DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(8), 1275-1287 (1989)

EVALUATION OF SUSTAINED RELEASE AQUEOUS SUSPENSIONS CONTAINING MICROENCAPSULATED DRUG-RESIN COMPLEXES

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ABSTRACT

Cellulose Acetate Butyrate coated resinates released chlorpheniramine faster if the microcapsules were hydrated by suspension prior to release studies when compared to dry, unsuspended microcapsules. Contrasting a sulfonic acid resinate with a carboxylic acid resinate showed a reduced rate of release for chlorpheniramine from both coated and uncoated sulfonic acid resinates. Microcapsules of smaller diameter released chlorpheniramine faster than larger coated resinates of a similar batch. Microcapsules prepared under identical conditions released pseudoephedrine, diphenhydramine, and chlorpheniramine at

different rates, with pseudoephedrine being released the fastest and chlorpheniramine the slowest. Aging of aqueous suspensions containing the coated resinates at room and elevated temperatures resulted in drug release profiles which were within experimental error.

INTRODUCTION

Much of the research effort in developing novel drug delivery systems has centered on sustained or controlled release of drug from dosage forms. Most of the new peroral sustained release preparations are solid dosage forms, i.e. tablets or capsules. Only recently has attention been devoted to liquid sustained release preparations which may be more palatable to pediatric patients (1).

Several publications have described methods by which drug-resin complexes were microencapsulated and which could be suspended in vehicles without premature release of drug occurring (1-4). Most of these reports did not elaborate on factors which may alter the rate of drug release from microcapsules which are suspended in aqueous media for a period of time.

In this investigation, several drug-resin complexes were microencapsulated using an emulsion-solvent evaporation technique. Drug release from the microcapsules was determined as influenced by hydration of the coating, resin type, drug type, and size of the capsule. The microcapsules were formulated into different suspensions and the effect of aging and temperature on the drug

release profile of the various suspended microcapsules was determined.

METHODOLOGY

Chlorpheniramine maleate[1] was complexed with a carboxylic acid cation-exchange resin (Amberlite CG-50^R)[1] and a sulfonic acid cation-exchange resin (Amberlite CG-120^R)[1]; diphenhydramine HCL[1] and pseudoephedrine HCL[1] were adsorbed onto a sulfonic acid cation-exchange resin. Complex formation occurred via a batch process.

The complexes were microencapsulated with cellulose acetate butyrate (CAB)[2] via an emulsion-solvent evaporation method using magnesium stearate[3] as an emulsion stabilizer. Briefly, a dispersion of the complexes in an acetone solution of CAB was emulsified in liquid paraffin containing magnesium stearate. The polymer solvent was allowed to evaporate under constant agitation and the microcapsules were washed with hexane.

Size distribution was determined by sieve analysis and drug release was determined using a modified USP paddle method at 100 rpm and 37°C with simulated intestinal fluid (SIF, pH 7.5) and a spectrophotometric assay at 260 nm. Dissolutions were conducted in triplicate on samples of microcapsules with a mean diameter of 362 μm and a 1:1 CAB:complex ratio.

The various microcapsules were formulated into aqueous suspensions containing 3.5% W/V solids with the aid of methyl cellulose 1500[3] (2%), methyl cellulose 4000[3] (1.6%), guar gum[1]

TABLE 1

Formulation Components Comprising the Various Suspensions of Cellulose Acetate Butyrate Coated Drug-resin Complexes

FORMULATION	DRUG	RESIN	ADJUVANT[a]
C_0	CHLORPHENIRAMINE	CARBOXYLIC ACID	NONE
C_1			METHYL CELLULOSE 1500
C_2			METHYL CELLULOSE 4000
C_3			GUAR GUM
C_4			XANTHAN GUM
D_0	DIPHENHYDRAMINE	SULFONIC ACID	NONE
D_1			METHYL CELLULOSE 1500
P_0	PSEUDOEPHEDRINE	SULFONIC ACID	NONE
P_1			METHYL CELLULOSE 4000

[a] All Suspensions Contained Deionized Water with 0.02% W/V Polyoxyethylene Sorbitan Monooleate as the Suspension Vehicle

(0.4%) and xanthan gum[1] (0.4%). The suspending agents were dispersed in deionized water containing 0.02% polyoxyethylene sorbitan monooleate and allowed to hydrate for 24 hours prior to suspension of the microcapsules.

Table 1 lists the various formulation components which comprised the suspension vehicles into which the microcapsules containing the complexes were dispersed. The suspensions were stored at 25°C for up to 28 weeks and those containing chlorpheniramine were also stored at 40°C, 55°C, and 70°C for 1 week. The drug release profiles were determined at the end of the test period.

RESULTS AND DISCUSSION

The uncoated chlorpheniramine-carboxylic acid resin complexes released the drug rapidly, with equilibrium being attained in one hour. Encapsulation of the complexes with cellulose acetate butyrate (CAB), at a 1:1 coating ratio, retarded the release of chlorpheniramine, so that 8.1 hours were required for 50% of the drug content to be released ($T_{50\%}$). If microcapsules from the same batch were suspended for 24 hours prior to release studies, the rate of drug release was slightly faster ($T_{50\%}$ of 6 hours), but not so rapid as to negate the sustained release effects (see Figure 1).

Diffusion of the drug molecule or the counter-ion can proceed through the membrane itself or through water filled pores. Hydration of the membrane requires time, which delays the release of drug. If the hydration step is removed by suspension of the microcapsules prior to release studies, this "delay" time is deleted and diffusion through these pores begins upon placing the hydrated microcapsules in dissolution fluid. The initial rate of drug release is, therefore, increased.

Drug release was also influenced by several manufacturing parameters, such as resin type, microcapsule size, and drug type. Chlorpheniramine release from either coated or uncoated carboxylic acid resin-complex was faster than from sulfonic acid resin-complex. The sulfonic acid resin slowed the release of chlorpheniramine from the uncoated complex so that equilibrium was not reached for approximately 12 hours compared to one hour for

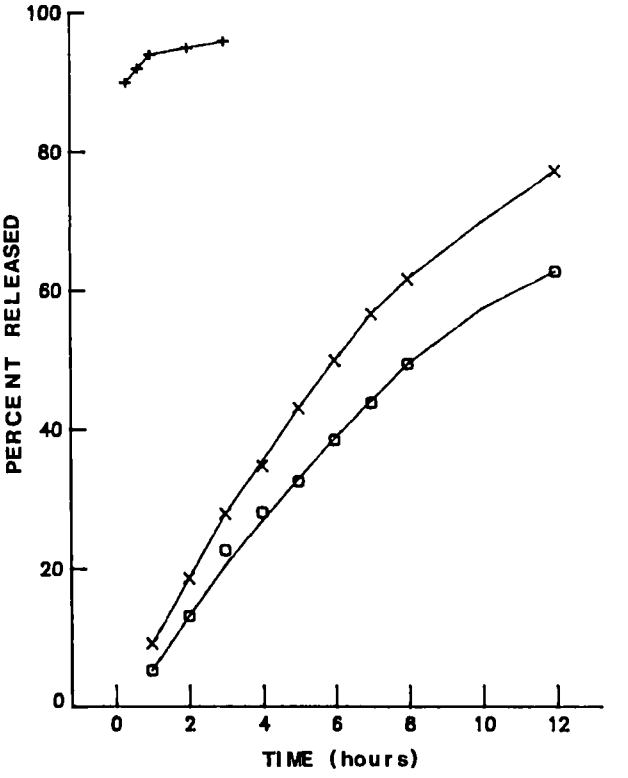

FIGURE 1

Comparison of Release of Chlorpheniramine from Suspended and Unsuspended Complexes Coated with CAB. KEY: (+) uncoated; (X) coated, suspended; (O) coated, unsupended

the carboxylic acid complex. Coating the complexes with cellulose acetate butyrate accentuated this retardation of drug release. The $T_{50\%}$ increased from approximately 6 hours for carboxylic acid to over 12 hours for sulfonic acid (see Figure 2).

Table 2 lists the times required for 25%, 50%, and 75% of the chlorpheniramine content to be released from microcapsules of various sizes. The $T_{25\%}$ ranged from 1.2 hours for 128 μm

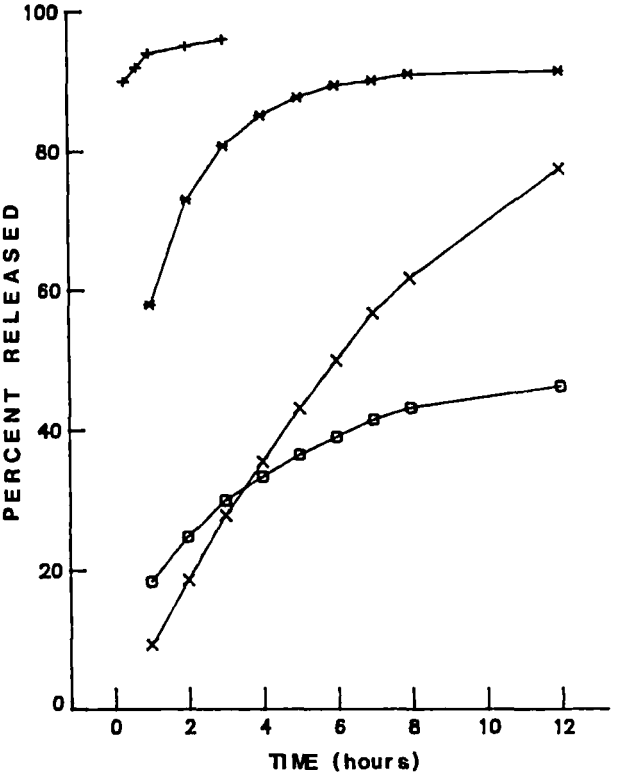

FIGURE 2

Effect of Resin Type on the Release of Chlorpheniramine from Complexes Coated with CAB. KEY: (+) uncoated, carboxylic acid; (✱) uncoated, sulfonic acid; (X) coated, carboxylic acid; (O) coated, sulfonic acid

microcapsules to 3.4 hours for 512 μm microcapsules. The $T_{75\%}$ for the same sizes of microcapsules ranged from 4.4 hours to 11.5 hours.

To acertain adaptability of the process to other drugs, pseudoephedrine HCL and diphenhydramine HCL were complexed with sulfonic acid resin and encapsulated.

The release rate for both pseudoephedrine and diphenhydramine from cellulose acetate butyrate coated complexes was faster than

TABLE 2

Effect of Microcapsule Size on 25%, 50%, and 75% Release Times of Chlorpheniramine from CAB Microcapsules of Drug-Resin Complexes

SIEVE SIZE	MICRONS	TIME IN HOURS FOR % RELEASED 25%	50%	75%
30/40	600/425	3.4 ± 0.00	6.8 ± 0.17	11.5 ± 0.40
40/50	425/300	2.0 ± 0.15	5.8 ± 0.25	10.5 ± 0.44
50/70	300/212	2.0 ± 0.06	3.9 ± 0.14	6.4 ± 0.20
70/100	212/150	1.8 ± 0.05	3.7 ± 0.08	5.9 ± 0.05
100/140	150/106	1.2 ± 0.02	2.7 ± 0.08	4.4 ± 0.02

for chlorpheniramine from microcapsules prepared under identical conditions. The $T_{50\%}$ ranged from 1.8 hours for pseudoephedrine to 3.3 hours for diphenhydramine, compared to 6 hours for chlorpheniramine. A higher percentage of pseudoephedrine and diphenhydramine was released at 12 hours when compared to chlorpheniramine (see Figure 3).

Diffusion of chemical entities through the coating polymer is dependent on the physico-chemical properties of both. Variation in the drug molecule affects the rate at which the drug traverses a certain thickness of the polymer membrane (5). This change in rates of diffusion may account for the differing rates of release for chlorpheniramine, pseudoephedrine, and diphenhydramine from encapsulated complexes prepared with identical procedures.

A comparison of times required for 50% of the drug content to be released from the various microcapsule suspensions after

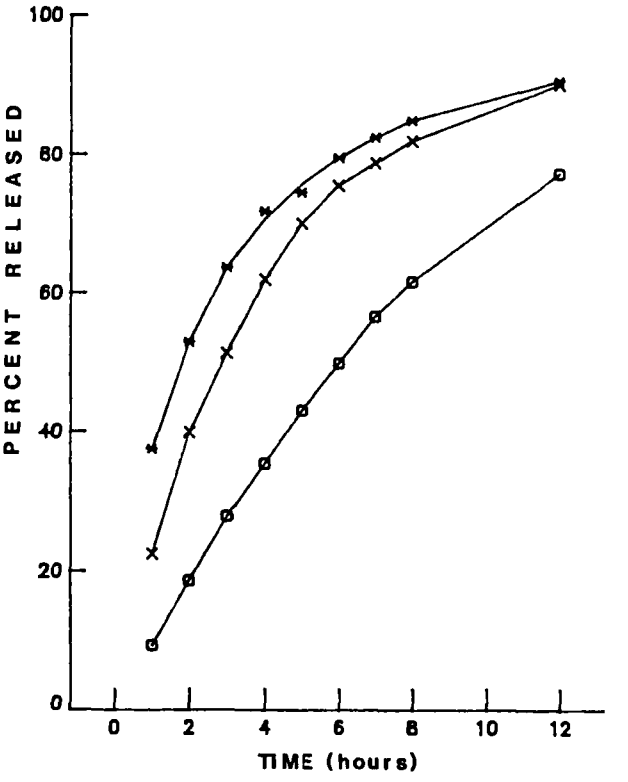

FIGURE 3

Effect of Drug Type on the Release Profiles of Suspensions Containing Complexes Coated with CAB. KEY: (✱) pseudoephedrine; (✕) diphenhydramine; (○) chlorpheniramine

storage for different time periods is displayed in Tables 3 and 4. Up to 16 days, the variation in $T_{50\%}$ with age for each suspending agent was within 1 hour. Guar gum showed the least variation (0.6 hours) and methyl cellulose 4000 had the largest variation (0.9 hours). For pseudoephedrine and diphenhydramine, with only methyl cellulose 1500, the variation in $T_{50\%}$ with age was small (see Table 3).

TABLE 3

Effect of Aging of Microcapsule Suspension Formulations on the Release of Chlorpheniramine, Diphenhydramine, and Pseudoephedrine from CAB Microcapsules

FORMULATION	2 DAYS $T_{50\%}$[a]	4 DAYS $T_{50\%}$[a]	8 DAYS $T_{50\%}$[a]	16 DAYS $T_{50\%}$[a]
C_0	7.0 ± 0.09	---	---	---
C_1	6.9 ± 0.09	6.2 ± 0.15	6.6 ± 0.07	6.5 ± 0.37
C_2	7.0 ± 0.11	6.1 ± 0.12	6.4 ± 0.13	6.8 ± 0.01
C_3	6.6 ± 0.03	6.3 ± 0.12	6.1 ± 0.02	6.0 ± 0.07
C_4	5.5 ± 0.04	5.8 ± 0.11	7.0 ± 0.47	5.2 ± 0.06
D_0	3.0 ± 0.02	---	---	---
D_1	2.9 ± 0.03	2.5 ± 0.06	2.7 ± 0.17	2.6 ± 0.06
P_0	2.0 ± 0.05	---	---	---
P_1	2.0 ± 0.17	1.8 ± 0.11	1.8 ± 0.05	1.9 ± 0.07

[a] Time, in hours, required for 50% of the drug to be released.

The chlorpheniramine microcapsule suspension with methyl cellulose 1500 as the suspending agent was selected for extended aging trials lasting up to 28 weeks. The deviation in $T_{50\%}$ between the different suspensions at various age periods in the expanded stability study, was a maximum of 1.6 hours from the control. No trend, decreasing or increasing, was apparent (see Table 4).

Most of the variation in the release profiles of the suspensions was probably due to sampling error when transferring the dosage form from the container to the dissolution vessel. This was indicated by a higher total amount of drug released for

TABLE 4

Effect of Extended Aging on the Release of Chlorpheniramine from Suspended CAB Microcapsules

AGE WEEKS	PERCENT RELEASED IN HOURS 4	8	12	T50%
0	37.30 ± 0.00	65.00 ± 0.25	78.50 ± 0.83	5.8 ± 0.07
4	40.66 ± 0.27	68.42 ± 0.55	78.88 ± 0.83	5.0 ± 0.03
10	45.51 ± 0.35	68.82 ± 0.39	82.90 ± 0.66	4.5 ± 0.03
16	39.85 ± 0.27	62.38 ± 0.27	73.45 ± 0.57	5.5 ± 0.00
28	43.07 ± 0.80	74.13 ± 1.46	88.54 ± 0.13	4.7 ± 0.13

TABLE 5

Effect of Aging at Elevated Temperatures on the Release of Chlorpheniramine from Suspended Microcapsules

DEGREES CELCIUS[a]	PERCENT RELEASED IN HOURS 4	8	12	$T_{50\%}$
25	37.47 ± 0.00	62.54 ± 0.46	75.77 ± 0.75	6.0 ± 0.05
40	34.05 ± 0.36	57.50 ± 0.40	76.07 ± 1.48	6.5 ± 0.00
55	31.11 ± 0.35	58.42 ± 0.37	75.65 ± 0.00	6.6 ± 0.09
70	32.79 ± 0.36	59.26 ± 0.00	74.18 ± 0.59	6.3 ± 0.01

[a] The temperature is in degrees celcius.

those release profiles with a decreased $T_{50\%}$. Therefore, the variations observed may not be significant.

Storing similar suspensions at 25°C, 40°C, 55°C and 70°C for one week had no adverse effects on the sustained release behavior of chlorpheniramine from suspended microcapsules (see Table 5). The accelerated stability studies offered further evidence of the physical stability of the cellulose acetate butyrate membrane surrounding the complexes.

The suspension stability studies showed that microcapsules could be suspended up to 28 weeks without seriously compromising the sustained release properties of the dosage form. These results indicate that the polymer membrane surrounding the core material remained intact throughout the storage period in contrast to results reported for unfilled drug-resin complexes spray coated with ethyl cellulose (1).

SUMMARY

1. Suspension of microcapsules prior to release studies, resulted in a small increase in the release rate of chlorpheniramine from the microcapsules.
2. Substituting sulfonic acid resin for carboxylic acid resin reduced the release rate of chlorpheniramine from coated and uncoated complexes.
3. Diphenhydramine and pseudoephedrine were released at a faster rate than chlorpheniramine from microcapsules prepared under similar conditions.

4. The drug release profile variations with aging of the microcapsule suspensions were within experimental error.
5. Storage of microcapsule suspensions at elevated temperatures did not adversely affect drug release from the microcapsules.

FOOTNOTES

1. Aldrich Chemical Co., Milwaukee, WI
2. Scientific Polymer, Ontario, NY
3. Fisher Scientific Co., Fair Lawn, NJ

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