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MICROENCAPSULATION OF SULFADIAZINE WITH CELLULOSE ACETATE PHTHALATE

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ABSTRACT

Microencapsulation of a relatively insoluble drug sulfadiazine was carried out by allowing drops of a suspension of the drug in an aqueous cellulose acetate phthalate solution to fall into an acetic acid hardening solution. Spherical microcapsules could readily be obtained when a surfactant polyoxyethylene 20 sorbitan monooleate was added to the suspension. Increased drug concentration in the suspension yielded larger microcapsules with shorter disintegration times. The incorporation of viscosity agents into the suspension yielded microcapsules with altered disintegration times.

INTRODUCTION

Cellulose acetate phthalate - CAP, one of the most useful coating agents for tablets and capsules has also been used to prepare microcapsules of drug products using mineral oil[1] or water[2,3]. In this research the capillary method[2] whereby an aqueous solution

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of CAP is introduced dropwise into an acid solution was further investigated. A model drug, sulfadiazine, with low water solubility was used to minimize losses due to dissolution of the drug, and the necessity for saturating the hardening solution with drug prior to microencapsulation. Various concentrations of CAP, drug, and excipients such as viscosity agents and a surface active agent were used to assess the effect on some of the properties of the microcapsules namely: formation, shape, size, percentage of drug incorporated and disintegration.

MATERIALS

The chemicals: cellulose acetate phthalate (Cellulose acetate hydrogen phthalate, Eastman Kodak Co., Rochester, N.Y.), sulfadiazine (Sulphadiazine, British Drug Houses, Toronto, Canada), polyoxyethylene 20 sorbitan monooleate (Tween 80, Atlas Chemical Ind., Wilmington, Del.), hydroxypropylmethylcellulose (Methocel K4M Premium, Dow Chemical Co., Midland, Mich.), microcrystalline cellulose-avicel PH 105 (Avicel, Type PH 105, FMC Corp., Philadelphia, PA.), glycerin, were used without further treatment.

METHODS

Solutions of CAP were prepared[3] by dissolving 1.85 g of Na_2HPO_4 in about 180 ml of distilled water, heating to 60°C, then adding 5 g of CAP, after dissolution the solution was filtered through a coarse porosity sintered glass funnel and made up to 180 ml with distilled water. Various quantities of drug - sulfadiazine, polyoxyethylene 20 sorbitan monooleate, and viscosity agents were added with stirring to appropriate volumes of the CAP

solution to yield satisfactory suspensions with compositions listed in the tables. Higher concentrations of viscosity agents were not satisfactory due to solubility, high viscosity and unsuitable suspending properties. The suspension, 50 ml, which was stirred throughout the experiment with a magnetic bar, was introduced into the hardening solution by means of a peristaltic pump (H.R. Flow Inducer, Watson-Marlow Ltd., Buckinghamshire, England) fitted with thick walled silicone tubing (2.5 mm id) a small lumen tygon tubing and finally a teflon capillary tubing approximately 380 μm in diameter. The aqueous hardening solution, 200 ml, contained 30 ml of glacial acetic acid.

The microcapsules were formed by introducing 60 drops per min, of the suspension into the hardening solution which was 3 cm below the teflon tubing. The hardening solution was stirred at 80 rpm. After all the suspension had been added the stirring was continued for an additional 10 min, then the microcapsules were collected on a nylon strainer and washed well with distilled water, air dried in a fume hood for 18 hr and then in a drying oven at 50°C for 48 hr. The size of 30 microcapsules was determined microscopically using a calibrated eyepiece, or directly with a calibrated scale. The mean size and the size range are given.

The assay for sulfadiazine in the microcapsules was performed by pulverizing about 50 or 100 mg in a mortar, dissolving the drug in 30 ml of 4 M HCl, filtering, neutralizing the solution with approximately 30 ml of 4 M NaOH and diluting to 1000 ml with phosphate buffer pH 7.50. Further dilutions of this solution with

the phosphate buffer were made and the absorbance at 239 nm was determined spectrophotometrically. The concentration of the drug was determined from a Beer Lambert plot. Preliminary studies showed that absorbance of CAP, the surfactant, hydroxypropylmethylcellulose and microcrystalline cellulose treated in the above manner was negligible.

The disintegration of the microcapsules was determined by placing about 50 mg in a 150 ml glass stoppered Erlenmeyer flask containing 50 ml of simulated gastric fluid without enzyme[4]. The flasks were placed in a pre-equilibrated incubator, shaken at 100 oscillations/min for 1 hr at 37 $\pm$ 0.5°C, and observed for disintegration. The microcapsules were removed from the incubator shaker and the gastric fluid was decanted. They were rinsed 3 times with distilled water, then 50 ml of simulated intestinal fluid without enzymes[4] were added and the shaking was continued as described. The end point was assessed when visible particles of the microcapsules could not be observed.

RESULTS AND DISCUSSION

In order to produce microcapsules containing a uniform amount of drug during the encapsulation procedure, it was necessary to prepare a satisfactory suspension of the drug. Although several concentrations, 0.5, 1.0, 2.5% of CAP were employed, it was found that the 2.5% concentration had appropriate characteristics to suspend various quantities, 0.25 to 3.0 g, of the drug with a mean particle size of 30 μm, during the encapsulation process. Microcapsules prepared in the absence of drug can also be made,

Table 1. All microcapsules described in the tables were prepared from 2.5% CAP solution.

The shape of the microcapsules with or without viscosity agents was improved considerably by the addition of surfactant to the suspension of the drug, Tables 1, 2. At 0 or 1% surfactant concentration, irregular shaped particles were produced, however, when glycerin was incorporated, spherical shaped particles were produced at the 1% concentration of surfactant. At the 2% surfactant concentration the microcapsules were spherical in shape, Table 2, and at a higher surfactant concentration, 3%, the product was spherical and sticky at low drug concentrations 0.25 to 0.75 g/50 ml and irregularly shaped at higher drug concentrations 1 to 3 g/50 ml. At higher surfactant concentrations only fluffy or fibrous products were produced. Spherical microcapsules retained their smooth surface until the drying procedure, whereupon due to loss of water the surface became rough.

The size of the microcapsules was primarily affected by the amount of drug contained in 50 ml of suspension. For example Table 2 shows that as the amount of drug increased, the diameter of the microcapsules also tends to increase. Viscosity agents did not affect the size appreciably, Table 3.

Spectroscopic analyses of the acidic extract of the microcapsules showed that most of the drug is incorporated into the microcapsules, thus the solubility characteristics of the process are satisfactory to minimize loss of the active ingredient. The use of 0.75 g of drug tends to optimize the percentage of drug

TABLE 1

Properties of CAP Microcapsules Containing Only Drug or Surfactant

Composition		Core to	Mean Particle Size	Shape	Disintegration	Percentage of Drug
Drug	Surfactant	Coat Ratio	and Range mm		Time/min	Encapsulated
——	1%	——	0.782 -0.992 - 1.06	a	40	——
——	2%	——	0.869 -0.992 - 1.13	a	27	——
——	3%	——	0.869 -1.17 - 1.34	a	18	——
0.50 g	——	0.320	1.07 - 1.48 - 1.79	b	39	68.9
0.75 g	——	0.636	1.21 - 1.52 - 1.86	b	42	90.1
1.0 g	——	0.545	1.14 - 1.50 - 1.72	b	40	70.1

[a] mainly spherical particles

[b] mainly irregular particles

TABLE 2

Influence of Drug Content on the Properties of CAP Microcapsules Prepared with 2% Surfactant

Drug g	Core to Coat Ratio	Mean Particle Size and Range mm	Shape	Disintegration Time/min	Percentage of Drug Encapsulated
0.25	0.141	0.87 - 1.09 - 1.43	a	43	83.6
0.50	0.204	0.87 - 1.11 - 1.37	a	40	72.3
0.75	0.418	0.87 - 1.34 - 1.95	a	38	89.4
1.00	0.449	0.95 - 1.22 - 1.61	a	39	84.4
1.50	0.731	0.94 - 1.38 - 1.63	a	30	82.2
2.0	0.960	1.06 - 1.51 - 1.83	a	21	76.0
3.0	1.55	0.87 - 1.60 - 1.91	b	19	83.5

[a] mainly spherical particles

[b] mainly irregular particles

TABLE 3

Influence of Viscosity Agents on the Properties of CAP Microcapsules Prepared with 0.75 g of Drug and 2% Surfactant

Viscosity Agent	Core/Coat Ratio	Mean Particle Size and Range mm	Shape	Disintegration Time/min	Percentage of Drug Incorporated
Hydroxypropyl-methylcellulose					
0.1%	0.438	1.08 - 1.32 - 1.46	a	33	95.3
0.5%	0.393	1.17 - 1.52 - 1.74	b	37	94.0
Avicel pH 105					
0.1%	0.398	0.97 - 1.25 - 1.51	a	28	88.6
0.5%	0.362	1.04 - 1.39 - 1.55	a	28	91.6
1.0%	0.328	1.04 - 1.34 - 1.48	a	23	92.4
glycerin					
0.5%	0.420	1.08 - 1.36 - 1.83	a	27	88.9
1.0%	0.400	1.04 - 1.30 - 1.60	a	27	81.0
4%	0.413	0.89 - 1.19 - 1.39	a	28	84.8
8%	0.383	1.04 - 1.36 - 1.63	a	27	85.4

[a] mainly spherical particles

[b] mainly irregular particles

incorporated, Tables 1, 2. In most other cases the percentage of drug incorporated was improved by about 10% when the surfactant was included in the suspension medium, Tables 1, 2.

The microcapsules did not disintegrate in the simulated gastric fluid even though some contained a considerable amount of excipient such as surfactant or glycerin. The disintegration of the microcapsules in simulated intestinal juice was affected by the amount of drug used in the suspension. It can be seen in Table 2 that increasing the amount of drug produces microcapsules which tend to disintegrate in a shorter period. Thus microcapsules with a low core to coat ratio, take a longer time to disintegrate indicating that the disintegration time can be controlled to some extent by the amount of CAP in the microcapsules. From Table 3 it can be seen that increasing the amount of microcrystalline cellulose effected both a decrease in the core to coat ratio and also the disintegration time, probably due to the inclusion of the agent in the microcapsules. The addition of hydroxypropylmethylcellulose decreases the disintegration time by only a few minutes. The incorporation of glycerin, however, decreased the disintegration time by about 10 minutes. The core to coat ratio was similar to that of the microcapsules prepared without glycerin at the same concentration of drug indicating that most of the glycerin was washed out during the procedure. This suggests a more porous structure for the microcapsules. The presence of a surfactant did not alter the disintegration time

appreciably, however, increasing amounts of surfactant effected a shorter disintegration time when no drug was present, Tables 1, 2.

CONCLUSIONS

Cellulose acetate phthalate - microcapsules containing a water insoluble drug can be readily prepared. However, the suspension of the drug should be uniform and have the surface tension lowered by means of a surfactant so that uniform spherical microcapsules are easily formed. The incorporation of a drug and agents altering the viscosity, and surface tension can affect the shapes and sizes of the microcapsules, their core to coat ratios and disintegration times in the intestinal fluid.

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