9 Evaluation of a Set of Parameters for the Optimum Microencapsulation of Chloroquine Phosphate with Ethylcellulose

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ABSTRACT

The effect of various formulation factors for the optimum encapsulation of chloroquine phosphate with ethylcellulose has been studied. The release of the drug from the microcapsules was dependent on the quantity of ethylcellulose employed, the quantity of drug used, the quantity of these substances in the isolated products and the ethylcellulose rejected during microencapsulation.

KEY WORDS: release, chloroquine phosphate, microcapsules, ethylcellulose.

INTRODUCTION

There are various new techniques in drug delivery. One of them is microencapsulation. Microencapsulation has been described by Luzzi (1) as a 'method of wrapping small entities in small protective coatings. Microencapsulation is a modified form of film coating, differing from conventional film coating only in the size of the particles (or liquid droplets) to be coated and the methods by which this is achieved (2).

Microencapsulation has been widely employed to modify drug release, to improve drug stability, to enable the mixing and storage of reactive or incompatible materials, to mask the bitterness of certain drugs etc. (3).

Microencapsulation has also found application in other areas other than pharmacy. Various microencapsulation techniques have been evaluated for fabrication of thermonuclear fuel pellets for use in existing facilities for studying inertial confinement fusion in future power reactors (4). The biomedical applications of microcapsules in enzyme replacement therapy or toxin removal from blood has also been considered and described in a number of reviews (5, 6). Recently, artificial red cells, termed neohaemocytes, were synthesized at an American School of Pharmacy (7). The neohaemocytes were a microencapsulated version of haemoglobin and were reported to have several advantages over their chief competitor, perfluorocarbon. In all these applications, optimum encapsulation is desirable to produce microcapsules of suitable characteristics. The parameters that should be controlled for the optimal encapsulation of chloroquine with ethylcellule is the subject of this study.

MATERIALS AND METHODS

Materials

Chloroquine phosphate (Bayer), was obtained commercially. Fractions of the drug which passed through a 150 mesh sieve but retained on a 200 mesh sieve (particle size 75-106 um) were used. Ethylcellulose 100 CP (Fluka AG), cyclohexane (E. Merck), hydrochloric acid (BDH) and distilled water were also used,

Methods

Preparation of Microcapsules

Polymer deposition by thermal induced coacervation was employed. This method was developed with modifications from the technique employed by Jalsenjak and co-workers (8). A 600 ml quantity of cyclohexane was introduced into a 1-litre round bottomed flask fitted with a two-way rubber stopper bearing a thermometer and a reflux condenser. With a stirring rate of 550 r.p.m. and a temperature of 50°C, ethylcellulose was added into the cyclohexane and the temperature was raised to 70°C over 20 minutes. The core material (chloroquine phosphate) was then added and over a period of 75 minutes the temperature was raised to 80°C. After being held constant for one hour at this temperature, the system was allowed to cool slowly with continuous stirring to a temperature of 35°C and then further cooled rapidly to 20°C with ice. The rigidized ethylcellulose coated microcapsules were filtered and gently passed through 1.7 mm sieve and dried overnight at 30°C.

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The yield was always greater than 92% for all the batches of the core: wall ratios prepared.

Table 1. Quantities employed for preparation of microcapsules.

Core:wall ratio	Chloroquine phosphate (gm)	Ethylcellulose (gm)
2:1	6	3
1:1	6	6
1:2	3	6

Spectrophotometric analysis

Solutions of chloroquine phosphate are known to obey Beer's Law. Dilutions of the drug were made to contain 0.1 to 3.0 mg/100ml. The absorbencies of the dilutions were determined at 257 nm on a Pye Unicam SP6-450 Uv/Vis spectrophotometer. All other concentrations were determined from the slope of the Beer's plot.

Free drug content of microcapsules

A 200 mg quantity of the microcapsules was shaken in 100ml of 0.1 N HCI at 37 $\pm$ 0.5°C for 3 minutes to dissolve any unencapsulated drug. The mixture was filtered through a Whatman filter paper (No.1) and assayed for the drug. The mean of three determinations was computed.

Total Drug Contents

A 200 mg quantity of the microcapsules was weighed on a Mettler balance (Model H20) and transferred to a clean glass mortar. The microcapsules were wetted with a little quantity of 0.1 N HCI and allowed to swell for 5 minutes. The microcapsules were then crushed and extracted with ten 25 ml portions of 0.1 N HCI to ensure complete removal of the drug. Each extraction was passed through a weighed Whatman filter paper (No.1) which retained the ethylcellulose. The filtrate was collected in a 1000 ml volumetric flask and the volume adjusted to the 1000 ml mark with 0.1 N HCI. Five ml portions were quantitatively transferred into a 100 ml volumetric flask and diluted to the 100 ml mark. The absorbencies of the diluted solutions were then read at the appropriate wavelength. Average of three determinations was calculated.

Ethylcellulose content of microcapsules

The ethylcellulose collected from the total drug content determination was dried to constant weight at 105°C for 1 hour in a Gallenkamp oven along with a control filter paper. After drying, the filter paper containing the ethylcellulose residue and the control filter paper were weighed and the ethylcellulose content was calculated. Average of three determinations was computed.

Dissolution rate studies

A 200 mg quantity of the microcapsules was introduced into a dissolution chamber containing 1000 ml of 0.1 N HCI at 37 $\pm$ 0.5°C in an Erweka dissolution apparatus (Model DT-D). One thousand ml of the dissolution medium was employed to maintain perfect or near perfect sink condition (solubility of chloroquine phosphate is 1 gm/4 ml). The stirring rate was adjusted at 100 r.p.m. and the microcapsules were freely suspended with a steel paddle employed as the stirrer. Samples of the dissolution medium were withdrawn at regular intervals and then immediately replaced with equivalent volume of fresh medium maintained at the same temperature. The samples were filtered, diluted and the absorbencies determined at 257 nm.

Dissolution efficiency

The efficiencies of dissolution were determined by the method of Khan (9). This was done by cutting areas under the dissolution-time curves and weighing them. Their ratios to weighed areas of 100% release were then calculated.

RESULTS AND DISCUSSION

Microcapsules contents

Table 2 shows the various contents of the microcapsules. The actual drug content is dependent on the core: wall ratio.

Table 2. Contents of microcapsules.

Core: wall ratios	2:1	1:1	1:2
Expected total drug content (%)	66.67	50.00	33.33
Actual total drug content (%)	81.82	56.73	35.37
Free drug content (%)	6.40	3.45	2.82
Ethylcellulose content (%)	20.00	43.08	61.88

The differences obtained between the actual total drug content and the expected total drug content only shows that not all the ethylcellulose employed participated in the microencapsulation process. This may be due to incomplete separation from the equilibrium liquid. Thus less of the ethylcellulose shared a larger quantity of the drug giving a higher percentage of drug in the isolated product.

Table 3. Ethylcellulose rejected during encapsulation

Core wall ratio	2:1	1:1	1:2
Ethylcellulose rejected (%)	55.20	21.39	8.62

The ethylcellulose rejected is a derived factor from the fractional drug content, the total drug and

encapsulation material as depicted by the equation below (10)

$$P = 100 \frac{W}{Wc}\left(1 - \frac{1}{F}\right) \quad \text{... Eq. 1}$$

where P is the percentage ethylcellulose loss,

W is initial amount of core material,

Wc is initial amount of coating material,

F is the fractional drug content of isolated product(2). This parameter is essential for predicting the encapsulation mechanism of the drug. Microencapsulation has been reported to occur by two main mechanisms (11).

(a) by the dispersed particles acting as a seeding nuclei around which the coacervate droplets form or (b) the droplets in the presence of dispersed particles may absorb them by an invagination mechanism. For the coacervate droplets to form by either of these mechanisms, it is essential that the molecules of the ethylcellulose aggregate. This aggregation is decreased in the presence of large quantity of the core material. Thus more of ethylcellulose does not participate in the microencapsulation process as can be observed from Table 3. In the presence of less core material, the ethylcellulose molecules can easily aggregate on cooling to form coacervates. The relationship between the quantity of core material and ethylcellulose rejected is shown in Fig. 1.

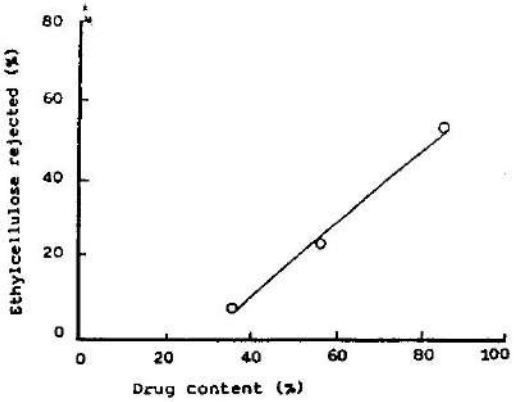

Fig. 1. Plot of ethylcellulose rejected as a function of chloroquine phosphate content of the microcapsules.

The core: wall ratio of 2:1 showed the highest actual total drug content. The free drug content is also dependent on the core: wall ratio with the highest free drug being obtained with the core: wall ratio of 2:1. This higher quantity of free drug has been attributed to the ethylcellulose content being too low to ensure complete microencapsulation (12). With the lower core: wall ratios, higher quantity of ethylcellulose is present in the preparation medium and this led to a lower free drug content.

From the ethylcellulose content shown in Table 2, it can be observed that higher quantity of ethylcellulose was obtained with low core: wall ratios than high core:wall ratios. It is expected that the higher the ethylcellulose, the thicker the wall of the microcapsules. This will eventually affect the release of the drug from the microcapsules.

Dissolution rate studies

During dissolution, the microcapsules did not disintegrate into visible smaller particles. In non-disintegrating dosage forms such as microcapsules, it is essential to maintain sink conditions in order that in vitro results will bear relationship to in vivo observations (13, 14). The dissolution profiles are shown in Fig. 2. The dissolution rates and efficiencies of dissolution were

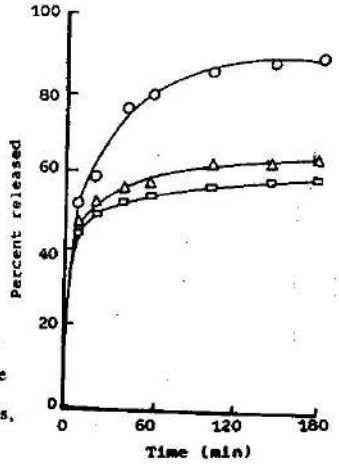

Fig. 2: Dissolution profiles of chloroquine phosphate from microcapsules of various core:wall ratios, 02:1 Δ 1:1 □ 1:2

observed to decrease with decreasing core:wall ratio (Table 4). The longer times observed for the smaller core:wall ratios than those for the higher core:wall ratios to release 50 per cent of their contents can be attributed to a number of factors.

Table 4. Some dissolution parameters for the release of chloroquine phosphate from microcapsules of various core:wall ratios

Core:wall ratio	2:1	1:1	1:2
t50 (min)	8.0	13.0	18.5
Dissolution efficiency (%)	84.20	58.10	47.00
Drug released at 3 hours (%)	91.10	64.10	39.60

Firstly, it may be due to the wall thickness, since as mentioned earlier, microcapsules with higher quantity of ethylcellulose have thicker walls. The effect of thicker wall is evident from Fick's law of diffusion:

$$dq = DA \frac{dc}{dx} dt \quad \text{..... Eq. 2}$$

where dq is the quantity of drug diffusing in a time, dt, across a plane of area, A, and this is directly proportional to the change in concentration, dc, with distance travelled, dx. D is known as the diffusion coefficient. However, thinness of the ethylcellulose film is low enough for this diffusion to be relatively rapid.

A more important factor is compactness of the film, a term that is better substituted with the word tortuosity. It could be expected that microcapsules with low core:wall ratios could have a more compact will, with higher tortuosity than those of high core:wall ratios. The dependency of the release rates on the wall thickness and tortuosity is made complex by the aggregation of the microcapsules. The effects of ethylcellulose contents on dissolution efficiency and t_{50} from microcapsules are shown in Fig.3.

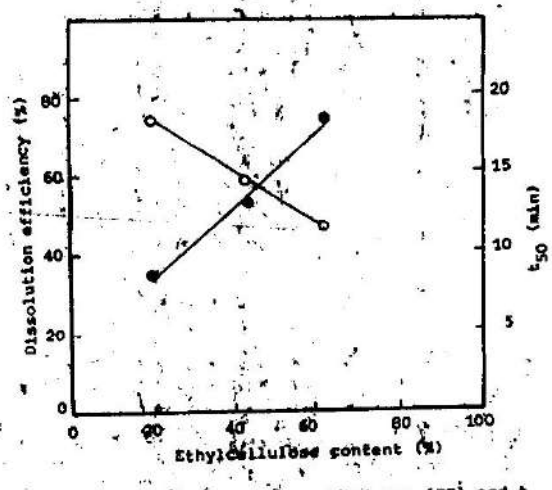

Fig. 3. Plots of dissolution efficiency (DE) and t_{50} as a function of ethylcellulose content of microcapsules ○ DE, ● t_{50}.

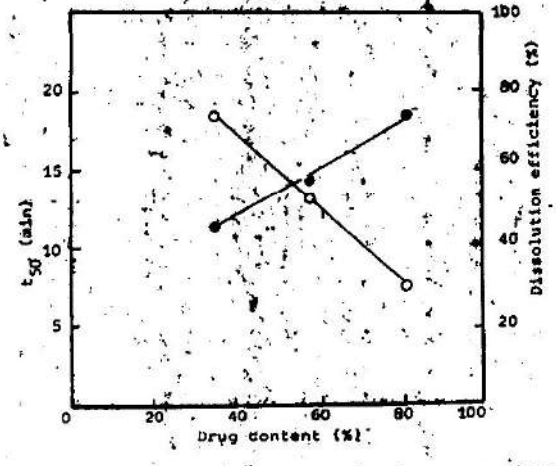

Fig. 4. Plots of t_{50} and dissolution efficiency (DE) as a function of drug content of microcapsules ● t_{50}, ○ DE

Another important factor that may affect the release rates and efficiencies of dissolution of the drug from the microcapsules is the concentration gradient as is indicated by the Fick's law of diffusion in equation 2. The effects of drug concentration on the t_{50} and efficiencies of dissolution of chloroquine phosphate from microcapsules are shown in Fig.4. The higher the drug content, the faster is the release rate. This could be attributed to the higher concentration gradient generated between the dissolution medium and the interval environment of the microcapsules.

CONCLUSION

Various factors were observed to affect the release of the water-soluble drug from microcapsules. While 91.1 per cent of the drug was released from a core:wall ratio of 2:1 in 3 hours, only 59.6 per cent was released during the same test period for a core:wall ratio of 1:2. The t_{50} for the release of the drug was also realised from 8 minutes to 18.5 minutes for a change in the core:wall ratio from 2:1 to 1:2. Microencapsulation, core and coat material modifications offer a good method of prolonging the release of water-soluble drugs such as chloroquine phosphate from microcapsules. The various parameters studied in this work has led to a set of criteria for the optimum microencapsulation of chloroquine phosphate.

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