Drug Development and Industrial Pharmacy, 23(11), 1131-1134 (1997)

COMMUNICATION

Design and Evaluation of Controlled-Release W/O/W Multiple-Emulsion Oral Liquid Delivery System of Chlorpheniramine Maleate

L. K. Ghosh,* N. C. Ghosh, R. S. Thakur, M. Pal, and B. K. Gupta

Division of Pharmaceutics, Department of Pharmaceutical Technology, Jadavpur University, Calcutta - 700 032, India

ABSTRACT

A type of dosage form (similar to the liposomal drug delivery system), w/o/w liquid membrane capsular delivery system, has been developed for controlling the drug release. Chlorpheniramine maleate was used as a model drug. Extensive work was planned and meticulously executed for evolving a stabilization process of the designed multiple emulsion. The problem was tackled from different angles such as choice of emulsifier and viscosity builder and their concentrations, the HLB values of the emulsifiers, phase volume ratio both in case of primary emulsification (ϕ w/o), and secondary emulsification (ϕ w/o/w), manufacturing procedures, etc., from the first to the last step. Study of various parameters ultimately culminated in a marketable stable product that is expected to keep its physical stability over a period of 12 to 18 months, which will cover the usual shelf-life of a pharmaceutical preparation. Evaluation of this system showed a gradual and consistent drug release from the delivery system by a modified dialysis method through Visking selective permeable tubing.

INTRODUCTION

A number of research workers have tried to stabilize the multiple emulsion by different methods (1-10). But these methods are highly complicated and required sophisticated instrumentation and novel chemical systems for external or internal phase polymerization using ^{60}Co-generated γ-irradiation (11). It was therefore felt that unless a simple and adaptable method of stabilization could be developed, the multiple emulsion as a system for drug delivery would remain only of theoretical interest. After a series of investigations (12,13), a very stable

*To whom correspondence should be addressed.

formulation was developed which is reported below.

EXPERIMENTAL

Materials

Dialysis tubing (Visking) was obtained from the Medicell International Ltd., London. All chemicals were of pharmacopoeial/analytical grade, obtained commercially and used without further purification.

Method

The multiple emulsion was prepared by the double-emulsification procedure shown schematically in Fig. 1.

Standardization of Primary Emulsion (i.e., First Emulsification)

During the first emulsification procedure the following parameters were strictly followed: i) ϕ w/o was 0.75. ii) Heavy liquid paraffin was used instead of light liquid paraffin for better result. iii) The concentration of Span 80 was 15% (v/v) of heavy liquid paraffin used. iv) The stirring rate was 3000–4000 rpm in a mechanical stirrer. v) 0.5% Hydroxypropylmethylcellulose (HPMC) sol is used as inner aqueous phase in which drug is dissolved.

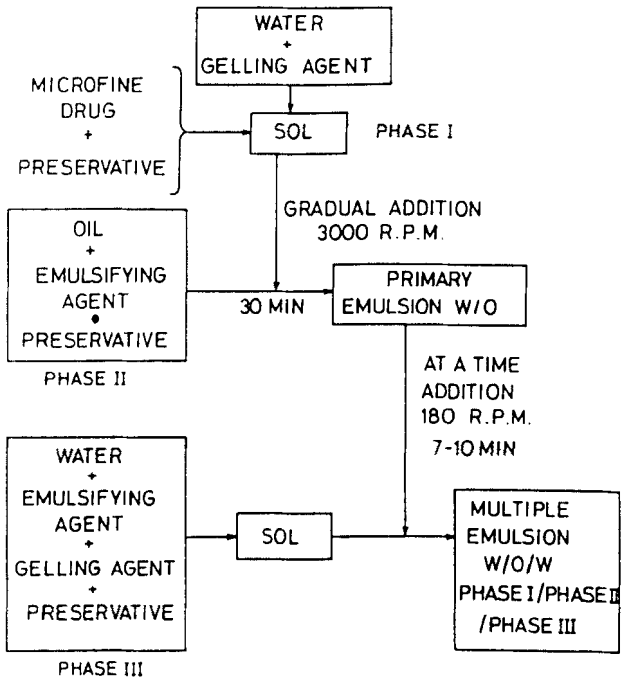

Figure 1. Flow sheet for w/o/w-type LMC preparation.

Composition of the Multiple Emulsion

Above primary emulsion, X ml; Y% (w/v) HPMC gel containing Z% (v/v), and Tween 80 and 0.2% (w/v) methyl paraben, K ml.

Observations

(1) If $x/k = 0.333$, $Y = 2.25\%$, and $Z = 0.8\%$, excellent emulsion is formed.
(2) If Y is $>2.25\%$ and other parameters remain constant, the viscosity will be too high to rotate the magnetic bar.
(3) If Z is $<0.7\%$ or $>0.9\%$ and other parameters remain constant, then gradually the instability increases.
(4) If Y is $<2.0\%$ then viscosity of the external media will be low, which will reduce the physical stability of the emulsion.

The HPMC gel is prepared by slow addition of HPMC powder into hot water (97°C) with continuous stirring. When the thick gel is formed, the volume is increased up to the mark with ice cold water (preferably in the form of ice).

The effects of the various thickening agents (acacia, tragacanth, sodium alginate, methyl cellulose, carboxy methyl cellulose, sodium carboxy methyl cellulose, and HPMC on the stability of the multiple emulsion were studied and it was found that HPMC gel gave the best stability.

Microscopic Study

The emulsion was subjected to microscopic examination for clear imaging of the different layers of the emulsified globules. Ponceau 4R (0.001%) was used for coloration of the aqueous phase and 0.01% of oil green was added for coloring the oil phase. Before microscopic imaging, the multiple emulsion was diluted 20-fold with the external phase. A gentle stirring in magnetic stirrer at 100 rpm was adapted for homogenization. Immediate microscopic examination showed nondiscrete particles the different layers of which were not clear. However, when the diluted emulsion was stored overnight and subsequently observed, distinct globules were seen as the inner aqueous phase, the middle oil layer, and the outer continuous aqueous phase.

Studies of the In Vitro Release Pattern of Chlorpheniramine Maleate from the Developed Formulation

A modified diffusion cell (12,13) was used for this purpose. Sink solution A (500 ml) was used, the composition of which is 2.13 ml concentrated hydrochloric acid with a pH of 1.35 ± 0.05. The temperature of the sink solution was kept constant at 37 ± 0.5°C. A suitable portion of the Visking tubing was cut off and treated with 2% sodium bicarbonate solution for 5–6 hr. After this pretreatment, the tubing was thoroughly washed with glass-distilled water. Ten milliliters of multiple emulsion, which contains 18 mg of chlorpheniramine maleate, is taken into the tube and the two ends of the tube are tied up with clean thread and kept fully immersed in the sink solution but suspended through the central aperture. The dissolution media was gently stirred at an optimum rate with a magnetic bar. After certain intervals, 5 ml of the sink solution was drawn and replaced with 5 ml of blank sink solution B, the composition of which was 20 g anhydrous sodium bicarbonate per 500 ml of the solution with a pH of 9.30 ± 0.05. After 10 such withdrawals and replacements each time with 5 ml of solution B, the pH of the dissolution media gradually came to 6.75 after 6 h, 15 min of the study.

The releases of chlorpheniramine maleate from the same primary emulsion and also from the simple sol of HPMC of equal concentration were also studied. The absorbances of the solution were measured at 263 nm. Using the standard curve of the amount of drug released, the cumulative percentages released are calculated and plotted against time (Fig. 2)

RESULTS AND DISCUSSION

The main problem is stabilization of the multiple emulsion. It has been observed that the multiple emulsion on storage becomes very unstable due to the negative sedimentation of the primary emulsion globules followed by the flocculation and ultimate formation of a loose cream over the continuous aqueous phase. It has also been observed that after a slight shaking, re-emulsification occurs. This phenomenon indicates that the surfactant system is functioning properly. After extensive study it has been concluded that the separation of the primary emulsion globules from the continuous aqueous phase is mainly due to the density difference between the dispersed primary emulsion globules and

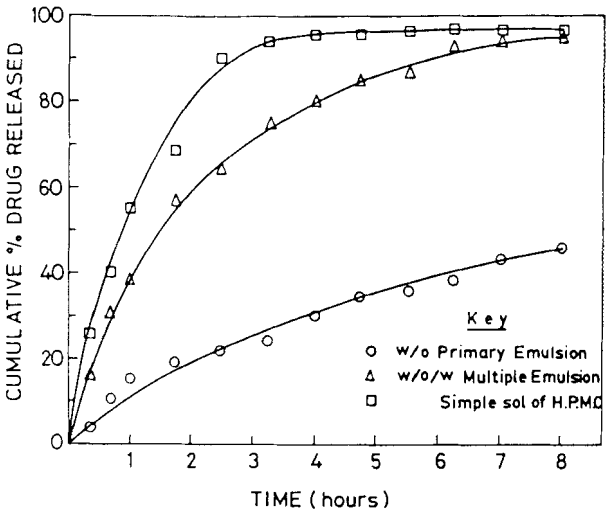

Figure 2. Cumulative percent drug released from three different formulations plotted as a function of time.

the continuous aqueous phase. Therefore, the reduction of particle size contributes greatly toward overcoming or minimizing creaming, since the rate of movement is a square root function of the particle diameter. There are, however, technical difficulties in reducing the diameter of droplets below a certain limit. In the case of multiple emulsion, this diameter is several microns. This problem is solved partly by raising the viscosity of the continuous phase to a certain limit using the HPMC gel.

The high viscosity decreases the rate of negative sedimentation and also the rate of flocculation, which results in an increase in diameters of the aggregates. The presence of surfactant is also of great importance to prevent the flocculation. Creaming, or negative sedimentation, brings the particles closer together and may facilitate the more serious problem of coalescence. To prevent this coalescence, an emulsifier with a high HLB value must be used. It has been observed that Tween 80 at a concentration of 0.8% (v/v) gives the best results. It can be concluded that 0.8% (v/v) Tween 80 is optimum to saturate the oil-water interface during the second emulsification. The destabilization, at higher concentration of Tween 80, may be due to the disturbances of the total HLB system of the formulation.

The in-vitro release profiles of chlorpheniramine maleate from w/o primary emulsion and w/o/w multiple emulsion were compared. It was observed that in comparison to simple w/o emulsion, which gave negligible drug release, multiple w/o/w emulsion exhibited significantly higher drug release. The negligible drug release

from w/o emulsion may be because of higher viscosity of w/o systems and also because the ionized drug molecules could not pass freely through the oil phase. The comparatively high release from w/o/w emulsion may be due to lower viscosity of this system. It was also thought that the resistance offered by the oil phase to the diffusion of the charged species of the drug from internal to the external aqueous phase in w/o/w emulsion is overcome by the pulling force exerted by the external aqueous phase on the charged species of drug in the internal aqueous phase. The factor causes greater diffusion of the drug from w/o/w emulsion than w/o emulsion, in which no such pulling force is operative.

The rate of release of chlorpheniramine maleate from the simple HPMC sol is very fast in comparison to w/o/w multiple emulsion. This is because the drug has to cross no phase boundaries that exist due to the middle oil layer of the emulsified globules in case of multiple emulsion.

REFERENCES

1. A. J. Collings, British Patent. 1235667 (1971).
2. S. Matsumoto, et al., J. Colloid Interface Sci., 57(2), 353 (1976).
3. A. F. Brodin and S. G. Frank, Acta Pharm. Suec., 15, 1, 111 (1978)
4. A. T. Florence and D. Whitehill, J. Pharm. Pharmcol., 31 (Suppl.), 64 (1979).
5. S. Matsumoto and P. Sherman, J. of Texture Studies, 12, 243 (1981).
6. T. Yoshioka, K. Ikeuchi, M. Hashida, S. Muranishi, and H. Sezaki, Chem. Pharm. Bull., 39(4), 1408 (1982).
7. S. Fukushima, K. Juni, and M. Nakano, Chem. Pharm. Bull., 31 (11), 4048 (1983).
8. S. Magdani, M. Frenkel, and N. Garti, Drug Dev. Ind. Pharm., 11(4), 791–798 (1985).
9. S. Matsumoto, T. Kitayama, and T. Koh, J. Japan Oil Chemists' Soc., 34(9), 688 (1985).
10. S. J. Duquemin and B. Warburton, J. Pharm. Pharmacol., 38, 865 (1986).
11. A. A. Al-Saden, A. T. Florence, and T. L. Whateley, Int. J. Pharmaceutics (1980).
12. L. K. Ghosh, B. K. Gupta, M. Pal, and S. Roy, The Eastern Pharmacist, 35, 119–122, May (1992).
13. L. K. Ghosh, I. Das, M. Pal, and B. K. Gupta, The Eastern Pharmacist, 35, 121–123, October (1992).