

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and evaluation of enteric coated HPMC capsule of diclofenac sodium

Ashlesha Kiran Meghal^{*}, Praful Sahebrao Chaudhari¹, Vijay B Mathur^{*}

^{*} Department of Pharmaceutics, Sharad Pawar College of Pharmacy, Wanadongri, Hingna Road, Nagpur- 441 110

¹ JSPM's Charak College of Pharmacy and Research, Wagholi, Pune- 412 207

ABSTRACT

Enteric coated products are designed to remain intact in the stomach and release the active substance in the upper intestine. Coating of the tablet with the suitable enteric coating material required to disintegrate and release the drug in intestine depending upon the compactness and percent content of additives, while process of coating of hard gelatin capsule lead to shell brittleness and poor adhesion of the coat. Capsules made out of HPMC could be the answer to this to avoid tablet excipients and different processing stages. Rough surface of HPMC capsule facilitated good adhesion for coating enteric polymer. In the present study, capsules were coated with enteric polymer Instacoat super II to the weight gain of 6, 8, 10, and 12%. Dissolution studies demonstrated that enteric coated capsules of coating level 10% were gastric resistant for 2h at pH 1.2 and completely disintegrated in small bowel in an average time of 3h. Capsule made from HPMC resulted in 'good polymer to polymer' adhesion providing gastric integrity and were found stable under accelerated stability studies. Thus HPMC can be considered as a good container for drugs independent of contents in it.

Key words: HPMC capsule, Enteric coating, Diclofenac sodium, Instacoat EN super-II, Capsule coating

**Corresponding author*

INTRODUCTION

Many pharmaceutical dosage forms irritate the stomach due to their chemical properties. Enteric coated products are designed to remain intact in the stomach and then to release the active substance in the upper intestine [1]. Site specific drug delivery of such therapeutic agent to the intestinal or targeted region can be accomplished by the application of coating on a solid dosage form. The purpose of enteric coating is to delay the release of drug until it reaches the intestine that is otherwise inactivated by the stomach content or may cause nausea or bleeding by irritating the gastric mucosa [2]. Acid sensitive drugs, which are degraded by water, present an additional challenge because of water permeation through the acid insoluble enteric film causing drug degradation [3]. Water permeation can also affect the disintegration and dissolution behavior of enteric coated dosage forms [4]. The process of coating of hard gelatin capsule shell is very sensitive, especially for aqueous coating system leading to shell embrittlement and poor adhesion of the coat to the smooth gelatin surface. A pre-coating of HPMC capsule can reduce interaction between the gelatin and the enteric polymer but is time consuming and complicated [5]. Capsule shell made itself of HPMC would result in 'good polymer to polymer' adhesion. Since, HPMC capsule coating process is independent of the capsule contents; it is more advantageous to coat a capsule rather than a tablet. Also, the numbers of equipments and excipients as well as steps involved in manufacturing of tablets are reduced in capsule dosage form. Diclofenac sodium, sensitive to acidic and a non-steroidal compound, exhibits pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic properties. In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac elicit a clinical response characterized by relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness and swelling of the joints as well as by an improvement in function [6]. Diclofenac sodium is completely absorbed from the enteric coated dosage form hence selected as a model drug.

MATERIALS AND METHODS

Materials

Diclofenac sodium was obtained from Aarti Drugs Pvt. Ltd. Mumbai, India. Instacoat EN super II and Hydroxypropyl methylcellulose (HPMC) capsules were gifted by Ideal Cures Pvt. Ltd. and Associated Capsules Group, Mumbai, respectively. The distilled water was used throughout the work. All other reagents were of analytical grade.

Methods

Formulation development

Weighed quantities of Diclofenac sodium (50mg) and Lactose (80mg) were mixed in geometric proportion after passing through sieve number 65 to obtain a homogenous mixture. Finally, the magnesium stearate (1.5mg) was added, and blended for an additional 3 minutes.



Evaluation of powder formulation

Powder formulation was evaluated before filling in capsule.

Carr's index

Carr's index value for powder formulation was determined using formula

$$\text{Carr's Index (\%)} = (\text{Tapped density} - \text{Fluff density}) / \text{Tapped density} \times 100$$

Angle of repose

The static angle of repose of powder formulation was measured by the fixed funnel and free-standing cone method using the formula

$$\text{Angle of repose } (\theta) = \tan^{-1} h/r$$

where: h-height of the heap; r-radius of the flat surface occupied by powder

Filling of capsules

Size two capsule bodies made of hydroxypropyl methylcellulose were filled with powder formulation by using capsule filling machine. Formulated capsules were evaluated for weight variation test and disintegration test.

Drug content

Ten capsules were selected randomly. Powder formulation in the capsule was removed, weighed equivalent to 50mg of diclofenac sodium and dissolved in 100ml methanol. Further dilutions made with phosphate buffer solution of pH 6.8. The amount of drug content was estimated at 276nm by U.V. spectrophotometer (JascoV- 530, UV /Vis double beam Spectrophotometer).

Coating dispersion

Aqueous coating suspension was prepared by adding water to the commercially available Instacoat EN super II (acrylate polymer type C) polymeric dispersion to decrease the solids content to approximately 15%. Triethyl citrate 20% (based on dry polymer weight) was added as a plasticizer. Polymer quantity was calculated on the basis of empty capsule weight to achieve 6 - 12% weight gain. Suspension was agitated for at least 30 min.

Enteric coating of HPMC capsules

Table 1. Coating parameters used in coater

Coating Parameter	Value
Speed of rotation of Pan	35 rpm
Inlet air temperature	40 °C
Outlet air temperature	25-30°C
Temperature of capsule bed	25-30°C
Spray rate	1ml/min
Drying conditions	5 min for 30°C

Filled capsules were coated with Instacoat EN super II in coating pan (Pharma R & D coater, Ideal cures Pvt. Ltd., Mumbai) by the solution layering technique. The coating mixture was stirred using a magnetic stirrer prior to and throughout the coating process. Coating parameters are as shown in Table1. During coating, coated capsules were withdrawn at various time intervals to check the dried coating weight gain of 6% (A1), 8% (A2), 10% (A3) and 12% (A4). To promote further coalescence of the polymeric film and to ensure that distribution of plasticizer was homogeneous the capsules were further cured at 30°C for 2 h [7].

Evaluation of enteric coated HPMC capsules

Disintegration test and acid uptake

Coated capsules A1, A2, A3, A4 were weighed individually, and placed in a USP disintegration apparatus for 2 h in acid media (0.1N HCl or acetate buffer pH 4.5) with discs to keep the capsules immersed at 37°C. The individual capsules that remained intact were then carefully removed from the basket assembly for visual inspection of any defects (bloating or swelling). The surface was gently blotted dry with a lint-free wipe. Capsules were then individually reweighed. The percent weight increase was reported as acid uptake (%). Intact capsules were further returned to the disintegration basket and exposed to phosphate buffer of pH 6.8 at 37°C to determine the total time for disintegration. Percent acid uptake was calculated by using following equation [8].

Percent acid uptake was calculated by using following equation.

$$\text{Percent Acid Uptake} = \frac{\text{Capsule Weight}_{\text{After Acid}} - \text{Capsule Weight}_{\text{Initial}}}{\text{Capsule Weight}_{\text{Initial}}} \times 100$$

In vitro dissolution study

In vitro dissolution study of coated capsules A3 and A4 was performed using USP dissolution apparatus II at $37 \pm 0.5^\circ\text{C}$ at a speed of 50 rpm. Drug release was performed in

900ml of 0.1 N hydrochloric acid for first 2h followed by 900ml of pH 6.8 phosphate buffer solution. Amount of drug released was estimated spectrophotometrically at 276 nm.

Scanning electron microscopy

To characterize the surface properties of HPMC uncoated and coated capsules, the scanning electron microscopy was used by cleaving the coat and the interface between capsule and the coat [9].

Stability study

Enteric coated formulations A3 and A4 were kept for accelerated stability testing in stability chamber (Thermo lab, Mumbai), at a temperature of 40°C/75% RH. The minimum period for testing was selected as per ICH guidelines. The samples were withdrawn from stability chamber periodically and tested after 15 days, one month, two months and three months.

RESULTS AND DISCUSSIONS

The percent acid uptake and disintegration time was measured for A1, A2, A3 and A4. Disintegration time of the capsules A3 and A4 was relatively rapid at pH 6.8 with less percent acid uptake compared to A1 and A2 capsules. Hence A1 and A2 capsules were not selected for further study. Table 2 indicated that increase in coating thickness (weight gain) varied the acid uptake and disintegration time of coated capsule.

Table 2. Disintegration time and percent acid uptake of coated capsule

Enteric coating weight gain (%)	Acid Uptake in pH 4.5 Acetate Buffer Solution (%)	Disintegration time (min)
	pH 1.2	pH 6.8
06	28	17
08	25	18
10	09	24
12	08	26

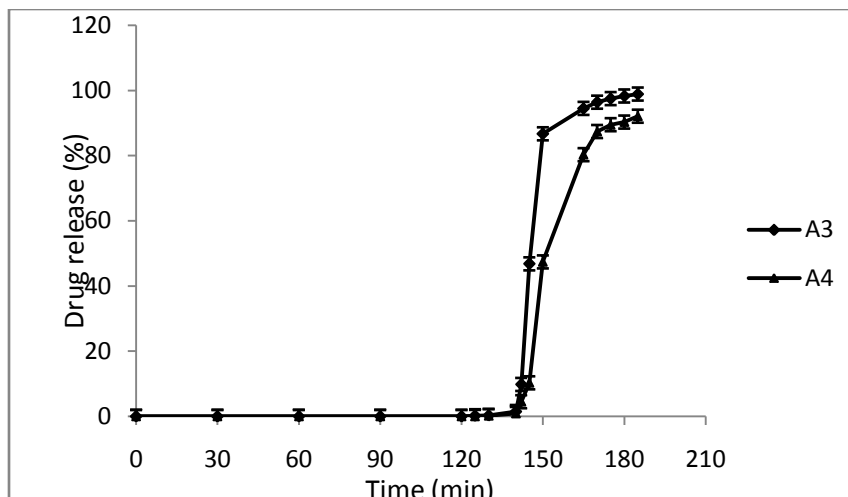


Figure 1. Dissolution profile of formulations A3 and A4 (n=3)

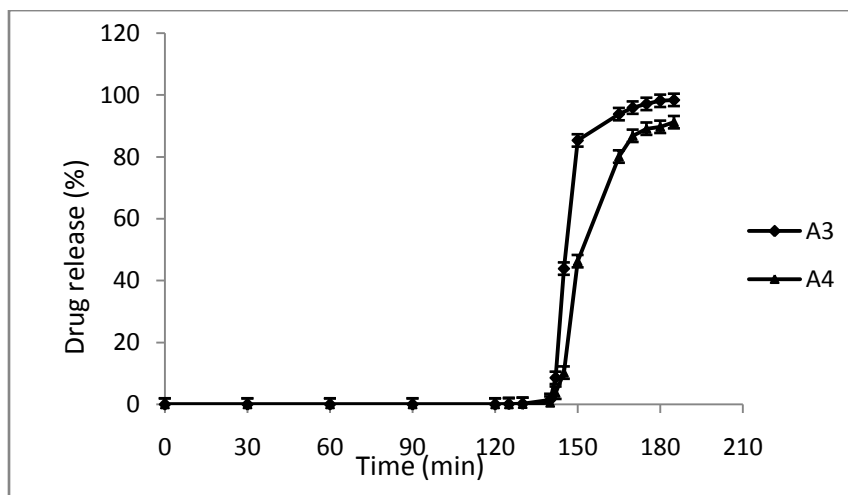


Figure 2. Dissolution profile of formulations A3 and A4 after three months (n=3)

In vitro dissolution profile of the enteric coated HPMC capsule A3 and A4 is shown in Figure 1. First two hours showed negligible drug release in 0.1N HCl for A3 and A4. At pH 6.8, faster drug release was observed for A3 (10% coating level) which was due to the faster dissolution of thinner layer compared to A4 (12% coating level). Enteric capsule A4 showed a lag phase of 10 min at pH6.8, where after that drug release was rapid within 53min. Capsule remained intact in simulated gastric fluid for 2h with very slow diffusion of drug, but at enteric pH 6.8, it swelled extensively, permitting enteric delivery of drug, following the first order kinetics of drug. Formulation A3 (10% coating layer) was considered better than A4 (12% coating layer) providing enteric protection with lesser polymer coat.

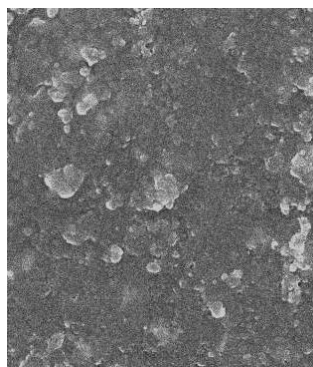


Figure 3. Scanning electron micrographs of surface of uncoated HPMC capsule at magnification of 100x.

HPMC capsules were found to have a matt surface providing a more irregular surface (Figure 3).

Scanning electron microscopy of the cross-section of a cleaved surface through A3 and A4 was depicted in Figure 4 and Figure 5. Coated capsules A3 and A4 showed no pores and cracks on surface. Coated capsules were found to have greater strength at the interface compared to uncoated capsule. During the coating process increase in temperature of capsule bed slightly heated the HPMC fixing the polymer film firmly on it. Secondly, higher amount of irregular surface also favored for good strength.

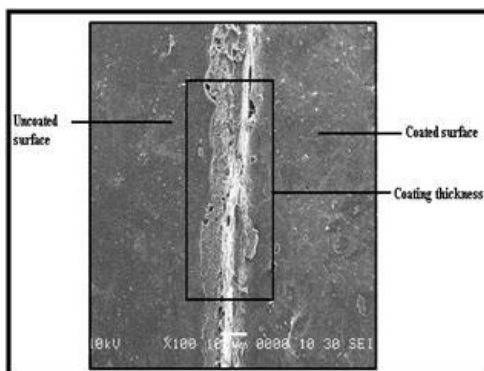


Figure 4. Scanning electron micrograph of coated surface of HPMC capsule of formulation A3

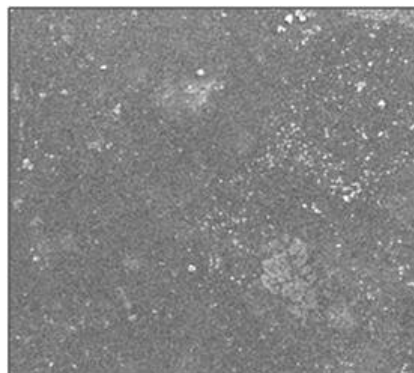


Figure 5. Scanning electron micrograph of coated surface of HPMC capsule of formulation A4

Table 3. Stability study of formulated enteric coated capsule

Weight gain	Drug Content (% w/w) After			
	15 Days	One month	Two month	Three Month
w/w				
10%	98.23	97.56	97.48	97.13
12%	97.64	97.86	96.31	97.54

Stability of enteric coated HPMC capsules A3 and A4 was found stable in presence of the excipients used, under accelerated conditions of temperature and humidity. Physical visualization of enteric coated HPMC capsules A3 and A4 showed no change in appearance. Acid resistance test of enteric coated capsules showed no drug release confirmed to acid protection (Figure 2). No major change in amount of drug release was observed during the storage conditions which reflected the stability of formulated capsule (Table3).

CONCLUSION

HPMC capsule shells play a significant role in the development of enteric coated dosage forms. The matt surface of the HPMC capsule provides a good substrate for adhesion of the uniform polymer coating, which results in an all round uniform film, providing gastric integrity. HPMC capsules can thus be a better alternative to hard gelatin capsule for enteric drug delivery as well as can be a good substitute for enteric coated tablets being irrespective of contents of capsule. Its vegetable source has wider customer acceptance. In conclusion, the present study confirmed the idea of providing excellent evidence of enteric protection for the coated capsules.

ACKNOWLEDGEMENT

The authors are thankful to Aarti pharma Pvt. Ltd., Associated Capsules Group, Mumbai and Ideal Cures Pvt. Ltd. for providing gift samples of required material and guidance on coating for this study.

REFERENCES

- [1] Cole G, Hogan J, Aulton M. Pharmaceutical coating technology. Taylor & Francis Publishers, UK, 2002, pp.409- 437.
- [2] Felton LA, Wiley CJ, Friar AL. AAPSPharmSci 2002; 4: 3320.
- [3] Guo HX, Heinämäki J, Yliruusi J. AAPSPharmSciTech 2002; 3:16.
- [4] O'Connor RE, Berryman WH. Drug Dev Ind Pharm1992; 18: 2123-2133.
- [5] Jones BE. Pharmaceutical Capsules Podczek, F. (Ed.), 2nd edition, Great Britain, 2004, pp. 61-77.
- [6] Biju SS, Saisivam S, Maria Gerald Rajan NS, Mishra PR. Eur J Pharm Biopharm 2004; 58 :61-67.
- [7] Pagay SN, Stetsko G. United States Patent 1994; 5330759.
- [8] Rege PR, Simon BH, Fegely KA, Rajabi-Siahboomi AR. AAPS Annual Meeting and Exposition. November 2005; Colorcon, West Point, PA, USA.
- [9] Cole E, Scott R, Conno A, Wilding I. Int J Pharm 2002; 231: 83-95.