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CARBOPOL-GELATIN COACERVATION AND DRUG MICROENCAPSULATION

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ABSTRACT

Carbopol-gelatin coacervates were recovered as water-insoluble powder which when suspended in water gave a highly disperse system.

Glycerol as a protective against coacervate deformation, formaldhyde as a denaturant and some monohydric aliphatic alcohols as flocculating agents were variables studied. The hypothesis that solid particles may be protectively encapsulated by coacervation led to the investigation of the encapsulation of sulfadiazine at four coat-core ratios. The surface-adhering drug as well as the percentage of drug in the microcapsule increased on raising the core ratio. The size distribution was determined by use of standard sieves and the influence of four coat/core ratios was noted. Availability studies show that sulphadiazine was readily accessable to the leaching effect of the artifical intestinal fluids.

INTRODUCTION

Drug encapsulation through coacervation has great potential applications in pharmacy (1-5).

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Gelatin in simple and complex coacervate systems has been extensively studied (6-9).

In our preceeding work, coacervation between carbopol and gelatin sols has been induced. Yield optimization in concern with choice of either gelatin or carbopol types, their ratios, the total colloid concentration, starting pH of gelatin sol and the stirring rate had been established. Type A gelatin sol (2% w/v) at pH 6.8 to be coacervated with carbopol 941 sol (0.2% w/v) in isovolumetric ratio at 40° C represent the optimal coacervate conditions (10).

The aim of the present work is to study the influence of some additives, denaturants and flocculating agents that may help in obtaining and recovery of uniform, discrete non-medicated coacervates.
Furthermore, application of this coacervation technique to encapsulate sulphadiazine, as a model drug, and determine the extent of encapsulation at four different coat to core ratios was achieved. Size distribution of sulphadiazine microcapsules obtained at these different coat/core ratios was determined. The susceptibility of the sulphadiazine microcapsules to the action of simulated gastrointestinal fluids was also studied.

EXPERIMENTAL

Materials : Carbopol 941 (Goodrich Aniline & Sodalime CO.) Gelatin B.P. Bloom 150 (acid type having an isoelectric point of 8.4) Sulphadiazine B.P. (B.D.H. majority

of particles 40 um). Glycerol (99%), formaldhyde solution B.P. (37% w/v), 1-propanol and 2-propanol (99%). All solvents and reagents were analytical reagent grade or purity.

Influence of Glycerol-Batches of coacervates were prepared by adding 40 ml gelatin sol (2% w/v) at pH 6.8 to 40 ml carbopol 941 sol (0.2% w/v) at 40°C. The coacervate was stirred at 300-350 r.p.m. for 20 minutes.

To separate batches 10, 20, 30, 40, 50, 60 and 80 ml of glycerol were added slowly with stirring for further 20 min at room temperature (25°C).

The experiment was repeated by coacervating 40 ml of 0.2% w/v carbopol sol, previously mixed with 10, 20, 30, 40, 50, 60 or 80 ml of glycerol; with 40 ml of gelatin sol (2% w/v).

Stirring was continued for 20 min at 40°C then for further 20 min at 25°C.

Coacervates were examined microscopically to assess the uniformity of size and smoothness of surface. Sediment volume and weight were determined as previously described.

A close procedure to that sited by Newton et al. (9), for the recovary of gelatin-acacia coacervates through denaturation and flocculation was followed with some modifications.

Coacervate Denaturation-Batches of coacervates were mixed separately with 25 ml of 5, 10, 20, 30, 37% v/v formaldhyde solutions and kept for four hours at room temperature (25°C). The sediment volume, clarity of

supernate and the appearance of the sediment were then recorded.

Batches of formaldhyde (20% v/v) treated coacervates were recovered at fixed time intervals over 0.5-6 hours to determine the minimum treatment period for obtaining of readily dispersable products;

Coacervate Flocculation-Batches of formaldhyde (20% v/v) treated microglobules were decanted. From the sediment a 10 ml-sample was mixed individually with 5, 15, 30, 60 and 90 ml of each of methanol, ethanol, 1-propanol or 2-propanol for 10 min. The percent (v/v) of these alcohols at which flocculation occurs were recorded.

Alcohols were decanted and the redispersibility of the coacervates in 10 ml distilled water were checked.

Sulphadiazine Microencapsulation- A quantity of 220, 440, 880 or 1760 mg of sulphadiazine (average particle size 40 um) was individually suspended in 40 ml carbopol (0.2% w/v) with stirring at 40 °C. 40 ml of gelatin sol (2% w/v) was added and stirring was continued for 20 minutes at 40 °C. Over 20 min, 30 ml of glycerol was added dropwise with stirring while cooling to room temperature (25 C). The supernate was decanted and the white sediment layer (30-60 ml) was vacuum dried and weighed. The separated microcapsules were shaken for two minutes with 20 ml of 0.1N HCl and refiltered rapidly. The filtrate was assayed for surface adhering sulphadiazine. The microcapsules were then diss-

olved in 20 ml of 5% w/v sodium hydroxide with frequent stirring and assayed for sulphadiazine content according to the USP XIX (11).

Our preliminary studies showed that the water-soluble residues of gelatin did not interfere with the USP XIX assay procedure for sulphadiazine.

Recovery of Sulphadiazine Microencapsulation-Batches of medicated microcapsules were prepared as previously described. The supernate was discarded and 12 ml of formaldhyde (20% v/v) was stirred for 5 minutes and left for 4 hours.

Formaldhyde was decanted, 40 ml of 2-propanol added and was shaken for 10 min and the supernate discarded. The batch was suspended in 40 ml of 2-propanol, filtered through a Buchner funnel and the microcapsules were vacuum dried. Their drug content was determined previously mentioned.

Screening of Microcapsules- The different sizes of microcapsules present in a batch were separated into suitable fractions by sieving on a mechanical shaker using a nest of standard sieves (63-250 um apertures, DIN 1171) and a shaking time of 10 min.

Availability of Sulphadiazine Microcapsules- Dry recovered microcapsules with coat:core ratio of 4:4 and sulphadiazine content of 44.96% w/w were prepared. An accurately-weighed amount (71-100 um) was added to 40 ml of distilled water in a dark amber-glass bottle. A set of 12 bottles was used and four bottles were

sampled at hourly intervals. The bottles were rotated at 50 r.p.m. at 37° ± 0.5° C in an apparatus similar to that of Sounder and Ellenbogen (12). The drug relased in solution as well as that remaining in the microcapsules was assayed according to USP XIX. An average of four determinations was obtained.

The same procedure was repeated with 0.1N HCl or phosphate buffer (pH 7.4) as artifical gastrointestinal fluids.

RESULTS AND DISCUSSION

The addition of glycerol and other polyoles were reported to inhibit deformation of the spherical droplets caused by the rotational velocity and turbulence of stirring in gelatin-acacia coacervated systems (9). Also, glycerol in concentration of 28.7 % v/v, but not other polyols, prevented vacuolation of gelatin-acacia coacervates (9).

In carbopol-gelatin system, glycerol in concentrations 20-33% v/v added after coacervation resulted in uniform smooth spherical coacervates as assessed by microscopic examination. On the other hand, the premixing of glycerol-carbopol sols prior to coacervation resulted in coarser coacervate which may by due to the reduced viscosity of carbopol sol caused by glycerol.

Also, it was found that neither the concentration of glycerol nor its order of addition affected the sediment volume or weight.

It was noticed that the presence of glycerol rendered the microglobules less coherent and reduced their adhesion to glass containers thus facilitating their collection.

Formaldhyde acts as denaturant to harden the wet gelatinous shell. In order to test this effect, concentrations from 1.2-8.8% v/v formaldhyde in the final mixture were used.

The variation of formaldhyde concentrations in the final coacervate mixture resulted in different sediment volumes as shown in Table 1. The higher the formaldhyde concentration the greater the sediment volume. This may be explained that formaldhyde condenses with gelatin's

TABLE 1

Effect of Formaldhyde Concentration (% v/v) on the Sediment Volume of Carbopol/Gelatin Coacervates

Formaldhyde (% v/v)	Sediment Volume (ml)	Appearance of Supernate	Sediment
8.8	20	Clear	Coacervates
7.1	18	Clear	Coacervates
4.7	16	Clear	Coacervates
2.4	15	Opalescent	Gelatinous
1.2	14	Turbid	Gelatinous

amino group to produce methylene-bridge (13). Thus the hydrogen bonding amino group on gelatin are rendered non-hydrophilic, thereby reducing the hydration of the gelatin and increasing the sediment volume of carbopol-gelatin coacervate particles. There is no reaction between the carboxylate group (such as carbopol) and formaldhyde (13).

A clear supernate with hard coacervates was obtained when formaldhyde concentration was 4% v/v and higher. At lower formaldhyde concentrations the supernate ranged from opalescent to turbid.

Treatment time of not less than four hours was necessary to get readily dispersable coacervates.

This finding is in agreement with the results obtained on gelatin-acacia coacervate system (9).

Flocculation and sedimention efficiency of formaldhyde-treated microglobules as a function of concentration, percent (v/v), of aliphatic solvents revealed the order: 2-propanol (60%) = 1-propanol (60%) > ethanol (75%) > methanol (85%) (Table 2).

However, only 2-propanol and 1-propanol were capable of flocculating the coacervates to produce filter cakes, which after drying would form highly dispersed suspension in water. A 2-propanol concentration of 75% (v/v) or greater produced complete sedimentation within 10 min, and 85% (v/v) provided the greater aqueous dispersibility of the recovered powders. These results are in agreement with reported literature (9,14).

TABLE 2

Effect of Concentration (% v/v) of Different Alcohols on the Flocculation of Formaldhyde-Treated Coacervates.

Alcohol	Flocculation caused at : 33%	60%	75%	85%	90%
Methanol	-	-	-	+	+
Ethanol	-	-	+	+	+
1-propanol	-	+	+	+	+
2-propanol	-	+	+	+	+

Sulphadiazine Microcapsulation-Evaluation of pharmaceutical microcapsules may be based upon the determination of the surface-adhering as well as encapsulated drug which measures to a large extent the efficiency and suitability of microencapsulation process to a specific drug.

By keeping the amount of coat constant a series of microcapsules with varying coat:core ratios; 4:1, 4:2, 4:4 and 4:8; were obtained.

It is clear from Table 3, that the surface adhering drug as well as the encapsulated drug increase on raising the core ratio. The amount of the encapsulated drug, expressed as a percentage of that started with, were 66.98%, 71.02%, 71.36% and 79.1% for 4:8, 4:4, 4:2 and 4:1 coat:core ratio, respectively.

As the coat ratio increase, it is reasonable to expect a higher percentage of the added drug to be encapsulated.

TABLE 3

Influence of coat-Core Ratio on the Encapsulation of Sulphadiazine

Coat-Core	Drug added (mg)	Drug found (mg) Surface	Core	Yield (mg)
4:8	1760	212	1179	2146
4:4	880	87	625	1390
4:2	440	60	314	977
4:1	220	32	174	781

TABLE 4

Size distribution of sulphadiazine microcapsules

Size range um	Mean size (d) um	% fraction for a given coat-core ratio 4:8	4:4	4:2	4:1
63-71	67.0	28.9	16.9	2.1	1.1
71-80	75.5	42.1	38.9	4.4	2.3
80-100	90.0	19.9	26.9	6.3	4.6
100-120	110.0	8.1	11.6	37.2	22.2
120-160	140.0	1.0	4.7	44.8	58.0
160-250	205.0	-	1.0	5.2	11.8
Average weight size (15) = $\frac{\Sigma(d \times \%\ \text{weight fraction})}{100}$		78.03	86.29	124.69	136.42

Table 4 shows the size distribution of the final recovered sulfadiazine microcapsules. The variation in coat/core ratio resulted in a marked variation in the final product size which ranges from 78.03 to136.42um. As the coat ratio increase, it is reasonable to expect a thicker walls and consequently larger average weight-size diameter. This finding is in agreement with that reported on phenobarbitone sodium microcapsules (16).

The method used to study the susceptibility of the microcapsules to the action of simulated gastrointestinal fluids was based upon the ability of these fluids to expose and/or extract the encapsulated sulphadiazine.

The release of sulphadiazine from recovered microcapsules (71-100 um) and having 4:4 coat to core ratio was studied in three dissolution media(Table 5). It was noticed that the microcapsules remain intact with no drug release when distilled water was used. This was expected since during recovery the free sulphadiazine was washed out of the surface. While in artificial gastric juice (0.1N HCl) no swelling of the coat was noticed and the release of sulphadiazine was 18, 22 and 25%, during 1,2 and 3 hours respectively. Although sulphadiazine at pH 1.2 is almost completely protonated (17), thereby favoring greater drug solubility, not more than 25% of drug was released after three hours. This is an indication to the success of the encapsulation process.

TABLE 5

Release of Sulphadiazine from Microcapsules (4:4 Coat:Core) in Different Media at 37 °C.

Medium	% Released after (hours)		
	1	2	3
Distilled water	N.S.*	N.S.*	N.S.*
0.1N HCl	18	22	25
Phosphate buffer (pH 7.4)	56	84	97

* N.S. no solubility.

As mentioned before that there is no significant reaction between carbopol and formaldhyde (13), the extension (swelling) of carbopol macromolecules in alkaline solution is predictable as noted in the product literature (18). This effect would create hydrated channels in the coacervate matrix which also contains denatured gelatin, and it would permit the subsequent and rapid dissolution of a coated drug from the recovered product.

At pH 7.4, the coat shows gradual swelling changing to translucent film thus permitting permeation to the artificial intestinal fluids. When the microcapsules were subjected to phosphate buffer (pH 7.4) 56, 84 and 97% of the drug was released during 1,2 and 3 hours respectively.

These results show that sulphadiazine was readily accessable to the leaching effect of the artificial intestinal fluids.

REFERENCES

1. R.E. Phares, Jr. and G.J. Sperandio, J. Pharm. Sci., 53, 515 (1964).
2. J.L. Anderson, G.L. Gardner, and N.H. Yoshida, U.S. Pat. 3, 341, 416 (1967).
3. B.K. Green and L. Schleicher, U.S. Pat. 2, 730, 457 (1956).
4. C. Brynko and J.A. Scarpelli, U.S. Pat. 2, 969, 331 (1961).
5. E.H. Jensen, U.S. Pat. 3, 265, 629 (1966).
6. L.A. Luzzi, and R.J. Gerraughty, J. Pharm. Sci., 53, 429 (1964).
7. Ibid., 56, 634 (1967).
8. Ibid., 56, 1174 (1967).
9. D.W. Newton, J.N. McMullen, and C.H. Becker, ibid., 66, 1327 (1977).
10. N.A. El-Gindy, and M.A. El-Egakey, Drug Develop. and Ind. Pharm., 7, 587 (1981).
11. "The United States Pharmacopeia", XIX th rev. Mack Publishing Co., Easton, Pa., 1975, pp. 476.
12. J.C. Sounder,and W.C. Ellenbogen, Drug Stand., 26, 77 (1958).
13. H.L. Fraenkel-Conrat, M. Cooper H.S. Olcott, J. Am. Chem. Soc., 67, 950 (1945).

14. J.R. Nixon, S.A.H. Khalil, and J.E. Carless, J.Pharm. Pharmacol., 20, 528 (1968).

15. T. Allen, "Particle Size Measurement", Chapman & Hall, London, 1974.

16. I. Jalsenjak, C.F. Nicolaidou and J.R. Nixon, J. Pharm. Pharmacol., 28, 912 (1976).

17. A. Albert and E.P. Serjeant, "Ionization Constants of Acids and Bases", Wiley, New York, N.Y., 1962, p. 148.

18. Service Bulletin GC-36, B.R. Goodrich Chemical Company.