

Preparation and Evaluation of Ethyl Cellulose Coated Microcapsules of Carbamazepine for Controlled Release

K.P.R. CHOWDARY* and MALLURU SUBBA RAO

*University College of Pharmaceutical Sciences
Andhra University, Visakhapatnam-530 003, India
Fax: (91)(891)2525611; Tel: (91)(891)2844925
E-mail: profkprc@rediffmail.com*

The objective of the study is to prepare and evaluate ethyl cellulose coated microcapsules of carbamazepine for controlled release. Ethyl cellulose microcapsules of carbamazepine were prepared by an industrially feasible emulsification-solvent evaporation method and evaluated for controlled release. These microcapsules were spherical, discrete, free flowing and multi nucleate monolithic type. Microencapsulation efficiency was in the range 80-95 %. Carbamazepine release from the microcapsules was slow over 24 h and depended on core:coat ratio, wall thickness and size of the microcapsules and was by Fickian diffusion mechanism. Good linear relationship was observed between wall thickness of the microcapsules and release rate. Ethyl cellulose was found suitable as a microencapsulating agent for carbamazepine and such microcapsules MC2 (size 20/30) exhibited good controlled release characteristics, fulfilling the official (USP 30) release requirement prescribed for carbamazepine extended release tablets and these microcapsules were found suitable for once daily administration of carbamazepine.

Key Words: Ethyl cellulose, Microencapsulation, Controlled release, Carbamazepine.

INTRODUCTION

In the last two decades, controlled-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Drug release from these systems should be at a desired rate, predictable and reproducible. Among the various approaches, microencapsulation and microcapsules are widely accepted for controlled release. The polymer used as release-regulating coat in microencapsulation plays a vital role in controlling the delivery of drug from the microcapsules. Ethyl cellulose is reported^{1,2} as an effective microencapsulating agent for controlled release. Carbamazepine is a widely used anticonvulsant drug belonging to the chemical category of iminostilbenes. It is used in doses of 100, 200 and 400 mg, 2 or 3 times

a day. It is absorbed slowly and erratically after oral administration³. This erratic absorption may lead to fluctuations in plasma concentrations, which are responsible for its side effects and neurotoxicity⁴. Hence controlled release formulations are needed for carbamazepine to avoid erratic absorption, fluctuating plasma concentrations and associated toxicity. Controlled release formulations also improve patient compliance in the long-term therapy with carbamazepine. Carbamazepine extended release tablets are official in USP 30⁵.

The objective of the present investigation is to prepare and evaluate ethyl cellulose coated microcapsules of carbamazepine for controlled release. Ethyl cellulose microcapsules containing carbamazepine were prepared by an industrially feasible method of microencapsulation and the microcapsules were evaluated for controlled release of carbamazepine.

EXPERIMENTAL

Carbamazepine was a gift sample from M/s Ranbaxy Research Laboratories, Gurgaon. Ethyl cellulose (having an ethoxyl content of 47.5 % by weight and a viscosity of 22 cps in a 5 % concentration by weight in a 80:20 toluene-ethanol solution at 25 °C), Chloroform (Merck), sodium carboxy methyl cellulose (sodium CMC with a viscosity of 1500-3000 cps of a 1 % (w/v) solution at 25 °C, Loba-Chemie) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Preparation of microcapsules: Ethyl cellulose microcapsules containing carbamazepine were prepared by an emulsification-solvent evaporation method employing chloroform as the solvent for the polymer.

Ethyl cellulose (2 g) was dissolved in chloroform (100 mL) to form a homogenous polymer solution. Core material, carbamazepine (0.8 g) was added to the polymer solution (10 mL) and mixed thoroughly. The resulting mixture was then added in a thin stream to 200 mL of an aqueous mucilage of sodium CMC (0.5 % w/v) contained in a 500 mL beaker while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A medium duty stirrer (Remi Model RQT 124) was used for stirring. The solvent, chloroform was then removed by continuous stirring at room temperature (28 °C) for 3 h to produce spherical microcapsules. The microcapsules were collected by vacuum filtration and washed repeatedly with water. The product was then air dried to obtain discrete microcapsules. Different proportions of core to coat materials namely 9:1 (MC1), 8:2 (MC2) and 6:4 (MC3) were used to prepare microcapsules with varying coat thickness.

Estimation of carbamazepine: Carbamazepine content in the microcapsules was estimated by UV spectrophotometric method⁶ based on the measurement of absorbance at 212 nm in 0.1 N HCl. The method was validated for linearity, accuracy and precision. The method obeyed Beer-

Lambert's law in the concentration range of 1-6 µg/mL. When a standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.92 and 0.86 %, respectively. No interference from the excipients used was observed.

Characterization of microcapsules

Size analysis: For size distribution analysis, different sizes in a batch were separated by sieving, using a range of standard sieves. The amounts retained on different sieves were weighed.

Microencapsulation efficiency: Microencapsulation efficiency was calculated using the equation:

$$\text{Microencapsulation efficiency} = \frac{\text{Estimated per cent drug content in microcapsules}}{\text{Theoretical per cent drug content in microcapsules}} \times 100$$

Scanning electron microscopy: The microcapsules were observed under a scanning electron microscope (SEM-LEICA, S340, UK). Microcapsules were mounted directly on to the SEM sample stub, using double sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

Wall thickness: Assuming the microcapsules to be uniform and spherical, wall thickness of the microcapsules was determined by the method described by Luu *et al.*⁷ using the equation

$$h = \frac{\bar{r} (1-p)d_1}{3 [pd_2 + (1-p)d_1]}$$

where h = wall thickness, \bar{r} = arithmetic mean radius of the microcapsule, d_1 = density of core material, d_2 = density of the coat material and 'p' = proportion of the medicament in the microcapsules. Mean radius of the microcapsules was determined by sieving. Densities were measured using petroleum ether as a displacement fluid at room temperature (28 °C).

Drug release study: Drug release from the microcapsules was studied using 8-station dissolution rate test apparatus (Labindia, Disso 2000) employing a paddle stirrer at 50 rpm and at temperature of 37 ± 1 °C. Purified water (900 mL) was used as dissolution fluid as prescribed in USP 30. A 5 mL aliquot of dissolution medium was withdrawn through a filter (0.45 µm) at different time intervals and assayed spectrophotometrically by measuring absorbance at 212 nm. All drug release experiments were conducted in triplicate.

RESULTS AND DISCUSSION

Ethyl cellulose microcapsules of carbamazepine could be prepared by an emulsification-solvent evaporation method employing chloroform as solvent for ethyl cellulose. The method involves emulsification of the polymer (ethyl cellulose) solution in chloroform containing the drug (carbamazepine) in an immiscible liquid medium as micro droplets and removal of solvent by continuous stirring to form rigid microcapsules of ethyl cellulose. The microcapsules were found to be discrete, spherical and free flowing. SEM (Fig. 1) indicated that the microcapsules are spherical with smooth surface. The nature of the method of preparation indicates that the microcapsules were multi-nucleated and monolithic type. The sizes could be separated and a more uniform size range of microcapsules could readily be obtained. A large proportion of microcapsules were in the size range 20/30 (35-45 %) and 30/50 (30-40 %) mesh.

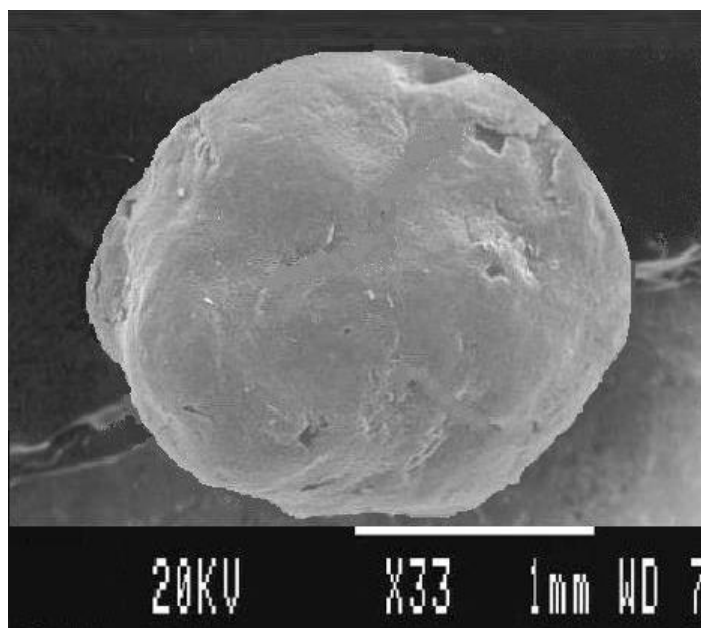


Fig. 1. SEM of ethyl cellulose microcapsule, MC2 (size 20/30) of carbamazepine

Low c.v. ($< 1.24\%$) in percent drug content indicates uniformity of drug content in each batch of microcapsules (Table-1). The microencapsulation efficiency was in the range of 80-95 %. Drug content of the microcapsules was found to be nearly the same in different sieve fractions. As the microcapsules are spherical, the theoretical mean thickness of the wall that surrounds the core particles in the microcapsule was calculated as

described by Luu *et al.*⁷. Microcapsules prepared by employing various ratios of core:coat were found to have different wall thickness. Smaller microcapsules had thinner walls.

TABLE-1
DRUG CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE CHARACTERISTICS OF ETHYL CELLULOSE MICROCAPSULES OF CARBAMAZEPINE PREPARED

Micro-capsules (core:coat ratio)	Carbamazepine content (%)	Microencapsulation efficiency (%)	Wall thickness (μm)	T_{90} (h)	Release rate K_1 (mg h^{-1})	'n' value in Peppas equation
Size 20/30						
MC1 (9:1)	74.92 (0.64)*	83.24	30.49	9.6	0.246	0.441
MC2 (8:2)	64.52 (0.98)	80.65	43.01	21.0	0.103	0.496
MC3 (6:4)	53.63 (0.35)	89.38	56.06	>24	0.069	0.497
Size 30/50						
MC1 (9:1)	79.87 (1.24)	88.74	15.17	7.2	0.281	0.365
MC2 (8:2)	65.20 (0.65)	81.50	26.16	8.2	0.261	0.389
MC3 (6:4)	57.10 (0.95)	95.17	32.18	22.0	0.097	0.367

*Figures in parentheses are coefficient of variation (c.v) values.

Carbamazepine release from the ethyl cellulose microcapsules was studied in water (900 mL) as prescribed for carbamazepine extended release tablets in USP 30. Carbamazepine release from the ethyl cellulose microcapsules was slow and spread over more than 24 h. The drug release parameters of various microcapsules are summarized in Table-1. The release data were analyzed as per zero order, first order, Higuchi⁸ and Peppas⁹ equation models. The correlation coefficient (R^2) values observed in fitting the release data into various kinetic models are given in Table-2. The drug release data more obeyed first order, Higuchi and Peppas equation models. When the release data were analyzed as per Peppas equation, the release exponent (n) was in the range 0.365-0.497 indicating Fickian diffusion as the drug release mechanism from the microcapsules. The release rate (K_1) depended on core:coat ratio, wall thickness and size of the micro-capsules. As the proportion of coat increased, carbamazepine release rate decreased. The release rate increased as the size of the microcapsules was decreased. Good linear relationship was observed between wall thickness of the microcapsules and drug release rate (K_1) (Fig. 2).

As the carbamazepine release from the ethyl cellulose microcapsules was extended over 12-24 h depending on core : coat ratio, wall thickness and size, these microcapsules are considered suitable for oral controlled release of carbamazepine. Carbamazepine extended release tablets are

TABLE-2
CORRELATION COEFFICIENT (R^2) VALUES IN THE ANALYSIS OF
RELEASE DATA OF ETHYL CELLULOSE MICROCAPSULES
AS PER VARIOUS KINETIC MODELS

Microcapsules (core:coat ratio)	Correlation coefficient (R^2 value)			
	Zero order	First order	Higuchi model	Peppas model
Size 20/30				
MC1 (9:1)	0.781	0.984	0.955	0.926
MC2 (8:2)	0.944	0.959	0.991	0.971
MC3 (6:4)	0.925	0.984	0.992	0.979
Size 30/50				
MC1 (9:1)	0.794	0.978	0.960	0.979
MC2 (8:2)	0.888	0.978	0.991	0.995
MC3 (6:4)	0.707	0.946	0.925	0.971

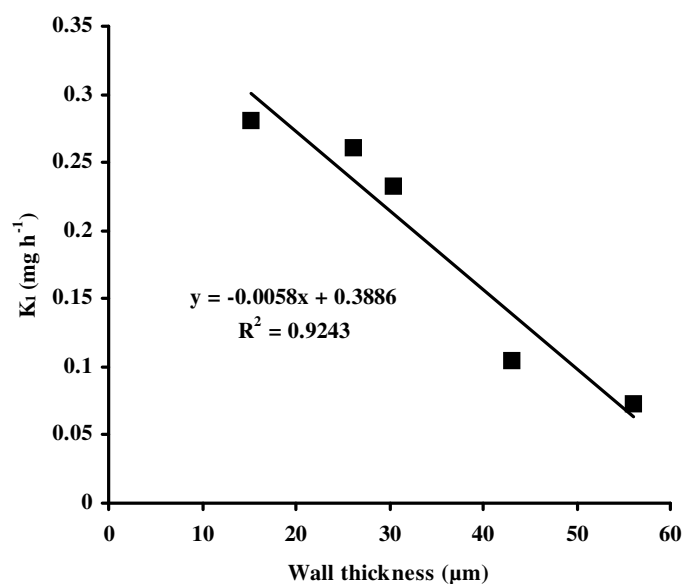


Fig. 2. Relationship between wall thickness and release rate (K_i) of ethyl cellulose microcapsules of carbamazepine

official in USP 30 for which a release of 10-35 % in 3 h; 35-65 % in 6 h; 65-90 % in 12 h and NLT 75 % in 24 h is prescribed. Ethyl cellulose microcapsules, MC2 (size 20/30) gave a release profile fulfilling the official (USP 30) release requirements. Hence, these ethyl cellulose microcapsules (MC2, size 20/30) are considered suitable for once daily administration of carbamazepine.

Conclusion

(i) Spherical ethyl cellulose microcapsules of carbamazepine could be prepared by the emulsification-solvent evaporation method developed. The method is industrially feasible as it involves emulsification and removal of the solvent, which can be controlled precisely. (ii) Microencapsulation efficiency was in the range 80-95 %. (iii) Carbamazepine release from the ethyl cellulose microcapsules was slow and extended over 24 h and depended on core:coat ratio, wall thickness and size of the microcapsules. Drug release from these microcapsules was by Fickian diffusion mechanism. (iv) Good linear relationship was observed between wall thickness of the microcapsules and release rate. (v) Ethyl cellulose was found suitable as a microencapsulating agent for carbamazepine and the ethyl cellulose microcapsules exhibited good controlled release characteristics and were found suitable for oral controlled release of carbamazepine.

REFERENCES

1. B. Mukherjee, B. Mahanti, P. Panda and S. Mahapatra, *Am. J. Ther.*, **12**, 417 (2005).
2. S. Baidya, S. Bedi and B.K. Gupta, *Biol. Chim. Farm.*, **5**, 140 (2001).
3. Goodman and Gilman's, in eds.: J.G. Hardman, L.E. Limbard, P.B. Molinoff, R.W. Ruddon and A.G. Gilman, *The Pharmacological Basis of Therapeutics*, McGraw-Hill, New York, edn. 10, p. 521 (2001).
4. M.C. Walker and P.N. Patsalos, *Pharm. Ther.*, **67**, 351 (1995).
5. United States Pharmacopoeia, *The United States Pharmacopoeial Convention, Inc.*, Rockville, MD, edn. 30, p. 1615 (2007).
6. K. Florey, *Profiles of Drug Substances, Excipients and Related Methodology*, Elsevier Inc., New York, Vol. 9, p. 87 (2006).
7. S.N. Luu, P.F. Carlier, P. Delort, J. Gazzola and D. Lafont, *J. Pharm. Sci.*, **62**, 452 (1973).
8. T. Higuchi, *J. Pharm. Sci.*, **52**, 1145 (1963).
9. P.L. Ritger and N.A. Peppas, *J. Control. Release*, **5**, 37 (1987).