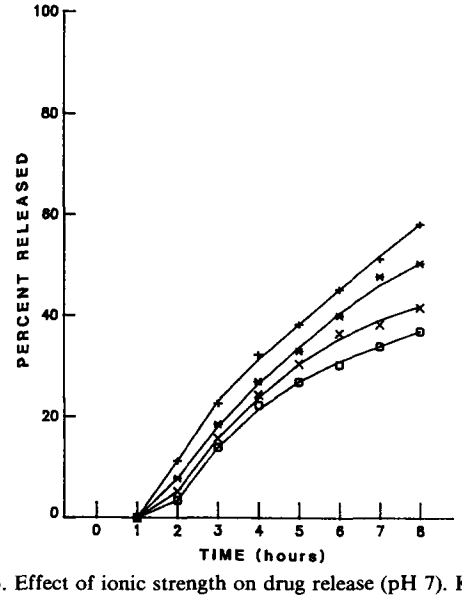

Fig. 5. Effect of ionic strength on drug release (pH 7). Key: □, 0.01; ×, 0.05; *, 0.10; and +, 0.20.

At a constant pH, the increased ionic strength corresponded to an increase in the concentration of counter-ions present in the eluant. As discussed previously drug release is dependent on the per-

TABLE 3

Effect of ionic strength on time required for 10%, 30% and 50% of drug to be released (pH 7)

Ionic strength	$T_{10\%}$ (h)	$T_{30\%}$ (h)	$T_{50\%}$ (h)
0.01	2.5 ± 0.11	6.8 ± 0.78	> 8
0.05	2.3 ± 0.06	4.9 ± 0.41	> 8
0.10	2.2 ± 0.10	4.5 ± 0.08	7.9 ± 0.32
0.20	1.8 ± 0.34	3.8 ± 0.27	6.8 ± 0.24

meation of the coating by the counter-ion and the subsequent drug exchange followed by diffusion of the drug outward. The rate at which these processes occurred depended on the concentration of counter-ion available. Hence, an increase in ionic strength will result in faster drug release.

Conclusions

The rate of phenylpropanolamine release from microencapsulated drug–resin complexes was greatest in media containing hydrogen counter-ions, having a low pH or having a high ionic strength. These results indicate a potential for in vivo variability. Of special concern should be a potentially rapid release of drug in the low pH environment of the stomach, which would negate the sustained release property of the dosage form.

References

Boyd, G.E., Adamson, A.W. and Meyers, L.S., The exchange adsorption of ions from aqueous solutions by organic zeolites. II. Kinetics. *J. Am. Chem. Soc.*, 69 (1947) 2836–2839.

Chaudhry, N.C. and Saunders, L., Sustained release of drugs from ion exchange resins. *J. Pharm. Pharmacol.*, 8 (1956) 975–983.

Chemotob, C., Chaumeil, J.C. and N'Dongo, M., Tablets of metronidazole microcapsules: release characteristics. *Int. J. Pharm.*, 29 (1986) 83–92.

Hays, E.E., Pharmaceutical composition containing a resin-narcotic compound and a resin-antihistamine compound. *U.S. Patent* 3, 035, 975 (1962).

Keating, J.W., Pharmaceutical preparations comprising phosphorous containing cation exchange resins having a basic drug adsorbed thereon; and treatment therewith. *U.S. Patent* 3, 143, 465 (1964).

Motycka, S. and Nairn, J.G., Influence of wax coatings on release rate of anions from ion-exchange resin beads. *J. Pharm. Sci.*, 67 (1978) 500–503.

Motycka, S. and Nairn, J.G., Preparation and evaluation of microencapsulated ion-exchange resin beads. *J. Pharm. Sci.*, 68 (1979) 211–215.

Raghunathan, Y., Prolonged release pharmaceutical preparations. *U.S. Patent* 4, 221, 778 (1980).

Raghunathan, Y., Amsel, L., Hinsvark, O. and Bryant, W., Sustained release drug delivery system: coated ion-exchange resin system for phenylpropanolamine and other drugs. *J. Pharm. Sci.*, 70 (1981) 379–384.

Reichenberg, D., Properties of ion-exchange resins in relation to their structure. III. Kinetics of exchange. *J. Am. Chem. Soc.* 75 (1953) 589–597.

Sayed, H.A.M. and Price, J.C., Tablet properties and dissolution characteristics of compressed cellulose acetate butyrate microcapsules containing succinyl sulfathiazole. *Drug. Dev. Ind. Pharm.*, 12 (1986) 577–587.

Sprockel, O.L. and Price, J.C., Particle size distribution and dissolution characteristics of microcapsules containing drug adsorbed on cation-exchange resin particles. *Abstracts, 37th National APhA/APS meeting Philadelphia, PA* 1984.

Sprockel, O.L. and Price, J.C., The effects of suspension adjuvants and suspension age on dissolution of chlorpheniramine, diphenhydramine, and pseudoephedrine from suspended, microencapsulated drug–resin complexes. *Abstracts, 39th National APhA/APS meeting, Minneapolis, MN* 1985.

Sprockel, O.L., Laskey, R.E. and Price, J.C., In vivo performance of a liquid sustained release dosage form of chlorpheniramine. *Pharm. Res.* 3 (1986) 70S.