Int. J. Chem. Sci.: 6(1), 2008, 390-398

FORMULATION AND CHARACTERIZATION OF ASYMMETRIC MEMBRANE CAPSULES OF CELLULOSE ACETATE

S. BHARATH[*] and R. H. SHOBHA RANI[a]

Dept. of Pharmaceutics, M. S. Ramaiah College of Pharmacy, BANGALORE – 54 (K. S.) INDIA
[a]Dept. of Pharmacy Practice, Al-Ameen College of Pharmacy, BANGALORE – 27 (K. S.) INDIA

ABSTRACT

Asymmetric membranes are commonly used in a variety of membrane separation processes such as reverse osmosis, ultrafiltration and dialysis. It consists of a relatively thin, denser outer membrane supported on a thick porous substrate. The use of asymmetric membranes as rate controlling systems are fairly new and novel. The asymmetric membrane capsule dosage form is a controlled drug delivery device that consists of a drug surrounded by a membrane, which has an asymmetric structure. The present investigation aimed for the development and evaluation of asymmetric membrane capsules of cellulose acetate, which could be used for the controlled drug delivery systems, independent of the drug core formulation and offer a major practical advantage in osmotic drug delivery systems.

Asymmetric membrane capsules of cellulose acetate was prepared by wet and dry process method of phase inversion technique using a designed pilot model manual capsule shell manufacturing equipment. Characterization of the asymmetric membrane capsule shells for their physical appearance, solubility, crushing strength and surface morphology by scanning electron microscopy and UV spectroscopy were studied. The process employed for the manufacture of capsule shells was novel, industrially feasible and cost effective.

Key words: Asymmetric membrane, Cellulose acetate, Phase inversion, Capsules.

INTRODUCTION

Among the various novel drug delivery systems available, per oral controlled release systems hold the major creditability because of its obvious advantage of ease of administration, reduced dose and dosing frequency, reduced fluctuation in drug levels, greater effectiveness in the treatment of chronic disease and greater patient convenience due to a simplified dosing schedule[1].

[*] Author for correspondence; E-mail: bharath1970in@yahoo.com

A number of design options are available to modulate the drug release from a dosage form and majority of them fall in the category of matrix, reservoir or osmotic systems. However, the drug release from the initial two delivery systems may be affected by pH, gastro-intestinal motility, presence of food in the GIT and the hydrodynamic conditions of the body[2], but an appropriately designed osmotically controlled oral drug delivery system can be a major advance toward overcoming some of these problems[3].

Several types of osmotic delivery devices are being developed like elementary osmotic pump, push-pull osmotic pump, controlled porosity osmotic pump etc., but most of them lag behind because of its process complication, more duration for the manufacture and also the cost factor. To overcome the above drawbacks, the concept of asymmetric membrane capsules for the osmotic drug delivery was developed. Asymmetric membranes are commonly used in a variety of membrane separation processes such as reverse osmosis, ultrafiltration and dialysis. The use of asymmetric membrane capsules as a controlled drug delivery device is new and novel[4], which consists of a drug-containing core surrounded by a membrane that has an asymmetric structure containing a relatively thin, dense region supported on a thicker, porous region

Similar to a conventional hard gelatin capsule, the asymmetric membrane capsule consists of a cap and a body that snugly fit into each other. The cap is shorter in length with slightly larger diameter and the body with longer length and smaller diameter. In contrast to gelatin capsules, the walls of asymmetric membrane capsules are made from a water-insoluble polymer that does not dissolve to instantly release the drug filled in it instead, the drug is released slowly over a period of time.

In the present investigation, cellulose acetate, a non-enteric cellulose ester was selected as the polymer and studies were carried out to design and characterize the asymmetric membrane capsule shells.

EXPERIMENTAL

Materials

Cellulose acetate (53.5% acetic acid content) was purchased from Central Drug House (P) Ltd., Mumbai. Acetone, ethanol and polyethylene glycol-400 were purchased from E. Merck (India) Ltd., Mumbai. Other chemicals used were of pharmaceutical grade.

Manufacture of cellulose acetate asymmetric membrane capsules

The manufacture of asymmetric membrane capsule shown schematically in Fig.1 and Fig. 2 were prepared by wet method and dry method of phase inversion process[5] using designed pilot model manual capsule shell manufacturing equipment. Different formulations of asymmetric membrane capsules as indicated in Table 1 using cellulose acetate as the polymer with multicomponent acetone – ethanol as solvent-nonsolvent system and PEG-400 as channelizing agent were prepared. The ratio of solvent and nonsolvent in the coating solution determined the formation of asymmetric membrane in contrast to dense membrane structure.

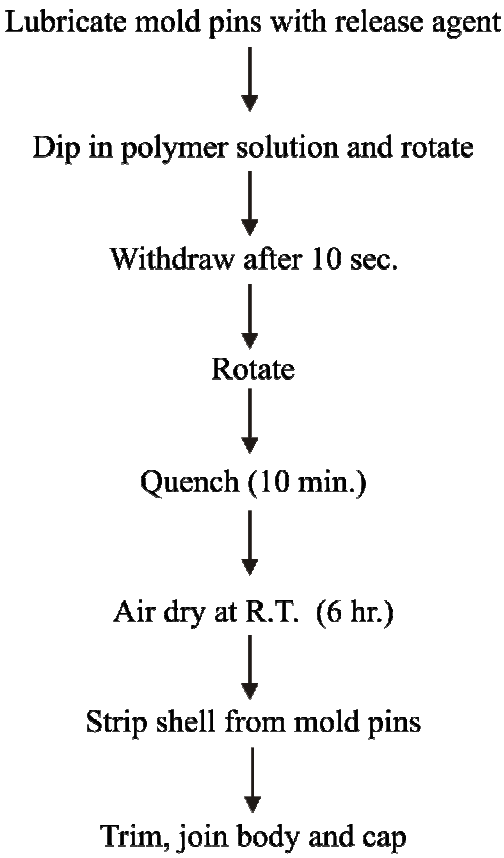

Fig. 1: Manufacture of asymmetric membrane capsules by wet process method

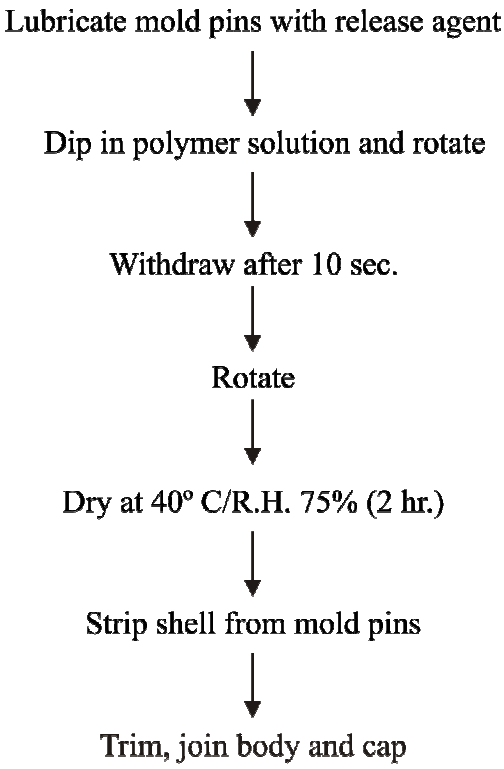

Fig. 2: Manufacture of asymmetric membrane capsules by dry process method

Table 1. Composition for manufacture of asymmetric membrane capsule

Ingredient	AMC-1	AMC- 2	AMC-3	AMC-4	PC	Quench solution
Cellulose acetate	5	10	15	20	10	----
Ethanol	40	30	20	20	----	----
PEG-400	5	10	15	10	10	5
Acetone q.s	100	100	100	100	100	----
Purified water	----	----	----	----	----	95

Note: **AMC**: Asymmetric membrane capsules / **PC**: Plain capsules

Evaluation studies

Physical characteristics

The asymmetric membrane capsule shells manufactured by both wet and dry methods were observed for uniformity, clarity and intactness of the cap and body after joining.

Solubility studies

The capsule shells were placed in the different test tubes containing distilled water, simulated gastric fluid and simulated intestinal fluid. The tubes were maintained at 37 ^{o}C in a water bath for 24 hours with occasional shaking and observed for solubility behavior.

Crushing strength

The body or cap of the empty capsules was placed vertically in the Monsanto hardness tester and the force in Kg /cm ^{2} required to crush the capsules were noted.

Surface morphology

The microscopic characterization of asymmetric membrane capsule wall was studied by observing the cross section of the capsule under the Jeol JSM - 840A scanning microscope. Each sample was coated with gold by an ion sputter (DMX-220A, Beijing, China) at 50 mA for 120s before SEM observation.

UV absorbance

The longitudinal film strips of asymmetric capsule and the plain cellulose acetate capsule were kept in the path of UV rays and the absorbance recorded between 200 - 400 nm against air as the blank using Shimadzu UV-1601 visible spectrophotometer.

Residual solvent analysis

Randomly the asymmetric membrane capsule shells were selected, weighed and cutted into smaller pieces and sonicated with 10 mL of distilled water for one hour. The resulting solution was filtered through 0.45 μm and 1 μL was injected into gas chromatography. Based on the peak areas recorded in the chromatograms, the amount of residual solvent present in the capsule shells was calculated against the standard prepared with 100 ppm of the required solvent in distilled water.

RESULTS AND DISCUSSION

A pilot model manual capsule shell manufacturing equipment was designed, fabricated and the manufacture of asymmetric membrane capsule shells of cellulose acetate by wet and dry method of phase inversion technique were stabilized.

Table 2. Statistical interpretation of capsules UV absorbance at different wave lengths carried out using graph pad prism version 3.0 software

Wave length (nm)	Mean of 3 absorbance readings ± S.D.			t	$t_{critical}$	Remarks
	Cellulose acetate films					
	Plain	Asymmetric				
		Wet	Dry			
400	0.2055 ± 0.0029	2.3328 ± 0.1667	0.4301 ± 0.0544			
350	0.2262 ± 0.0030	2.3651 ± 0.2120	0.4685 ± 0.0596	Plain film vs. Asymmetric dry film = 3.488		
325	0.2537 ± 0.0111	2.4160 ± 0.1920	0.5149 ± 0.0649			
300	0.2905 ± 0.0236	2.4685 ± 0.1737	0.5758 ± 0.0722			
275	0.2988 ± 0.0183	2.5799 ± 0.1827	0.6563 ± 0.0791	Plain film vs. Asymmetric wet film = 14.79	2.1448	Significant difference at 95% confidence interval
250	0.3518 ± 0.0169	2.7215 ± 0.2129	0.7634 ± 0.0888			
225	0.4423 ± 0.0173	3.0249 ± 0.1245	0.9354 ± 0.1031			
200	0.5838 ± 0.0165	3.5995 ± 0.2309	1.2035 ± 0.1240			

It was observed that the factors like the concentration of the polymer, viscosity of the solution, dip time and rotational speed of the mold pins inside the polymer solution, temperature and humidity changes determine the nature of the capsule shells formed. It was found that a minimum concentration of cellulose acetate 10%w/v (ASM-2) was required to form uniform and reproducible capsules and hence, the same batch capsules

were used for further studies. The asymmetric membrane capsule shells manufactured were uniform, transparent and flexible by dry method and less flexible by wet method of preparation.

They were found to be intact and insoluble in water, simulated gastric and intestinal fluid even after 24 hours and the average crushing strength of the capsules shells were found to be between 4.0 - 4.5 Kg/cm^2. The surface morphology of the capsule shells was studied by Scanning Electron Microscopy Fig. 3 and Fig. 4 showed the asymmetric wall structure with denser, continuous and imperforate outer surface below, which were inner thick interconnected porous membrane. The comparative absorption characteristics between asymmetric membrane capsule films and plain cellulose acetate film. Table 2 interpreted statistically showed significant difference at 95% confidence interval revealed that the membrane changes occurred during the phase inversion process.

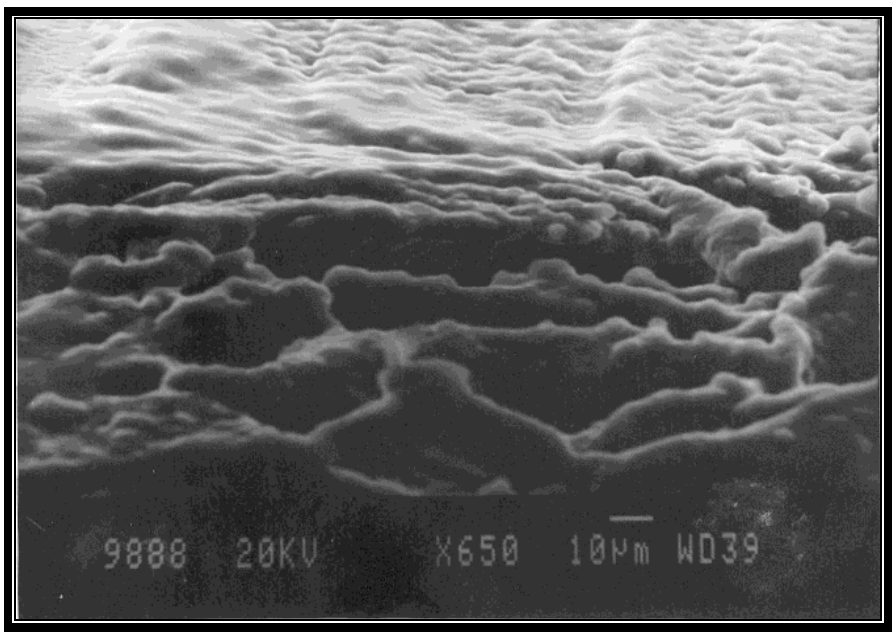

Fig. 3: SEM photomicrograph of C.S of asymmetric membrane capsule (650X magnification)

The residual solvent analysis for acetone was 14 ppm and the ethanol was not detectable by GC, were well below the permissible ICH limits (5000 ppm) for residual solvents[6]. Thus, it confirmed the safety of the organic solvents used in the manufacture of capsule shells.

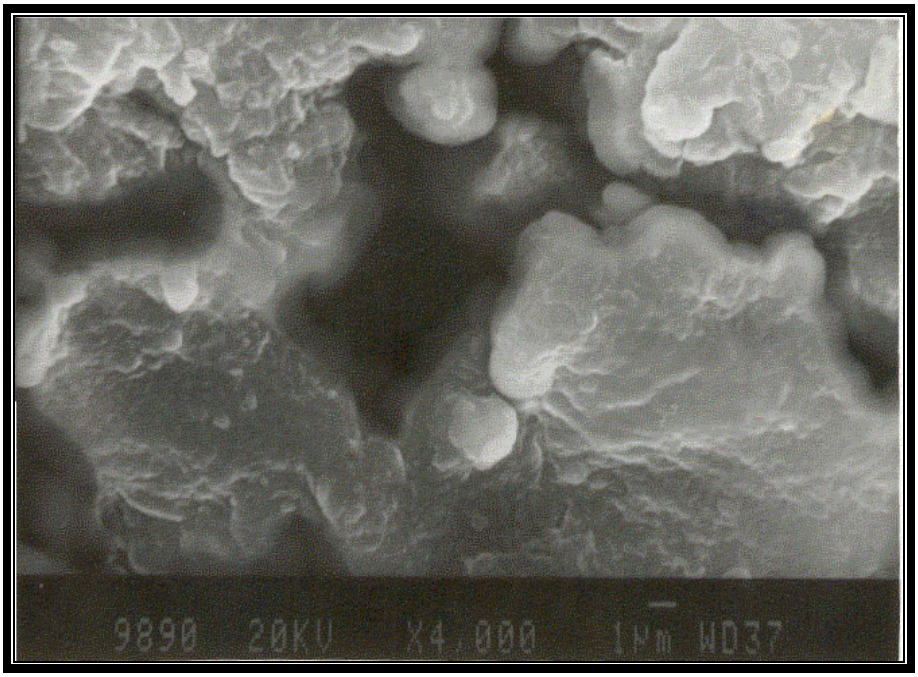

Fig. 4: SEM photomicrograph of C.S of asymmetric membrane capsule (4000X magnification)

CONCLUSION

Thus, the formulation of cellulose acetate asymmetric membrane capsules was successfully scaled up using designed manual capsule shell manufacturing equipment and studied for its membrane and shell characteristics. The capsules with a range of membrane permeability could be prepared independent of the drug core formulation, offering a major practical advantage in the development of controlled osmotic drug delivery systems. The process employed in the preparation was simple, industrially feasible and cost effective.

ACKNOWLEDGEMENT

The authors are thankful to Prof. B.G. Shivananda, Principal Al-Ameen College of Pharmacy, Bangalore and Dr. V. Madhavan, Principal, M. S. Ramaiah College of Pharmacy, Bangalore for providing the necessary facilities to carry out the research work.

REFERENCES

1. L. F. Prescott, Novel Drug Delivery and Its Therapeutic Application, John Wiley and Sons, West Susset, UK, (1989) pp.1-11.
2. S. V. Sastry, M. D. DeGennaro, I. K. Reddy and M. A. Khan, Drug. Dev. Ind. Pharm., **23**, 157 (1997).
3. F. Theeuwes, R Swanson, G. Guittard, A. Ayer and S. Khanna, Br. J. Clin. Pharmacol., **19**, 698 (1985).
4. A. G. Thombre and J. R. Cardinal, J. Control. Release, **57**, 65 (1999).
5. U. S. Patent 5,612,059, Use of Asymmetric Membranes in Delivery Devices.
6. ICH.Org [homepage on the internet]. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline 'Q3C' from: http: ww.ich.org/Mediaserver.jser?@ID=423&@Mode=GLB/.

Accepted : 09.01.2008