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CARBOPOL-GELATIN COACERVATION : INFLUENCE OF SOME VARIABLES

Nazik A. Elgindy and Mohamed A. Elegakey
Department of Industrial Pharmacy
Faculty of Pharmacy, Alexandria University, Egypt

ABSTRACT

The extent and integrity of microencapsulation is hypothesized to be dependent on the optimization of sediment weight and volume. This led to the investigation of the effects of the type of gelatin or carbopol, the ratios of the coacervate materials, the total colloid concentrations, the starting pH of gelatin sol and the stirring rate. Investigation showed that gelatin, type A, at pH 6.8 together with carbopol 941 gave best results. Optimum carbopol-gelatin ratio was found to be 1/10, above which the sediment weight and volume decreased significantly. Increase in the total colloid concentration results in a parallel increase

in sediment weight till concentration of 1.1% w/v above which the increase in sediment weight was less pronounced. A stirring rate of 300-350 r.p.m. gave an almost spherical, uniform coacervates with average diameter of 59 u.

INTRODUCTION

The term "coacervation" was introduced by Kruyt and Bungenberg de Jong (1) to describe the flocculation or separation of liquids from solutions, where at least one of the liquids contained a colloidal solute.

Previous studies on complex coacervation specifically of gelatin-acacia system were reported (2,3). The gelatin-acacia coacervate system and its application to the drug microencapsulation field were intensively investigated (4-10).

Carbopol being a hydrophilic anionic vinyl polymer rich in carboxylic groups suggests itself to form a coacervating system with positively charged gelatin. Toxicity studies showed the possible pharmaceutical use of carbopol in oral dosage forms (11).

In the present work, a trial to induce coacervation between gelatin and carbopol was done. A number of some selected variables e.g. type of gelatin or carbopol, ratio of mixture of the oppositely charged colloids, the total colloid concentration, initial pH of gelatin sol and the stirring rate were critical areas and therefore, should be controlled and examined individually. It is the purpose of this paper to investigate the above mentioned variables as they are related to the optimization of coacervate weight and volume in a carbopol-gelatin coacervate system.

EXPERIMENTAL

Materials - Carbopol 934, 940 and 941 (Goodrich Aniline & Soda-Lime Co.) Gelatin B.P. bloom 150, type A having an isoelectric point of 8.4 and type B with an isoelectric point of 4.9. All other ingredients were analytical reagent or purity.

Preparation of Coacervates - The primary coacervating sols were made by dissolving carbopol and gelatin each separately in distilled water at 40°C. In all cases, 40 ml of carbopol sol was stirred at moderate speed (300 r.p.m.) in a water bath at 40°C. To this sol, 40 ml of gelatin sol at 40°C., was gradually added and stirring was continued for 20 minutes. The presence of either carbopol or gelatin in excess was tested on one-ml sample of the supernate. A drop of either carbopol or gelatin sol was added to this sample on a watch glass and any observed turbidity indicates the component in excess.

Colloid Combination and Ratio - Carbopol 934, 940 or 941 was coacervated with each of gelatin type A or B, in varying ratios, in order to find out the proper combination and its optimal ratio. The carbopol sol concentration was kept constant at 0.2% w/v while the concentration of gelatin sol ranged from 0.2-4% w/v. Microscopical examination was made to assess coacervation.

Sediment Weight - Using a pipette, 5 ml quantity of the final coacervate mixture was then centrifuged in a tared tube at 2000 r.p.m. for 5 minutes. The supernatent was discarded. Tube was dried in an oven, at 40°C., till a constant weight. The weight of the sediment was then calculated as a percentage of the total suspension volume. An average of four determinations was recorded.

Sediment Volume - The rest of the final coacervation mixture was immediately poured in a graduated glass-stoppered cylinder. The coacervate phase was allowed to settle at room temperature for 3 hours and then measured directly from the graduate. It was found that the coacervate volume was reproducible (± 0.5 ml) at the end of three hours and thenafter . An average of four determinations was recorded and expressed as percentage.

Total Colloid Concentration - Various concentrations of gelatin (type A) sol were coacervated with the corresponding carbopol 941 sol concentrations at 40°C., keeping the ratio 1:10 (carbopol:gelatin) constant. The sediment weight and volume were recorded. Since the approximate gelatin temperature of most gelatin is about 35°C. (12,13), a drop of the coacervate was placed on a cold slide to assist gelation and prevent droplet coalescence. The average diameter (um) was determined microscopically.

Effect of Gelatin pH - A series of 2% w/v gelatin (type A) sol were adjusted to various pH values by dropwise addition of either 10% v/v hydrochloric acid or 10% w/v sodium hydroxide solution. Each of these solutions was coacervated as previously mentioned with 0.2% w/v carbopol 941 sol. The sediment weight and volume were determined.

Effect of Stirring Rate - A sol of 0.2% w/v carbopol 941 was coacervated with 2% w/v gelatin (type A) sol at three different stirring rates (100-150, 300-350 and 600-650 r.p.m.). At each rate, the statistical diameters for particle size distribution were determined microscopically. Photomicrographs were taken.

RESULTS AND DISCUSSION

Choice of a Coacervating Combination :

A trial was done to select a proper combination of gelatin type B or A on one side and one of the carbopols (934, 940 or 941) on the other side, that gives a higher sediment weight and volume (Fig. 1 and 2).

Inspection of the results of different colloid combinations showed that gelatin (type A) sol combined with carbopol 941 sol gave the highest values for sediment weight and volume in all the ratios studied. Figure 2 showed the effect of varying the ratios of carbopols to gelatin A on the yield expressed as sediment weight and volume. At carbopol 941 : gelatin (type A) ratio ranging from 1:1 to 1:7.5, excess carbopol was detected in the supernate layer of the coacervated mixture, which explains the low sediment weight and volume values obtained. Upon increasing the gelatin ratio, the sediment weight acquires a peak at 1:10 carbopol : gelatin ratio where no excess of either colloids was detected in the supernate. For carbopol : gelatin ratios above 1:15 excess gelatin in the supernate was detected. To conclude, a working range of 1:10 - 1:15 carbopol 941 to gelatin (type A) ratio could be considered to proceed with.

Effect of Total Colloid Concentration - Studies were

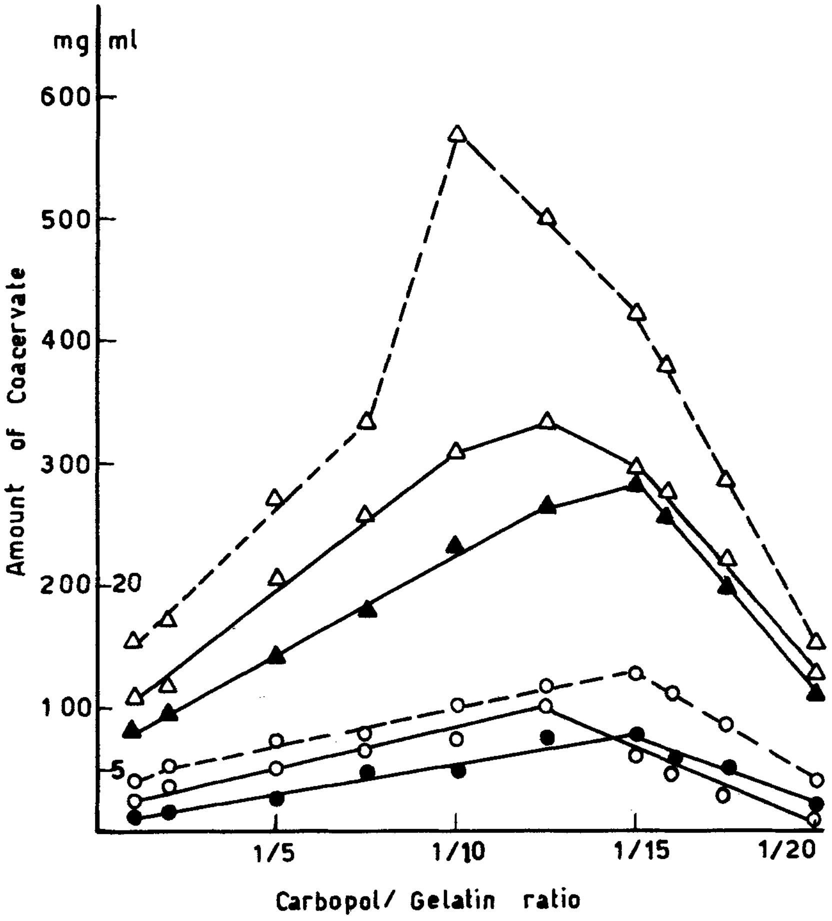

FIGURE 1

Amount of carbopol-gelatin (type B) coacervates at different ratios.

Carbopol 934 : weight △——△, volume ○——○.

Carbopol 940 : weight ▲——▲, volume ●——●.

Carbopol 941 : weight △----△, volume ○----○.

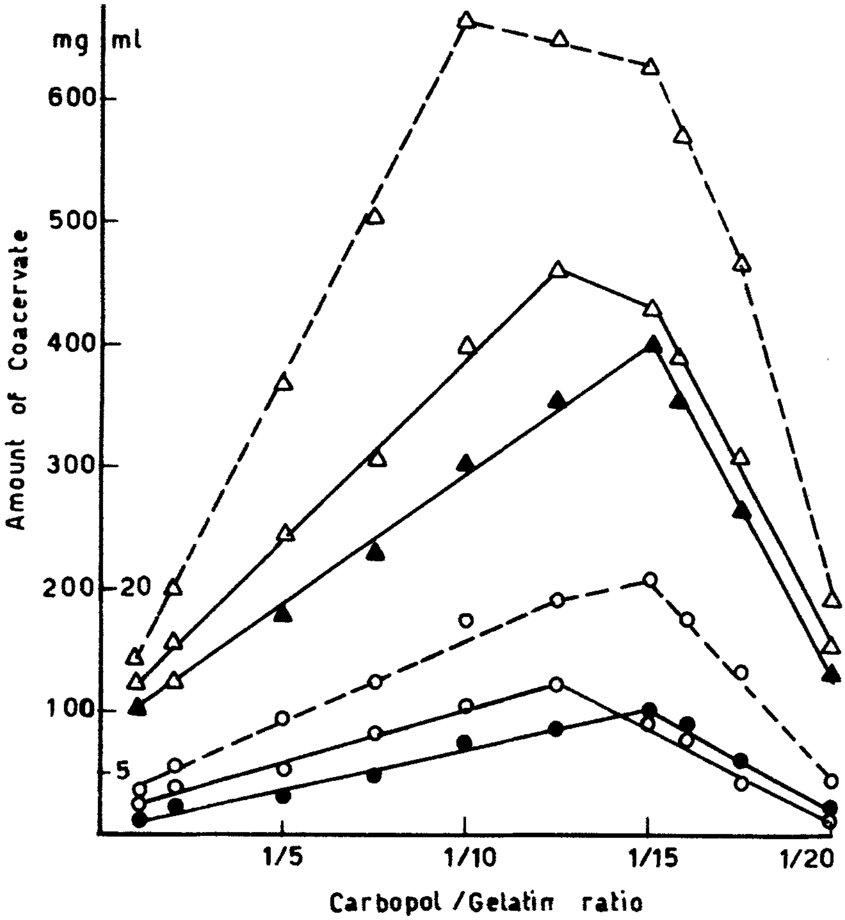

FIGURE 2

Amount of carbopol-gelatin (type A) coacervates at different ratios.

Carbopol 934 : weight △———△, volume ○———○.

Carbopol 940 : weight ▲———▲, volume ●———●.

Carbopol 941 : weight △- - - - -△, volume ○- - - - -○.

carried out to determine the effect of varying the total colloid concentration at carbopol 941 / gelatin (type A) of 1/10 ratio on the sediment weight and volume. Figure 3 shows that the sediment volume increased upon raising the total colloid concentration. The sediment weight showed a sharp increase from 1-2% w/v gelatin concentration. Then-after the increase was less pronounced but gradual. In addition, it was difficult to proceed with carbopol sols of concentration higher than 0.5% w/v owing to the difficulty in obtaining such sols in a homogenous dispersion. When expressing the sediment weight as percentage of the total amount of colloid added, at a fixed carbopol / gelatin ratio, the results indicate a maximum value at gelatin concentration of 2% w/v (Table 1).

Other gelatin concentrations gave lower values. Thus suggesting a concentration of 0.2% w/v carbopol 941 sol to be coacervated with 2% w/v of gelatin (type A) sol to give an optimal yield.

It was also shown in Table 1 that the change in total colloid concentration caused a wide variation in the corresponding coacervate size. At gelatin concentration from 1-3% w/v, the microscopical determination of average diameter ($d_{av.}$) showed a gradual increase ranging from 50.3-70.2 um. Higher total colloid concentrations affected markedly the coacervate particle size.

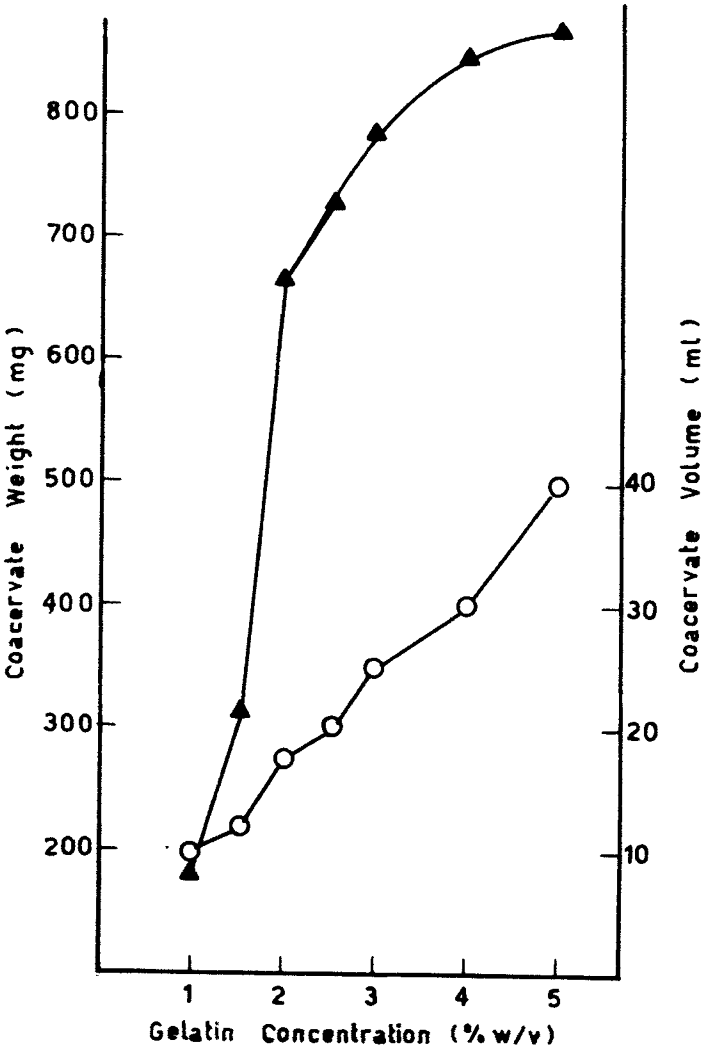

FIGURE 3

Weight (▲, mg) and volume (●, ml) of 1/10 carbopol 941 to gelatin (type A) coacervates at different colloid concentrations.

TABLE 1

Sediment Weight and Average Coacervate Diameter of 1:10 Carbopol 941 : Gelatin (Type A) at Different Total Colloid Concentrations

Total colloids added (mg)	Sediment weight (mg)	$\frac{\%\ \text{Sediment weight}}{\text{Total colloid}}$	Average diameter (d av) um
440	175	39.8	50.3
660	310	47.0	56.4
880	666	75.7	59
1100	730	66.4	64.1
1320	785	59.5	70.2
1760	850	48.3	108
2200	870	39.5	135

Effect of pH of Gelatin Sol - Data present in Table 2 show that all over a pH range of 1.8-8.7 coacervation between carbopol 941 and gelatin (type A) can take place. Also, coacervation of gelatin sol (i.e.p. 8.4) was markedly suppressed by lowering its pH to values less than 6.8. In other words, the greater the difference between the starting pH of gelatin sol and its isoelectric point, the higher the suppression in coacervation (2).

TABLE 2

Sediment Volume (ml) and Weight (mg) Yields of 0.2% w/v Carbopol 941 Sol Coacervated with 2% w/v Gelatin Sol (Type A) of Varying pH Values

Gelatin pH	Sediment volume ml	Sediment weight mg
11.7	—	—
8.7	33.15	544
6.8	18.30	666
4.8	5.32	600
2.8	3.75	78
1.8	2.25	67

When gelatin (type A) sol at pH 6.8 was coacervated, a maximum sediment weight was obtained, while at pH 8.7 the sediment volume was at maximum. This could be attributed to the swelling of carbopol at higher pH value (11).

Effect of Stirring Rate - Carbopol 941 sol was coacervated with gelatin (type A, pH 6.8) sol at 40°C. in a ratio of 1:10, at three different stirring rates. The results in Figure 4 and Table 3 show the effect of stirring rates on the coacervate shape and size distribution. At high stirring rate, 600-650 r.p.m.,

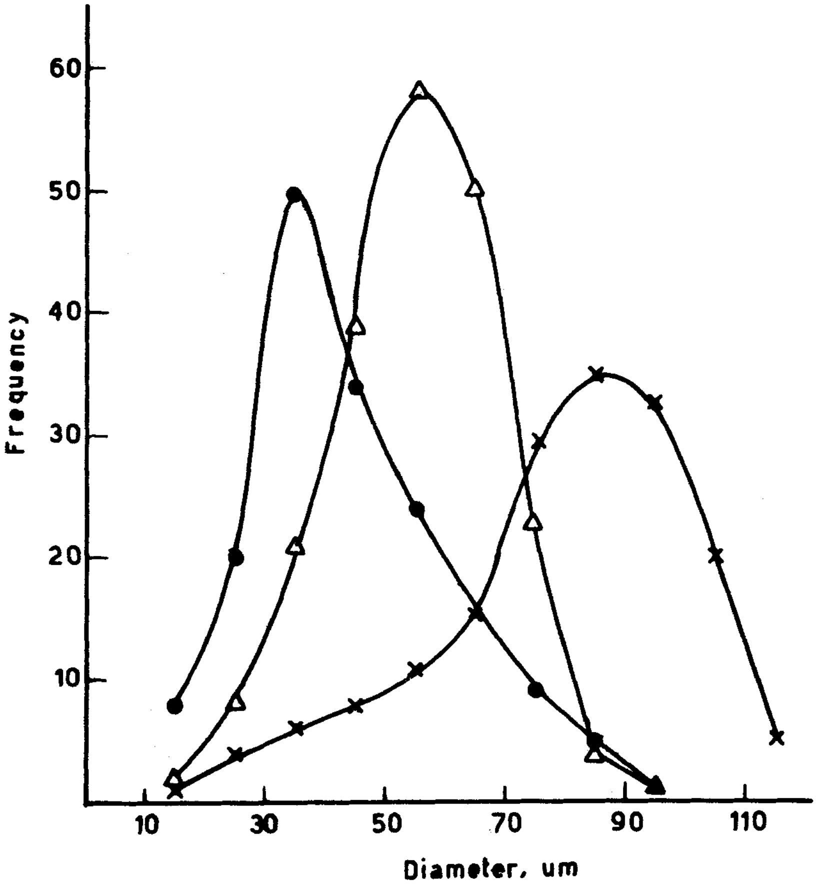

FIGURE 4

Size frequency distribution curve of 1/10 carbopol 941/ gelatin (type A) coacervates at different stirring rates.

● ———— ● 600 - 650 r.p.m.

△ ———— △ 300 - 350 r.p.m.

× ———— × 100 - 150 r.p.m.

TABLE 3

Particle Size and Yield of 1/10 Carbopol 941/Gelatin (Type A) Coacervates at Different Stirring Rates

r.p.m.	Sediment Weight (mg)	Sediment Volume (ml)	*Diameters (um) $d_{av.}$	d_s	d_v	d_{vs}	Coacervates
100-150	576	16.6	78.68	81.47	83.90	88.95	coarse, uneven
300-350	666	18.3	55.05	56.88	58.48	61.82	uniform,spherical
600-650	648	17.1	44.64	47.73	50.65	57.03	floating by air entrainment

* d_{av} = average diameter

d_s = surface diameter

d_v = mean volume diameter

d_{vs} = volume surface diameter

the coacervates were fine with an average diameter (d_{av}) of 44.6 um but suffering from floatation caused by air entrainment. On the other hand, at 100-150 r.p.m. the coacervates were coarse, uneven in shape with an average diameter (d_{av}) of 78 um. Stirring in the range of 300-350 r.p.m. resulted in almost spherical uniform coacervates with an average diameter of 59 um. This finding is in accordance with that reported by Newton et al (10) on gelatin-acacia coacervates. A photomicrograph of this coacervate mixture is shown in Figure 5.

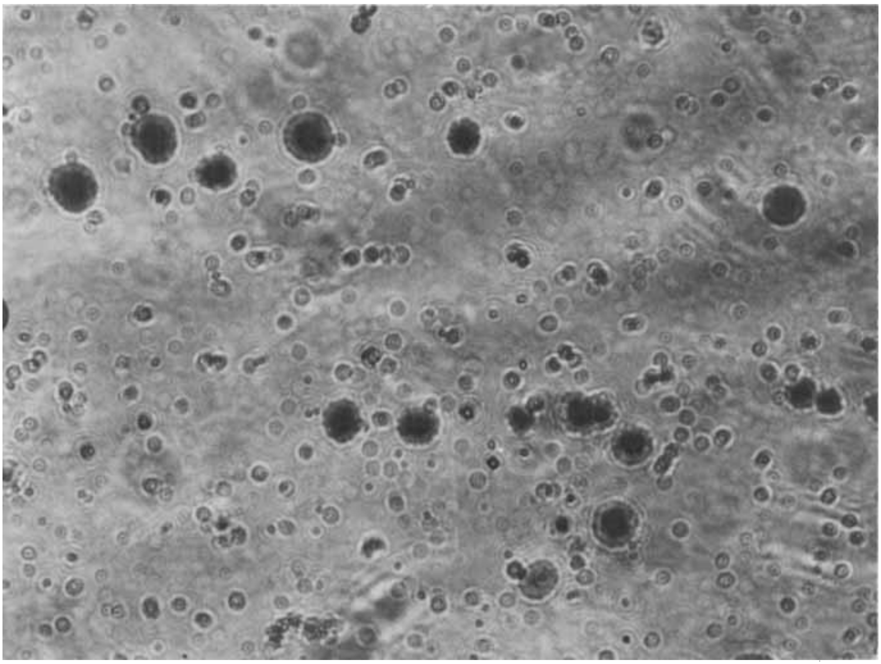

FIGURE 5

Microscopical examination of carbopol-gelatin coacervates (magnification x 100)

On the basis of the above mentioned results, the optimal coacervation conditions are : Type A gelatin sol of pH 6.8 together with carbopol 941 sol at a ratio of 1:10 with a total colloid concentration of 1.1% w/v.

The recovery of these coacervates and the application of the technique to encapsulate drugs will be the subject of our next publication.

REFERENCES

(1) H.R. Kruyt and H.G. Bungenberg de Jong, Proc. Koninkl, Ned. Wet., Amsterdam, 32, 849 (1929).

(2) H.R. Kruyt in "Colloid Science", Vol. 2, Elsevier Publishing Co., Amsterdam, 1949, p. 338-384, 433-450.

(3) M. Glicksman and R.E. Sand in "Industrial Gums", 2nd ed., R.L. Whistler, Ed., Academic Press, New York, N.Y., 1973, p. 243-240.

(4) L.A. Luzzi, J. Pharm. Sci., 59, 1367 (1970).

(5) L.A. Luzzi and R.J. Gerraughty, ibid., 53, 429 (1964).

(6) S. Javidan, R.U. Haque and R.G. Mrtek, ibid., 60, 1825 (1971).

(7) P.L. Madan, L.A. Luzzi and J.C. Price, ibid., 61, 1586 (1972).

(8) A.B. Dhruv, T.C. Needham Jr. and L.A. Luzzi, Can. J. Pharm. Sci., 10, 33 (1975).

(9) P.A. Kramer, J. Pharm. Sci., 63, 1646 (1974).

(10) D.W. Newton, J.N. McMullen and C.H. Becker, ibid., 66, 1327 (1977).

(11) Service Bulletin GC-36, B.R. Goodrich Chemical Company.

(12) H. Boedtker and P. Doty, J. Phys. Chem., 58, 968 (1954).

(13) A. Veis, "The Macromolecular Chemistry of Gelatin", Academic, New York, N.Y., 1964, p. 255, 267.