Controlled release of Microencapsulated Indomethacin by colophony resin

Kora Pattabhi Ram Chowdary[1], **Prithwiraj Mohapatra**[1], **and Priyabrata Pattanayak**[2]*
[1]University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, India-530003.
[2]Jeypore college of pharmacy, Rondapalli, Jeypore(K), Orissa, India-764002.
*Corresponding author. E-mail: priyabrata2005@gmail.com

Abstract

Colophony resin was evaluated as a microencapsulating agent and to prepare resin-coated microcapsules. Resin-coated microcapsules of indomethacin were prepared by an industrially feasible emulsification-solvent evaporation method and the microcapsules were investigated. The resin-coated microcapsules are spherical, discrete, free-flowing and multinucleate monolithic type. Microencapsulation efficiency was in the range 96-107%. Indomethacin release from the resin-coated microcapsules was slow over 24 h and depended on core: coat ratio, wall thickness and size of the microcapsules. Drug release was by Fickian diffusion mechanism. Good linear relationships were observed between wall thickness of the microcapsules and release rate and T_{50} values. Resin-coated microcapsules of indomethacin exhibited good controlled release characteristics and were found suitable for once a day oral controlled release products.

Key words: Colophony, indomethacin, microcapsules, controlled release

1. Introduction

Controlled release drug delivery systems (CRDDS) are aimed at controlling the rate of drug delivery, sustaining the duration of the activity and targeting the delivery of the drug to a tissue. Drug release from these systems should be at a desired rate, predictable and reproducible. Microencapsulation and microcapsules are widely accepted for controlled release. Polymers and release retarding materials used as a coat play a vital role in controlling drug release from microcapsules. Microencapsulation by various polymers and their applications are described in standard textbooks [1, 2]. Though a variety of polymeric materials are available to serve as release retarding coat materials, there is a continued need to develop new, safe, and effective release retarding coat materials for microencapsulation.

Colophony is the oleoresin obtained from the plant *Pinus roxburghii* family Pinaceae. Colophony contains [3] resin acids (90%), a neutral inert substance called resene and esters of fatty acids. The resin contains a large amount of pimaric acid. Preliminary studies indicated that the resin has good film forming properties when dried from chloroform solution. In the present work, the colophony resin was evaluated as a coating material for microencapsulation. Studies were carried out on microencapsulation of indomethacin by the resin and evaluation of the resin-coated microcapsules of indomethacin for controlled drug release. Indomethacin is a widely used non-steroidal anti inflammatory, analgesic and antipyretic drug with a short life. The half life is 2.4 h. The oral dose is

25 mg, 3 to 4 times a day. It is also associated with G.I. side effects and peptic ulceration with bleeding if present in a larger concentration. Hence, it requires controlled release formulation to slow down its release in the G.I. tract, not only to prolong its therapeutic action, but also to minimize its side effects and to enhance patient compliance. Indomethacin Extended Release Capsules are official in USP XXIV [4].

2. Materials and Methods

Indomethacin was a gift sample from M/s Cipla Ltd., Mumbai. Chloroform GR (Merck), diethyl ether (Qualigens), methanol (Qualigens), sodium carboxy methyl cellulose (sodium CMC having a viscosity of 1500-3000 cps of a 1% w/v solution at 25 °C) were used.

The resin used as coat material was extracted from colophony as follows: Powdered colophony (10 g) was extracted repeatedly with 4 × 50 ml quantities of solvent ether. The ether extracts were collected in a porcelain dish and concentrated to dryness at 40 °C . The dry mass was powdered and the size was reduced to 120 mesh.

2.1. Preparation of microcapsules:

An emulsification-solvent evaporation method was tried to prepare resin-coated microcapsules. Resin (0.2 g) was dissolved in chloroform (5 ml) to form a homogeneous solution. Core material, indomethacin (0.8 g) was added to the polymer (resin) solution (5 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 450 ml beaker, while stirring at 1000 rpm to emulsify the added dispersion as fine droplets. A Remi medium duty stirrer with speed meter (Model RQT 124) was used for stirring. The chloroform was then removed by continuous stirring at room temperature (28^0) 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:coat namely 9:1 (MC1), 8:2 (MC2) and 7:3 (MC 3) were used to prepare microcapsules with varying coat thickness.

2.2. Estimation of indomethacin:

Indomethacin content of the microcapsules was estimated by a UV spectrophotometric method, based on the measurement of absorbance at 318 nm in a phosphate buffer of pH 6.2. The method was validated for linearity, accuracy, and precision. The method obeyed Beer's law in the concentration range 1-10 µg/ml. When a standard drug solution was assayed repeatedly (n = 6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.6 and 0.8 percent, respectively.

2.3. Characterization of microcapsules:

For the size distribution analysis, different size fractions in a batch were separated by sieving, using a range of standard sieves. The amounts retained on different sieves were weighed. Encapsulation efficiency was calculated using the equation, encapsulation efficiency = (estimated percent drug content/ theoretical percent drug content) ×100. Theoretical mean wall thickness of the microcapsules was determined by the method of Luu *et al* [5] using the equation, $h= \bar{r}\,(1\text{-}p)\, d_1/3[p\bar{d}_2+(1\text{-}p)\, d_1]$ where h is the wall thickness, $\bar{r}$ is the mean radius of the microcapsules, d_1 is the density of the core material, d_2 is the density of the coat material and p is the proportion of the medicament in the microcapsules. The microcapsules were observed under a scanning electron microscope (SEM-LEICA, S430, UK). For SEM the

microcapsules were mounted directly onto the SEM sample stub, using double sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

2.4. Drug release study:

Release of indomethacin from the resin-coated microcapsules of size 20/30, 30/50 and 50/80 was studied in phosphate buffer of pH 6.2 (900 ml) using an eight station dissolution rate test apparatus (model Disso-2000, M/s Lab India) with a paddle stirrer at 50 rpm and 37±0.5 °C as prescribed for indomethacin extended release capsules in USP XXIV. A sample of microcapsules equivalent to 75 mg of indomethacin was used in each test. Samples (5 ml) were withdrawn through a filter (0.45 μ) at different time intervals over 24 h and were assayed at 318 nm for indomethacin using a Shimadzu UV-150 double-beam spectrophotometer. The sample (5 ml) taken at each sampling time was replaced with fresh dissolution medium (5 ml). The drug release experiments were conducted in triplicate.

3. Results and Discussion

An emulsification-solvent evaporation method was developed for microencapsulation of indomethacin by the resin. The method involves emulsification of the polymer (resin) solution in chloroform containing the dispersed drug particles in an immiscible liquid medium (0.5% w/v solution of sodium CMC) as microdroplets, followed by removal of the solvent chloroform by continuous stirring to form rigid microcapsules. Resin-coated microcapsules of indomethacin can be prepared by the emulsification-solvent evaporation method developed. The microcapsules were found to be discrete, spherical and free flowing. The nature of the method of preparation indicated that the microcapsules were of multinucleate and monolithic type. SEM (Fig. 1) indicated that the microcapsules were spherical with smooth surface and completely covered with the polymer (resin) coat.

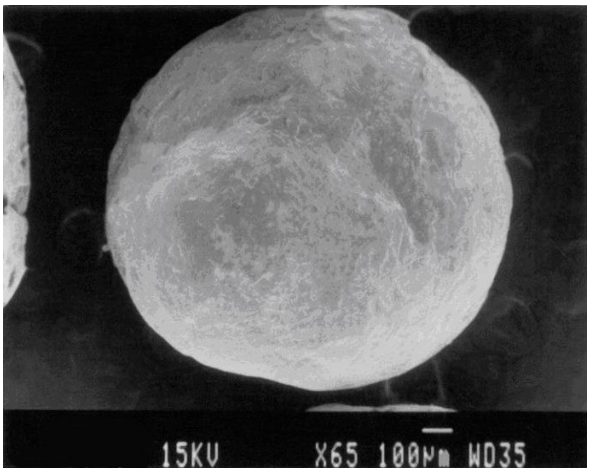

Figure 1 SEM of resin-coated microcapsules MC1.

The sizes can be separated by sieving and a more uniform size range of microcapsules can readily be obtained. The sieve analysis of different microcapsules showed that a large proportion of microcapsules (60-70 %) in a batch were in the size range of –20 to +30 (715 μm) mesh. A log-normal size distribution of the microcapsules was observed in all the batches prepared.

Low coefficient of variation in percent drug content (< 1.0 %) indicated uniformity of drug content in each batch of microcapsules (Table 1). The microencapsulation efficiency was in the range: 96-107%. Drug content of the microcapsules was found to be the same in different sieve fractions. As the microcapsules are spherical, the theoretical average wall thickness of the microcapsules was calculated as per Luu *et al*. Microcapsules prepared with various ratios of core:coat were found to have different wall thickness (Table 1).

Table 1 Indomethacin Content, Microcapsulation Efficiency, Wall Thickness and Release Characteristics of Resin Coated Microcapsules

Microcapsules (size)	Indomethacin content (%)	Microencapsulation Efficiency (%)	Wall thickness (μ)	T_{50} (h)	K_1 (h^{-1})
MC1 (20/30)	89.59 (0.13)*	99.54	67.15	4.4	0.133
MC1 (30/50)	89.73 (0.11)	99.70	41.26	4.3	0.136
MC1 (50/80)	89.59 (0.12)	99.54	22.26	4.0	0.183
MC2 (20/30)	77.74 (0.11)	96.88	90.51	4.4	0.120
MC2 (30/50)	80.60 (0.13)	100.75	53.66	4.3	0.122
MC2 (50/80)	79.03 (0.12)	98.78	29.43	3.4	0.129
MC3 (20/30)	75.15 (0.13)	107.35	93.53	5.2	0.107
MC3 (30/50)	74.60 (0.11)	106.57	58.34	5.0	0.115
MC3 (50/80)	75.15 (0.12)	107.35	31.00	4.3	0.123

*Figures in parentheses are coefficient of variation (CV) values, T_{50} is the time for 50% release and K_1 is first order release rate constant.

Indomethacin release from the microcapsules was studied in phosphate buffer of pH 6.2 as prescribed for indomethacin extended release capsules in USP XXIV. Indomethacin release from the microcapsules was slow and spread over a period of more than 24 h and depended on core:coat ratio, wall thickness, and size of the microcapsules. As the proportion of the coat was increased, indomethacin release rate decreased. Smaller microcapsules gave higher release rates due to increased surface area.

Analysis of the release data as per zero and first order kinetic models indicated that the indomethacin release from the microcapsules followed first order kinetics. Correlation coefficient (r) values in the first order kinetic model were higher than those in the zero order model in all cases. When the release data were analyzed as per the Peppas equation [6],the release exponent 'n' was < 0.5 with all the microcapsules indicating Fickian diffusion as the release mechanism. Plots of percent released vs square root of time were found to be linear ($r > 0.9820$), indicating that the drug release from the microcapsules was diffusion controlled. Linear relationships were observed between wall thickness of the microcapsules, release rate (K_1) and T_{50} (time for 50% release) values (Fig. 2).

Thus, spherical resin-coated microcapsules of indomethacin can 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 more precisely. Indomethacin release from the resin-coated microcapsules was slow and extended over longer periods of time, depended on core:coat ratio, wall thickness, size of the microcapsules and was by Fickian diffusion mechanism. Hence, colophony resin was found suitable as a microencapsulating agent

and the resin-coated microcapsules exhibited good controlled release characteristics and were found suitable for oral controlled release products. Since colophony resin is of natural origin, it is biocompatible and cheap.

4. References

[1] Kondo, A., Microcapsule Processing and Technology. New York: Marcel Dekker, 1979.

[2] Gutcho, M. H., Microcapsules and Microencapsulation Techniques. New Jersey: Noyes Data Corporation, pp. 236-270, 1976.

[3] William, C.E., "Treas and Evans' Pharmacognosy". London, (UK): WB Saunders Company Ltd, pp. 268, 1996.

[4] The United States Pharmacopoeia XXIV, The United States Pharmacopocial Convention. Rockville, MD, pp. 874, 2000. [5] Luu, S. N., Carlier, P. F., Delort, P., Gazzola, J., and Lanfont, D., Determination of Coating Thickness of Microcapsules and Influence upon Diffusion. J. Pharm. Sci., Vol. 6, pp. 452-456, 1973.

[6] Ritger, P. L., and Peppas, N. A., A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J. Control. Release., Vol. 5, pp. 23-26, 1987.

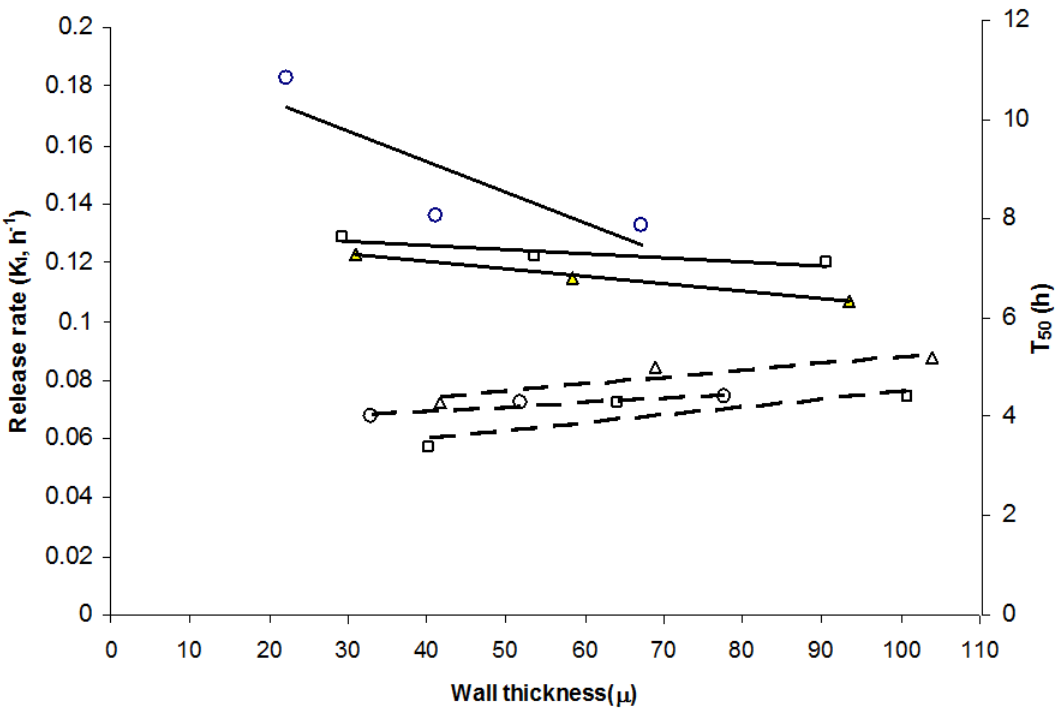

Figure 2 Relationships between wall thickness, release rate and T_{50} values of the resin-coated microcapsules.

Relationships between wall thickness of resin-coated microcapsules and the release rate (—) and T_{50} values (— — —) for microcapsules, MC1 (○), MC2 (□) and MC 3 (Δ).