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COMMUNICATION

Formulation and Evaluation of Methocel K15M Bioadhesive Matrix Tablets

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ABSTRACT

Methocel K15M is a bioadhesive polymer. Its adhesion and bioadhesion characteristics were evaluated by shear stress measurement and detachment force measurement methods, respectively. The effect of pH on adhesion was studied, and it was found that the maximum adhesion was between pH 5 and pH 6. Adhesion strength at different parts of the sheep intestine was studied; in the duodenal portion of the intestine, the adhesion was maximum. Chlorpheniramine maleate and diclofenac sodium drugs are formulated with Methocel K15M as matrix tablets. In vitro release studies revealed that some of the formulations showed initial first-order behavior followed by zero-order release behavior.

Key Words: *Bioadhesives; Evaluation; Matrix tablets; Methocel K15M; Mucoadhesives.*

INTRODUCTION

Mucoadhesive drug delivery systems localize the drug at a particular site and release the drug. Since many drugs are absorbed only from the upper small intestine, localizing oral drug delivery systems in the stomach or duodenum would significantly improve the extent of drug absorption. The intimate contact may increase the local permeability of high molecular weight drugs such as peptides and proteins (1). Methocel K15M is a polymer used for controlling the release of drugs. A mucoadhesive drug delivery system consisting of polymer and drug in matrix form could be prepared. The objective of the present investigation was to study the adhesion strength of Methocel K15M using shear stress measurement and detachment force measurement techniques, to develop a controlled-release formulation for a highly water soluble drug like chlorpheniramine maleate and a sparingly soluble drug like diclofenac sodium, and to study the drug release profiles with an aim to prepare a controlled-release bioadhesive dosage form.

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Table 1

Formulas of Chlorpheniramine Maleate Matrix Tablets

	Formulation				
Ingredients (mg)	Conventional	1:0.5	1:1	1:1.5	1:2
Drug	10	10	10	10	10
Methocel K15M	—	5	10	15	20
Lactose	100	100	90	85	80
Talc (%)	2	2	2	2	2
Magnesium stearate (%)	0.5	0.5	0.5	0.5	0.5

EXPERIMENTAL

Materials and Equipment

The following materials and equipment were used: diclofenac sodium (Nacto Pharma, Hyderabad, India); chlorpheniramine maleate (biological E. Ltd., Hyderabad, India); Methocel K15M (Colorcon, Mumbai, India); potassium dihydrogen orthophosphate, HCl, talc, and magnesium stearate (S.D. Fine Chemicals, Boisar, India); Cadmach single-punch tablet machine, USP 21 six-stage dissolution rate test apparatus (Tab Machines); and a UV-Visible spectrophotometer (Elico-SL150).

Methods

Measurement of Adhesion Strength of Methocel K15M

Shear Stress Measurement Method

The shear stress measurement method was developed and reported (2,3). Using this method, the preliminary adhesion testing of polymers can be done. The adhesion strength at different pH conditions can also be performed to check whether there is any effect of pH on adhesion strength. The measurements were done six times, and average values were taken.

Detachment Force Measurement Method

The detachment force measurement method was used to measure in vitro mucoadhesive capacity of different polymers. It is a modified method of Marvola (4) to assess the tendency of mucoadhesive materials to adhere to the esophagus. This method was discussed in our earlier work (2). The mucoadhesive strength of Methocel K15M was tested, and this property was further tested at different parts of sheep small intestine (viz., duodenum, jejunum, and ileum) by conducting the studies six times.

Formulation and In Vitro Release Studies of Methocel K15M Matrix Tablets

The compositions of matrix tablets with chlorpheniramine maleate and diclofenac sodium are given in Tables 1 and Table 2 respectively.

Method of Preparation

The drug and polymer were physically mixed and granulated by the wet granulation method (5). These granules were subjected to drying at 50°C. After drying, magnesium stearate and talc were mixed and subjected to compression using the Cadmach single-punch tablet machine.

Table 2

Formulas of Diclofenac Sodium Matrix Tablets

	Formulation							
Ingredients (mg)	Conventional	1:0.2	1:0.4	1:0.6	1:0.8	1:1	1:1.2	1:1.4
Diclofenac sodium	100	100	100	100	100	100	100	100
Methocel K15M	—	20	40	60	80	100	120	140
Lactose	100	80	60	40	20	—	—	—
Talc (%)	2	2	2	2	2	2	2	2
Magnesium stearate (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

In Vitro Release Studies

In vitro release Studies (5) were carried out using the USP ZI six-stage dissolution rate test apparatus with six baskets. The bottom outside surface of the basket was covered with butter paper; paraffin wax was poured on this paper by melting. During solidification of the wax, the tablet was pressed onto it such that only one surface of tablet was exposed to dissolution medium; therefore, the release of drug from the tablet was only from one surface. The tablets were placed in 0.1 N HCl (900 ml), and the dissolution test was continued for 2 hr. Samples were collected periodically. After 2 hr, the medium was replaced with phosphate buffer of pH 6.8. Then, the samples of medium were collected periodically at different time intervals, and drugs were assayed by measuring the extinction using a UV-Visible spectrophotometer (Diclofenac sodium, 0.1 N HCl [273 nm]; phosphate buffer, pH 6.8 [275 nm]; chlorpheniramine maleate, 0.1 N HCl [262 nm]; phosphate buffer, pH 6.8 [265 nm]). All the in vitro release studies were performed six times, and average values with standard deviation are shown. During the entire experiment, the speed of the basket shaft was 100 rpm, and the temperature was 37°C ± 0.5°C.

RESULTS AND DISCUSSION

Methocel K15M is a high-viscosity grade (6138–9030 m Pa · sec, nominal value 7382 m Pa · sec by rotation) (6) hydroxypropylmethylcellulose compound. Before developing bioadhesive controlled-release matrix systems, the adhesion characteristics of the polymer were evaluated using two different adhesion testing methods. Preliminary adhesion testing was performed with the shear stress measurement method; further, the bioadhesion testing was performed with a biological membrane such as sheep intestines. In the shear stress measurement method, weight required to break the adhesion was recorded at different time intervals. From Table 3, it can be observed that increasing the contact time for adhesion increased the force required to break the adhesion (i.e., increasing the time of contact increased adhesion strength). Effect of pH on adhesion was studied. From Fig. 1, it can be seen that the maximum adhesion occurred between pH 5 and pH 6. After pH 6, the adhesion

Table 3

Adherence Strength of Methocel K15M by Shear Stress Measurement Method

Contact Time (min)	Adherence Strength, g (Mean ± SD)
5	94.67 ± 9.83
10	140.17 ± 7.10
15	668.42 ± 11.00
20	804.50 ± 14.82
30	872.83 ± 22.18

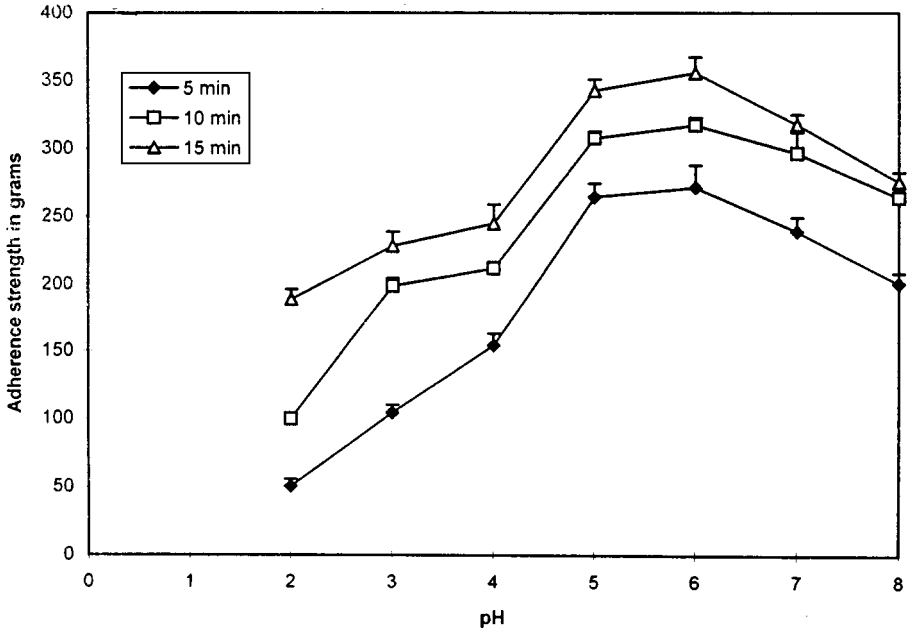

Figure 1. Effect of pH on adhesion strength of Methocel K15M.

Table 4

Adherence Force of Methocel K15M by Detachment Force Measurement Method

Contact Time (min)	Adherence Strength, g (Mean ± SD)
30	1.46 ± 0.02
60	1.72 ± 0.03

decreased. Similar results were obtained by earlier workers, and it was reported that maximum adhesion was seen at pH 5–6 for most of the polymers checked (7).

To confirm whether the polymer exhibited the same strength in contact with the mucous membranes and formulations, it was further checked by the detachment force measurement method for the bioadhesive strength of Methocel K15M tablets. The detachment force in newtons and the corresponding weight required to detach tablets adhered to sleep intestine are shown in Table 4. Increasing the contact time enhanced the force required. The detachment force at different parts of the gastrointestinal tract (duodenum, jejunum, and ileum) was also studied. From Fig. 2 it was found that maximum adherence force was at the duodenum, followed by the jejunum and ileum. This may be due to pH variation throughout the gastrointestinal tract. The pH in the duodenum and ileocecal junction were 5.8 ± 0.8 and from 6.5 to 8.5 (8). In simple adhesion testing, it was found that the adhering force was greater between pH 5 and pH 6. The results correlated well.

Adhesion was reported to be effected by hydration (9). Hydration of the mucoadhesive polymer is essential to initiate the mucoadhesive bonding process. In case of tablets applied in the dehydrated state, which is most convenient, it is essential that sufficient water be available so that rapid hydration takes place, and a flexible rubbery state occurs. The capillary force arising when water from the space between the mucosa and the polymer is taken up by a dry system may be considerable (10). It is of great importance that the mucoadhesive material will develop a bond with only minimum applied force. Once the bond is formed, reduction in the rate of swelling due to water uptake from the tissue surface may only prolong the association of the tablet with the mucosa. Removal of water from the underlying mucous layer by the hydrating polymer may increase the cohesive forces of mucus; this plays a vital role in the establishment of an effective mucoadhesive bond (2).

In the formulation of matrix-type drug delivery systems, the drug is usually dissolved or dispersed uniformly throughout the device (11). Methocel K15M matrix tablets were prepared with two different drugs (chlorpheniramine maleate and diclofenac sodium) separately by a compaction process, and their in vitro release behavior were studied.

From Fig. 3 it was observed that the control tablet of chlorpheniramine maleate released the total drug within

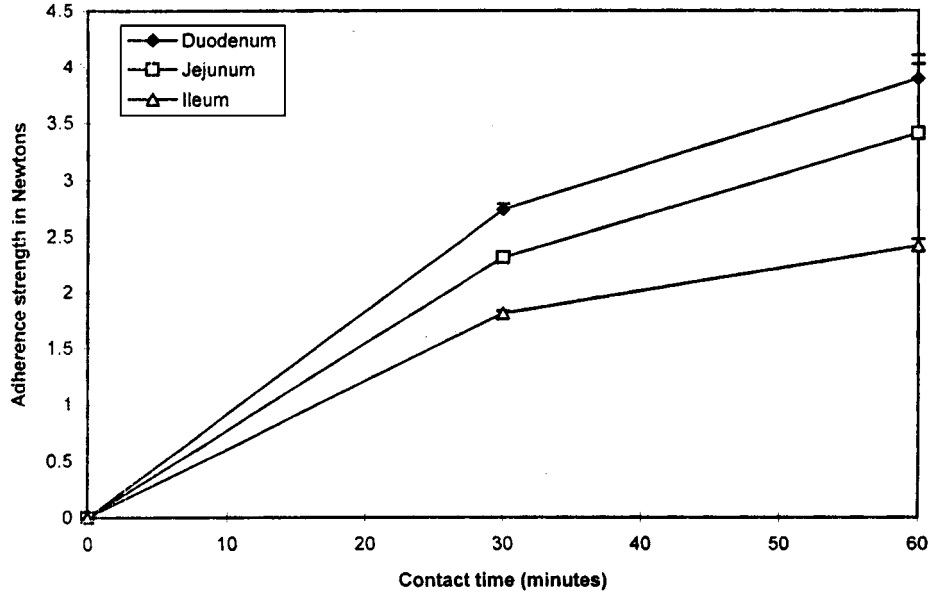

Figure 2. Detachment force measurement at different parts of sheep intestine.

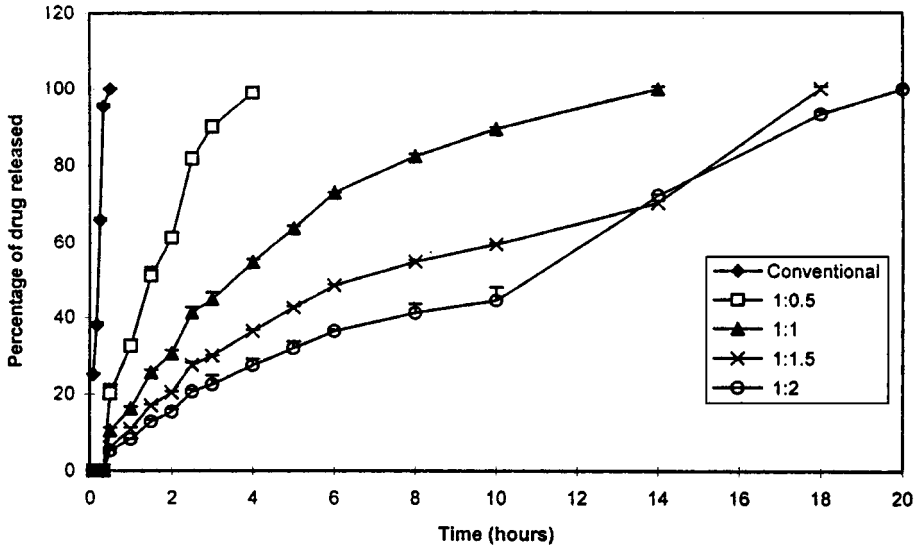

Figure 3. Dissolution profiles of chlorpheniramine maleate and Methocel K15M bioadhesive matrix tablets.

20 min. The matrix tablets containing drug in the ratios 1:0.5, 1:1, 1:1.5, and 1:2 released drug completely in 4, 14, 18, and 20 hr, respectively. As the polymer concentration increased, the dissolution of drug decreased. In the case of the 1:0.5 formulation, the drug was released completely within 4 hr. For the formulation containing drug and polymer in the ratio 1:1, almost 50% of the drug was released within 4 hr, and the remaining drug was released slowly in a zero-order fashion over 14 hr. In the case of the 1:1.5 and 1:2 formulations, the initial release of drug was also slow and steady. The times for drug release were 18 and 20 hr, respectively.

From Fig. 4, it was found that the control tablet of diclofenac sodium released the drug within 4 hr. The matrix tablets containing drug and polymer in the ratios 1:0.2, 1:0.4, 1:0.6, 1:0.8; 1:1, 1:1.2, and 1:1.4 released drug completely in 4, 8, 10, 14, 16, 20, and 24 hr, respectively. Increasing the polymer proportion decreased the

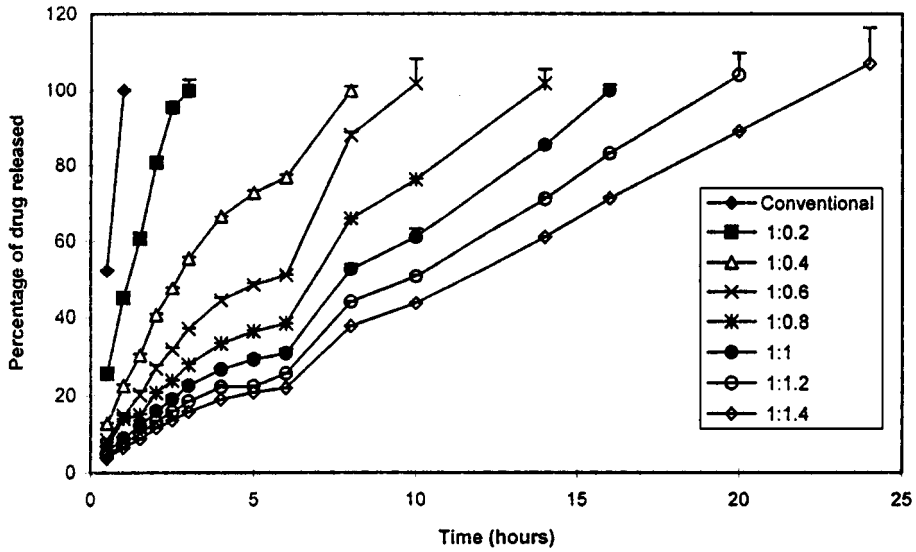

Figure 4. Dissolution profiles of diclofenac sodium and Methocel K15M bioadhesive matrix tablets.

drug release from the matrix system. The drug release from all the formulations was slow and followed zero-order release.

The mechanism involved in the dissolution of matrix tablets may be diffusion/erosion. The process of dissolution is a key step during drug release from many non-cross-linked hydrophilic polymer matrices involved in controlled-release tablets of granules (11). Initial hydration of hydrophilic polymer leads to the diffusion, and the polymer gel layer slowly leads to dissolution of the polymer; the process is generally referred to as *erosion*. In both the drug formulations, the uniform parabolic initial drug distribution showed first-order release behavior with a continuously diminishing rate. This type of phenomenon can be observed in the formulations of chlorpheniramine maleate (1:1, 1:1.5, and 1:2) in 4 hr release and diclofenac sodium (1:0.4, 1:0.6, 1.08, 1:1, 1:1.2, and 1:1.4) in 6 hr release. After these times, the drug release was found to follow zero-order release. This may be due to erosion. The release of a dissolved or dispersed drug from an erodible polymer matrix can be controlled by either a bulk erosion or a surface erosion mechanism. The situation in which polymer erodes by a pure surface erosion mechanism is of special interest because the rate of drug release from such devices will be constant. This probably explains the release profiles obtained in the present investigation.

CONCLUSIONS

The preliminary adhesion characteristics of Methocel K15M with shear stress measurement and detachment force measurement methods showed that the polymer has good adhesion characteristics. The adhesion was found to be maximum between pH 5 and pH 6. In the duodenum, maximum mucoadhesion was observed. The in vitro release behavior of drugs in the polymer matrix was studied; it was found that the release with chlorpheniramine maleate (1:1 and 1:1.5) and with diclofenac sodium (1:1, 1:1.2, and 1:14) followed initial first-order release behavior and then zero-order release behavior. The polymer concentration required to get an optimum drug delivery system was higher for chlorpheniramine maleate as it is a walter-soluble drug. Diclofenac sodium is a sparingly soluble drug and obviously required less polymer to obtain a similar dissolution profile.

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