phatidylcholine. The use of a charged membrane as well as the addition of other membrane adjuvants may affect the entrapment of methantheline and other compounds by liposomes.

These ion-pairing techniques can be used to increase liposomal loading of a large number of ionic compounds. The liposome-entrapped compounds can be used to overcome some traditional problems in the oral administration of drugs such as acid lability, inadequate intestinal absorption, and poor palatability.

The administration of methantheline bromide *via* liposomes is particularly desirable considering the poor absorption observed for quaternary ammonium compounds. In addition, ion-pairing of quaternary ammonium compounds increases the loading of these poorly entrapped drugs in liposomal membranes.

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pH-Sensitive Microcapsules for Drug Release

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Received July 24, 1981, from the **Centre for Biomedical Engineering, All India Institute of Medical Sciences*, and the *‡Centre for Rural Development and Appropriate Technology, Indian Institute of Technology, Hauz Khas, New Delhi-110 016 India.* Accepted for publication November 3, 1981.

Abstract □ Microcapsules were designed for a sustained drug release, where the external medium controls the rate of release of the drug. As a model, secretin was encapsulated in acryloyl chloride–lysine capsules, and the conditions of formation are described. The scanning electron micrographs show the formation of good spherical microcapsules in the size range of 5–10 μm. The release of secretin was studied in four media having different pH. Polymer dissolution was pH sensitive, and the capsules placed in different media eroded at a constant rate, depending on the pH of the medium. Dissolution of the microcapsules was limited to the polymer buffer media and the drug was released by zero-order kinetics. The possible use of such a system is in the treatment of duodenal ulcers and the diagnosis of pancreatic diseases.

Keyphrases □ Microcapsules—pH sensitive, drug release □ Drug release—pH sensitive microcapsules, polymerization □ Polymerization—pH sensitive microcapsules for drug release □ Dosage forms—pH-sensitive microcapsules for drug release

Microencapsulation is a process by which individual entities of a solid, liquid, or gas are discretely enclosed in a shell of inert polymeric materials. These inert shells may be designed to release their ingredients at a specific rate and/or under a specific set of conditions. Microencapsulation of a material may permit the alteration of its physical properties so that the desired availability is achieved and at the same time the encapsulated material is protected from its environment. Release of drug may be achieved *via* erosion, dissociation, or diffusion. Dosage forms have become more complex and now include such forms as sustained release, prolonged action, and repeat action. The technique of microencapsulation is one of the newer methods for sustained delivery which is receiving increasing attention (1, 2).

Precisely controlled sustained delivery does not always correspond to the optimum therapeutic regimen, however. In many applications a better delivery system is the one that delivers the active agent only when needed. In the present study secretin was microencapsulated in acryloyl chloride–lysine microcapsules, and the rate of release was studied in different media of varying pH.

BACKGROUND

Secretin (3), a small polypeptide (molecular weight ~3400), is present in the mucosa of the upper small intestine in the inactive form of prosecretin. When chyme enters the intestine, it causes the release and activation of secretin, which is subsequently absorbed into the blood. The constituent that causes greatest secretin release is hydrochloric acid, although almost any type of food will cause at least some release. Secretin is released any time the pH of the duodenal contents falls below ~4.0. This immediately causes large quantities of pancreatic juice containing abundant amounts of sodium bicarbonate to be secreted. Carbonic acid is formed by reaction of sodium bicarbonate with hydrogen chloride. The carbonic acid is immediately dissociated into carbon dioxide and water, and the carbon dioxide is absorbed into the body fluids, thus, leaving a neutral solution of sodium chloride in the duodenum. In this way, the acid contents emptied into the duodenum from the stomach become neutralized and the peptic activity of the gastric juices is immediately blocked. Since the mucosa of the small intestine cannot withstand the intense digestive properties of gastric juice, this is a highly important protective mechanism against the development of duodenal ulcers (4). A second function of hydrolytic secretin by the pancreas is to provide an appropriate pH for action of pancreatic enzymes. All such enzymes

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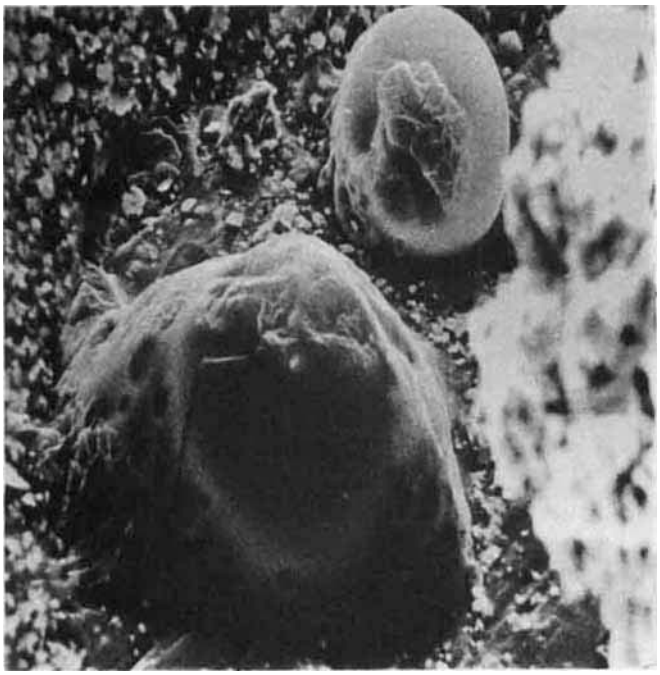

Figure 1—*Scanning electron micrograph of polyacryloyl chloride–lysine microcapsules containing secretin (5000×).*

function optimally in a slightly alkaline or neutral medium. The pH of the hydrolytic secretion averages 8.0.

Secretin release *in vivo* is pH-sensitive. To simulate this system, it was proposed to design a secretin microcapsule that would become more permeable at low pH. The acryloyl chloride–lysine encapsulation system was chosen as the wall material, since it was anticipated that the presence of unreacted amino groups in the capsule wall would likely cause the erodibility of the polymer to become pH dependent.

EXPERIMENTAL

Microcapsules were prepared by interfacial polymerization as described previously (5). Acrylic acid distilled under reduced pressure was polymerized under vacuum by gamma radiation from a cobalt 60 source. The polyacrylic acid was dissolved in distilled 1,6-dioxane and then converted into the acid chloride with thionyl chloride. The polyacryloyl chloride that precipitated out was dissolved in dimethylformamide.

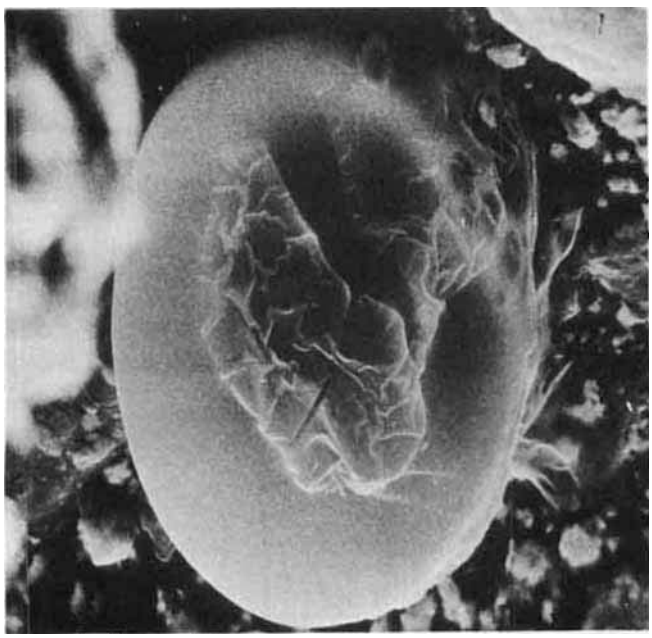

Figure 2—*Scanning electron micrograph of polyacryloyl chloride–lysine microcapsules containing secretin (5000× 2.5).*

Table I—Cumulative Release of Secretin at Different pH

Time, days	I pH 2 Amount, mg	I pH 2 Secretin, %	II pH 4 Amount, mg	II pH 4 Secretin, %	III pH 7 Amount, mg	III pH 7 Secretin, %
1	10.0	20	5.0	10	2.5	5
2	21.0	42	10.0	20	5.0	10
3	29.0	58	15.0	30	7.0	14
4	40.0	80	20.0	40	9.5	19
5	44.0	88	25.0	50	12.0	24
6	47.0	94	31.0	62	15.0	30
7	—	—	35.0	70	18.0	36
8	—	—	40.0	80	20.0	40
9	—	—	42.5	85	22.5	45
10	—	—	44.0	88	26.0	52
12	—	—	47.0	94	30.0	60
14	—	—	—	—	35.0	70
16	—	—	—	—	40.0	80
18	—	—	—	—	44.0	88
20	—	—	—	—	47.0	94
22	—	—	—	—	48.0	96

Secretin (50 mg) was mixed with an equal volume of 0.8 *M* lysine dissolved in a tromethamine buffer (pH 7.4), containing 2 ml of 0.45 *M* sodium bicarbonate solution. This mixture was freshly prepared and stirred in a 100-ml beaker at room temperature. The organic phase [a 15-ml mixture of chloroform–cyclohexane (1:4)] was added with stirring to the beaker. Stirring was continued for 45–60 sec at the maximum speed to disperse the aqueous droplets and to reduce their size, and polyacryloyl chloride solution in dimethylformamide was added. The amount of polyacryloyl chloride used was approximately equivalent to lysine. In this way polyacryloyl chloride–lysine microcapsules containing secretin were prepared.

The microcapsules were separated from the organic phase by centrifugation and transferred to the aqueous phase with the aid of polyoxyethylene sorbitol washed repeatedly with saline solution and dispersed in isotonic buffer. Scanning electron micrographs of the capsules were taken[1]. Release of encapsulated drug was studied by following its elution in buffer solutions of different pH. For a typical experiment the microcapsules were equilibrated with 15 ml of buffer for 24 hr. The supernate was separated by centrifugation and its optical density was determined at 245 nm. A fresh buffer (5 ml) was equilibrated until no more elution of the drug occurred.

RESULTS AND DISCUSSION

To check the reproducibility of the method of encapsulation and release, three sets of samples (labeled I, II, and III) were prepared under the same conditions just described. The electron micrograph of each sample was taken separately. In all cases, the capsules were 5–10 μm in diameter (Figs. 1 and 2).

The release rates of secretin at different pH values are given in Table I. Figure 3 shows the cumulative release of secretin as a function of time for all samples. In all cases, at least up to 80% of the drug was released by a zero-order mechanism; however, the rate of release was fastest at pH

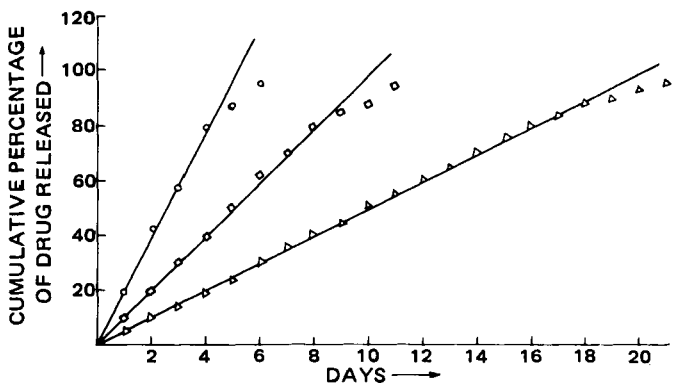

Figure 3—*Cumulative percentage of secretin released from acryloyl chloride–lysine microcapsules. Key: (○) pH 2, (□) pH 4, (△) pH 7.*

[1] Micrographs taken by a Cambridge Steroscan S_4-10 instrument.

2, and was prolonged for up to 6 days. At pH 4, the release sustained for up to 12 days, and on increasing the pH to 7, the duration of the release increased to 22 days. Thus, it was also observed that as the pH increased, the solubility of the wall material decreased and the quantity of drug released per day decreased. When the pH was raised to 10, no dissolution of the polymer wall occurred and no release of secretin was observed for several days.

The data indicated that the drug was perhaps released by polymer dissolution at the polymer–water interface by a mechanism similar to that discussed previously (6, 7). Detailed study of this polymer will be necessary before the complete mechanism for erosion can be understood; the mechanism of release is the subject of further study. However, in the present study the interest was more on controlled release of the drug at low pH, which has been achieved. The above type of capsules would be suitable for sustained drug release at low pH. Further, since the polymer was erodible up to pH 8, it can form a suitable biosoluble wall material for encapsulating other drugs. The biocompatibility of this material is being studied.

Notable features of the microcapsules described in this report are: their ability to undergo surface erosion and, hence, release of the core material by zero-order kinetics, and sensitivity of the erosion rate to the surrounding aqueous environment (pH). A pH environment has a major effect on the erosion rate and, thus, controls the drug release which is increased by decreasing the pH.

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Reaction of Phenobarbital with Diphenhydramine

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Abstract □ A compound of low water solubility, consisting of phenobarbital–diphenhydramine in a 1:1 ratio and mp 109.5–110.5° was isolated from a prescription which had been dispensed as a clear solution and later returned with a white sediment. The information obtained suggested that it was either an easily dissociated complex or a salt.

Keyphrases □ Phenobarbital—reaction with diphenhydramine, complexation, salts □ Diphenhydramine—reaction with phenobarbital, complexation, salts □ Complexation—phenobarbital and diphenhydramine, salts

A number of salts, complexes, or addition compounds formed by barbiturates, particularly by phenobarbital, have been recorded previously (1–6). Similarly, there are recorded complexes and salts for diphenhydramine, the best known being dimenhydrinate, USP (7). The products formed by heating diphenhydramine and barbital or allobarbital in alcohol at 100–120° are reported to be 1:1 salts melting at 86 and 102–103°, respectively (8).

Literature pertaining to intravenous admixtures refers to diphenhydramine hydrochloride as being incompatible with phenobarbital sodium (9–11) as well as several other barbiturate salts; forming particulate matter (12, 13), forming a precipitate (14), or as not remaining clear for 24 hr after mixing (15). The only explanation provided is that solutions of sodium barbiturates and sodium diphenylhydantoin are alkaline and may lead to the formation of precipitates from solutions of acid salts. A previous study (16) pointed out that aqueous solutions of diphenhydramine hydrochloride and phenobarbital sodium will form a precipitate when mixed in low concentrations, even at pH values at which phenobarbital would be soluble. It was assumed that the precipitate was an undissociated, less soluble diphenhydramine–phenobarbital complex. No characteristics for this substance were reported.

The reported compound was first obtained from the crystalline settlement in a compounded prescription consisting of 250 ml of diphenhydramine hydrochloride elixir in which 750 mg of phenobarbital sodium had been dissolved in accordance with physician's instructions. When prepared, the mixture slowly became cloudy and then deposited crystals over several days. Upon filtration and recrystallization of the solid from ~75% alcohol, the hard, colorless crystals melted at 109.5–110.5° (uncorrected). The product was found to be composed of phenobarbital–diphenhydramine (1:1).

The formation of the crystals could be avoided by dissolving the equivalent amount of phenobarbital in 10 ml of alcohol and mixing it into the elixir. Such a sample was still free of crystals after 1 year. Since the crystals are very soluble in alcohol, somewhat soluble in water, and the pH of the elixir results in only a low concentration of diphenhydramine base, the product probably does not form in an amount sufficient to exceed its solubility in the hydroalcoholic medium.

EXPERIMENTAL

Diphenhydramine hydrochloride elixir[1], diphenhydramine[1], diphenhydramine hydrochloride[1], phenobarbital[2], and phenobarbital sodium[2] were obtained as indicated. The various solvents were USP or reagent grade.

[1] Elixir Benadryl, Parke-Davis & Co.; the diphenhydramine and its hydrochloride were provided by Parke-Davis & Co.

[2] Merck & Co., Rahway, N.J., commercial packages.

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