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# PREPARATION AND EVALUATION OF HPMC-ALGINATE MUCOADHESIVE MICROCAPSULES OF DICLOFENAC FOR CONTROLLED RELEASE

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## ABSTRACT

A new, novel promising technology for obtaining controlled release and enhancing the bioavailability is a combination of mucoadhesion principle and microencapsulation to result in mucoadhesive microcapsules. Mucoadhesive microcapsules consist of either entirely of a mucoadhesive polymer or having an outer coating enclosing the drug particles. They facilitate an intimate and prolonged contact with the absorption surface to provide controlled release and enhanced bioavailability of the contained drug over longer period of time to prolong its therapeutic action. The objective of the present work is to prepare HPMC based mucoadhesive microcapsules of diclofenac and to evaluate the microcapsules for mucoadhesiveness and controlled drug release characteristics. Spherical HPMC-alginate mucoadhesive micro-capsules of diclofenac could be prepared by the orifice – ionic gelation method. Microencapsulation efficiency was in the range 98.7 % - 103.5 %. Drug release from the HPMC – alginate microcapsules was slow and spread over a period of 12 h and depended on core: coat ratio and wall thickness of the microcapsules. Drug release mechanism from these microcapsules was by non- Fickian diffusion. Good linear relationships were observed between wall thickness of the microcapsules and release rate [$K_0$ and $K_1$] of the microcapsules. Mucoadhesion testing by *in vitro* wash-off test indicated good mucoadhesive property of HPMC-alginate microcapsules with a slower wash-off when compared to non-mucoadhesive EVA microcapsules. Thus controlled release mucoadhesive microcapsules of diclofenac could be designed employing HPMC-alginate. HPMC-alginate microcapsules of diclofenac exhibited good mucoadhesion and controlled release characteristics and were found suitable for oral controlled release of diclofenac.

**INTRODUCTION:** In recent years, increasing attention has been focused on the manner in which the drugs are delivered. Drugs are being incorporated into polymeric systems and devices for controlled and targeted drug release. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve the desired drug concentration and then maintain it. The delivery system should fulfill spatial placement and temporal delivery of the drug. The controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of the drug to tissue. Drug release from these systems should be at a desired rate predictable and reproducible.

Among various oral controlled release systems, microencapsulation and microcapsules are widely accepted [1, 2]. A new novel promising technology for obtaining controlled release and enhancing the bioavailability is a combination of mucoadhesion principle and microencapsulation to result in mucoadhesive microcapsules. Mucoadhesive microcapsules consist of either entirely of a mucoadhesive polymer or having an outer coating enclosing the drug particles.

They facilitate an intimate and prolonged contact with the absorption surface to provide controlled release and enhanced bioavailability of the contained drug over longer period of time to prolong its therapeutic action. The polymer used in mucoadhesive microcapsules plays a vital role in either controlling the drug delivery or enhancing bioavailability of the contained drug.

Hydroxypropylmethylcellulose (HPMC) is reported [3] to have excellent mucoadhesive properties and is widely used in controlled release matrix tablets and also in coating for obtaining controlled release. The objective of the present work is to prepare HPMC based mucoadhesive microcapsules of diclofenac and to evaluate the microcapsules for mucoadhesiveness and controlled drug release characteristics. Diclofenac has short biological half-life and is required to be administered repeatedly 3 or 4 times a day. It causes gastric disturbances such as nausea, ulceration with bleeding, vomiting, abdominal pain and constipation if present in large concentration in the gastrointestinal tract.

Hence, controlled release mucoadhesive formulation is needed for diclofenac to enhance its oral bioavailability, duration of action and to reduce unwanted gastric disturbances

## MATERIALS AND METHODS:

**Materials:** Diclofenac was a gift sample from M/s. Micro Labs Ltd., Pondicherry. Hydroxy propyl methyl cellulose, K 100 was a gift sample from M/s Natco Pharma Ltd., Hyderabad. Sodium alginate (Qualigens) and Calcium chloride (Qualigens) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

**Preparation of Microcapsules:** An orifice – ionic gelation method was developed for HPMC - alginate microcapsules based on the ionic gelation principle, which has been extensively used to prepare large sized alginate beads [4, 5]. Sodium alginate (0.2 g) and HPMC (0.8 g) were dissolved in purified water (50 ml) to form a homogenous polymer solution. Core material (diclofenac) (1.0 g) as a fine powder passed through mesh No. 120 was added to the polymer solution and mixed thoroughly to form a smooth viscous dispersion.

The resulting dispersion was then added drop wise into calcium chloride (10 % w/v) solution (100 ml) through a syringe with a needle of size No. 18. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce spherical, rigid microcapsules. The microcapsules were collected by decantation and the product thus separated was washed repeatedly with water and dried at 65°C for 12 h. Different proportions of core: coat viz. 1:1(HDMCI), 1:2 (HDMC2), 1:3 (HDMC3) and 1:4 (HDMC4) were used to prepare microcapsules with varying coat thickness.

**Estimation of Diclofenac:** A UV-spectrophotometric method based on the measurement of absorbance at 276 nm in phosphate buffer of pH 7.4 was used to estimate the diclofenac content of the microcapsules. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range of 0-10 µg/ml. When a standard drug solution was assayed repeatedly (n=6) low RSD (< 0.5%) values ensured reproducibility of the method**.** No interference from the excipients 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.

**Angle of Repose:** To assess the flow property of the microcapsules, angle of repose was determined by the fixed funnel method [6].

**Microencapsulation Efficiency:** Microencapsulation efficiency was calculated using the equation;

$$\text{Microencapsulation Efficiency} = \frac{\text{Estimated percent drug content in microcapsules}}{\text{Theoretical percent drug content in microcapsules}} \times 100$$

**Scanning Electron Microscopy:** The microcapsules prepared were observed under a scanning electron microscope (Jeol JXA 8100 LTD, Tokyo, Japan). The samples were fixed on a brass stub using double sided sticking tape and then gold coated in vacuum by a sputter coater. The pictures were the taken at an excitation voltage of 15 Kv.

**Wall Thickness:** Assuming the microcapsules to be uniform and spherical, wall thickness of the microcapsules in the present study was determined by the method described by Luu *et al* [7] using the equation:

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

where 'h' is the wall thickness, '$\overline{r}$' is the arithmetic mean radius of the microcapsule, '$d_1$' 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 microcapsule. Densities were determined using petroleum ether as displacement fluid for drug and water as displacement fluid for resin at room temperature. Mean radius of the microcapsules was determined by sieving.

**Drug Release Study:** Diclofenac release from the HPMC-alginate microcapsules prepared was studied using an eight station dissolution rate test apparatus (model Disso-2000, M/s LABINDIA) with a paddle stirrer at 50 rpm and 37±0.5°C. The dissolution medium used was 900 ml of pH 6.8 phosphate buffer. A sample of microcapsules equivalent to 100 mg of drug was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter (0.45 μm) at different time intervals and were assayed for diclofenac at 276 nm. The sample (5 ml) taken at each sampling time was replaced with fresh dissolution medium (5 ml). A suitable correction was applied for the loss of drug in the samples taken while calculating the amount of drug released at different times. The drug release experiments were conducted in triplicate (n=3).

**Evaluation of Mucoadhesiveness:** The mucoadhesive property of the HPMC-alginate microcapsules was evaluated by an *in vitro* adhesion testing method known as wash-off method [8]. The mucoadhesiveness of the microcapsules prepared was compared to that of non-bioadhesive material, ethylene vinyl acetate (EVA) microcapsules. Pieces of goat intestinal mucosa (2×2 cm) were mounted onto glass slides (3×1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung on to the arm of a USP tablet disintegration test machine.

By operating the disintegration test machine, the tissue specimen was given a slow regular up and down movement in 900 ml test fluid at 37°C taken in a 1 L vessel of the disintegration test machine. At the end of 30 min, 1 h and later at hourly intervals up to 8 h, the machine was stopped and the number of microcapsules still adhering on to the tissue was counted. The test was performed in 0.1 N HCl and in phosphate buffer of pH 6.2.

**RESULTS AND DISCUSSION:** Preliminary studies indicated that microcapsules with a coat of HPMC alone could not be prepared due to its water soluble nature. Microcapsules with a coat consisting of HPMC-alginate (80:20) could be prepared by orifice - ionic gelation method. The method gave spherical, discrete and free flowing microcapsules of HPMC-alginate with an angle of repose in the range 20° - 25°. The nature of the method indicated that the microcapsules prepared were of multinucleate and monolithic type. The SEM photograph (**Figure 1**) also indicated that the microcapsules were spherical and completely covered with the polymer and have smooth surface.

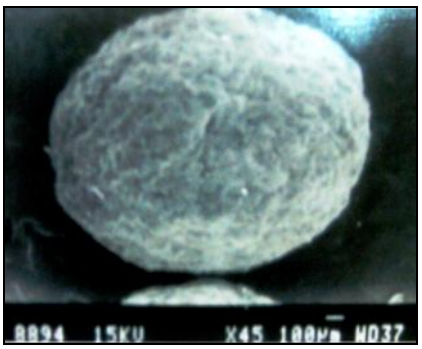


**FIG. 1: SEM PHOTOGRAPH OF HPMC-ALGINATE MICROCAPSULE (SIZE 18/20) OF DICLOFENAC**

The HPMC- alginate microcapsules prepared were uniform in size with a mean size of 920 µm (i.e. mesh size 18/20). Percent drug content of different microcapsules is shown in **Table 1**. Low coefficient of variation in percent drug content (< 1.4 %) indicated uniformity of drug content in each batch of microcapsules. The microencapsulation efficiency was in the range of 98.7 % - 103.5 % (Table 1). As the microcapsules are spherical, the theoretical average wall thickness of the microcapsules was calculated as per the Luu *et al* [7]. Wall thickness of various microcapsules is shown in Table 1. Microcapsules prepared with various ratios of core: coat was found to have different wall thickness.

**TABLE 1: DRUG CONTENT, MICROENCAPSULATION EFFICIENCY, WALL THICKNESS AND RELEASE CHARACTERISTICS OF HPMC-ALGINATE MICROCAPSULES OF DICLOFENAC**

| Microcapsules (Core: Coat Ratio) | Drug Content (%) | Micro-encapsulation Efficiency (%) | Wall Thickness (µm) | $T_{50}$ (h) | $T_{90}$ (h) | $K_0$ (mg/h) | $K_1$ ($h^{-1}$) | 'n' in Peppas Equation |
|---|---|---|---|---|---|---|---|---|
| HDMC1 (1:1) | 49.37 (1.37)* | 98.7 | 41.6 | 3.1 | 7.4 | 10.9751 | 0.4590 | 0.7529 |
| HDMC2 (1:2) | 33.02 (1.06) | 99.2 | 58.2 | 3.4 | 8.5 | 8.8182 | 0.3929 | 0.6575 |
| HDMC3 (1:3) | 25.5 (1.25) | 102 | 63.4 | 3.9 | 9.4 | 8.2855 | 0.3158 | 0.5857 |
| HDMC4 (1:4) | 20.07 (0.84) | 103.5 | 72.1 | 4.3 | 11.5 | 7.0407 | 0.1804 | 0.5835 |

*Figures in parentheses are % C.V. values

Drug release studies were carried out for diclofenac in 900 ml of pH 7.4 phosphate buffer. Drug release from the HPMC – alginate microcapsules of diclofenac was slow and spread over a period of 12 h and depended on core: coat ratio and wall thickness of the microcapsules. The release data were analyzed as per zero order, first order, Higuchi [9] and Peppas [10] equation models. Diclofenac release from the HPMC – alginate microcapsules followed zero order kinetics. Coefficient of determination ($R^2$) values in the zero order model were higher than those in the first order model (**Table 2**). The release exponent 'n' was in the range 0.5835 – 0.7529 indicating that the release mechanism from these microcapsules was by non – Fickian diffusion. Good linear relationships were observed between i) wall thickness of the microcapsules and release rate ($K_0$) values and ii) wall thickness of the microcapsules and release rate ($K_1$) values (**Figures 2, 3**).

**TABLE 2: COEFFICIENT OF DETERMINATION ($R^2$) VALUES IN THE ANALYSIS OF RELEASE DATA OF HPMC-ALGINATE MICROCAPSULES OF DICLOFENAC AS PER VARIOUS KINETIC MODELS**

| Microcapsules (core : coat ratio) | $R^2$ values | | | |
|---|---|---|---|---|
| | Zero Order | First order | Higuchi | Peppas |
| HDMC1(1:1) | 0.9752 | 0.7734 | 0.9775 | 0.9944 |
| HDMC2(1:2) | 0.9672 | 0.8321 | 0.9870 | 0.9958 |
| HDMC3 (1:3) | 0.9753 | 0.7625 | 0.9762 | 0.9717 |
| HDMC4 (1:4) | 0.9604 | 0.9706 | 0.9927 | 0.9983 |

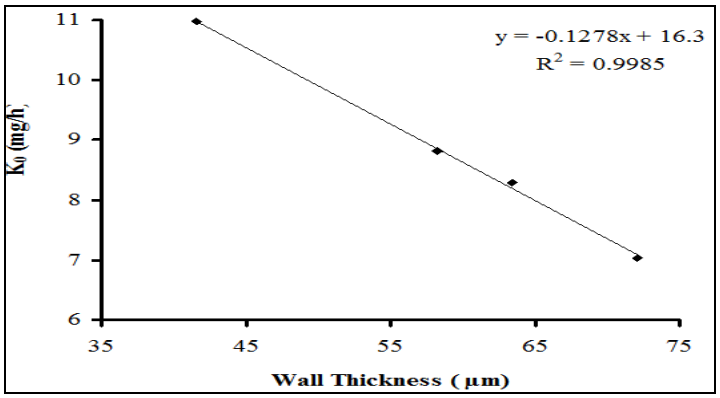


**FIG. 2: RELATIONSHIP BETWEEN WALL THICKNESS AND RELEASE RATE $K_0$ FOR HPMC-ALGINATE MICROCAPSULES OF DICLOFENAC**

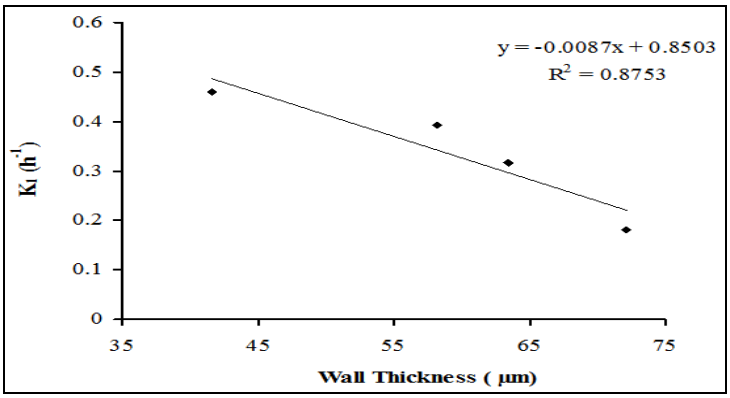


**FIG. 3: RELATIONSHIP BETWEEN WALL THICKNESS AND RELEASE RATE $K_1$ FOR HPMC-ALGINATE MICROCAPSULES OF DICLOFENAC**

HPMC – alginate microcapsules of diclofenac exhibited good mucoadhesive property when compared to non-mucoadhesive EVA microcapsules. The wash-off was slow in the case of HPMC – alginate microcapsules when compared to EVA microcapsules. With HPMC – alginate microcapsules, the wash-off was similar and equal at acidic (pH 1.2) and intestinal (pH 6.2) (**Table 3**).

**TABLE 3: RESULTS OF *IN VITRO* WASH-OFF TEST TO ASSESS MUCOADHESIVE PROPERTY OF HPMC-ALGINATE MICROCAPSULES OF DICLOFENAC**

| Microcapsules (Size 18/20) | Percent Microcapsules Adhering to Tissue After Time (h) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | In 0.1 N HCl, pH 1.2 | | | | | In Phosphate Buffer, pH 6.2 | | | | |
| | 1 | 2 | 4 | 6 | 8 | 1 | 2 | 4 | 6 | 8 |
| HDMC3 | 71 (2.4)* | 56 (2.6) | 38 (2.6) | 22 (1.8) | 8 (1.4) | 72 (2.1) | 53 (1.6) | 38 (1.8) | 25 (2.4) | 10 (2.0) |
| EVA | 56 (2.8) | 40 (3.1) | 10 (2.6) | -- | -- | 51 (2.4) | 39 (3.2) | 9 (1.8) | -- | -- |

*Figures in parentheses are % C.V. values.

**CONCLUSION:** Spherical HPMC-alginate mucoadhesive microcapsules of diclofenac could be prepared by the orifice – ionic gelation method. Microencapsulation efficiency was in the range 98.7 % - 103.5 %. Drug release from the HPMC – alginate microcapsules was slow and spread over a period of 12 h and depended on core: coat ratio and wall thickness of the microcapsules. Drug release mechanism from these microcapsules was by non- Fickian diffusion. Good linear relationships were observed between wall thickness of the microcapsules and release rate ($K_0$ and $K_1$) of the microcapsules. Mucoadhesion testing by *in vitro* wash-off test indicated good mucoadhesive property of HPMC-alginate microcapsules with a slower wash off when compared to non-mucoadhesive EVA microcapsules.

Thus, controlled release mucoadhesive microcapsules of diclofenac could be designed employing HPMC-alginate. HPMC-alginate microcapsules of diclofenac exhibited good mucoadhesion and controlled release characteristics and were found suitable for oral controlled release of diclofenac.

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