

Full Length Research Paper

**FORMULATION DEVELOPMENT OF MUCOADHESIVE
MICROCAPSULES OF METFORMIN HYDROCHLORIDE USING
NATURAL AND SYNTHETIC POLYMERS AND IN VITRO
CHARACTERIZATION**

Yellanki Shiva Kumar ¹, Deb Sambit kumar ², Goranti Sharada ³, Nerella Naveen kumar²

¹ Department of Pharmaceutics, Ganga Pharmacy College, Jawaharlal Nehru Technological University, Nizamabad, Andhra Pradesh, India.

² Department of Pharmaceutical Analysis, Ganga Pharmacy College, Jawaharlal Nehru Technological University, Nizamabad, Andhra Pradesh, India.

³ Department of Pharmaceutical Chemistry, Ganga Pharmacy College, Jawaharlal Nehru Technological University, Nizamabad, Andhra Pradesh, India.

ABSTRACT

The objective of this work was to develop optimized and systematically evaluate performances of mucoadhesive microcapsules of antihyperglycemic agent drug Metformin. Alginate microcapsules coated with mucoadhesive natural or synthetic polymers were prepared by Orifice-Ionic Gelation technique utilizing calcium chloride as a cross linking agent. The effect of type (natural or synthetic) and concentration of coating polymers and concentration of alginate on formulation was investigated. Prepared microcapsules were evaluated for Drug content, Entrapment efficiency, Shape, size, In vitro Mucoadhesion and In vitro release. The microcapsules obtained were spherical and free flowing. The microcapsules coated with mucoadhesive polymer Carbopol exhibited good mucoadhesive property in the in vitro Mucoadhesion test and also showed high percentage drug entrapment efficiency. The in vitro release study indicates that carbopol as coating polymer containing formulations showed controlled drug release up to 10 h from microcapsules.

Keywords: Mucoadhesive microcapsules, Metformin, Natural and Synthetic Polymers, Orifice-Ionic Gelation technique.

Introduction

Multiparticulate systems made up of biodegradable polymers have paid considerable attention for several years in controlling and sustaining of release rate of drugs. Recently, dosage forms that can precisely control the release rates and targets drugs to a specific body site have made enormous impact in the formulation and development of novel drug delivery systems. Oral multiunit dosage forms such as microcapsules and microspheres have received much attention as modified/controlled drug delivery systems. [1, 2]

Microencapsulation has been accepted as a process to achieve controlled release and drug targeting. Mucoadhesion has been a topic of interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs. [3, 4, 5]

Gastric mucoadhesive drug delivery offers a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. Metformin is an antihyperglycemic

***Address for Correspondence:-**

Shiva kumar Yellanki

Mobile :- 09966959818.

E mail: shiva_kmr1984@yahoo.com

agent, which improves glucose tolerance in type II diabetes. It has been reported that the absolute bioavailability of Metformin when given orally is 50–60%. Biological half life of Metformin is 1.5–1.6 h and the main site of its absorption is proximal small intestines. [6, 7]

Thus in this study an attempt was made to prepare oral controlled release natural and synthetic polymers coated mucoadhesive microcapsules of Metformin hydrochloride. The mucoadhesive microcapsules were characterized by *in vitro* methods for controlled release.

Materials and Methods:

Materials

Metformin was obtained as a gift sample from USV limited Mumbai. Sodium alginate was purchased from loba chemie (Bombay). Chitosan (85% deacylated) of viscosity grade 200-800 cps, was kindly gifted by Central Institute of Fisheries Technology (Kochi., India). Hydroxy Propyl Methyl Cellulose (E15LV), Gelatine and Carbopol 934P were procured from Thomas Baker, Mumbai and Loba Chemie Pvt. Ltd. respectively. All other chemicals and solvents were of reagent grade or higher.

Preparation of Microcapsules by Orifice-Ionic Gelation Method

Microcapsules containing Metformin were prepared employing sodium alginate in combination with four natural and synthetic mucoadhesive polymers- Hydroxy Propyl Methyl Cellulose, Carbopol, Chitosan and Gelatine as coat materials. An orifice-ionic gelation process that has been extensively used to prepare large alginate beads was employed to prepare the microcapsules. [8, 9]

Sodium alginate (1.0 g) and the mucoadhesive polymer (1.0 g) were dissolved in purified water (30 ml) to form a homogeneous polymer solution. The active substance, Metformin (2.0 g), was added to

the polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added manually drop wise into calcium chloride (10% w/v) solution (40 mL) through a syringe 22 gauge. The added droplets were retained in the calcium chloride solution for 15 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 40°C for 3 hours. The microcapsules prepared along with their coat composition are listed in Table 1.

Evaluation of prepared Mucoadhesive Metformin Microcapsule:

Yields of production

The yields of production of microcapsules of various batches were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of microcapsules and percent production yields were calculated as per the formula mentioned below. [10]

$$\text{Production Yield} = \frac{\text{Practical mass (microcapsules)} \times 100}{\text{Theoretical mass (drug+polymers)}}$$

Drug content and Entrapment efficiency:

Actual drug content and encapsulation efficiency of the microcapsules was determined by following method [11, 12], 100 mg of dried beads were crushed using mortar and pestle. The ground beads were placed in 100 ml of 0.1 N HCl (pH 1.2) and shaken for 1 h at 37±0.5°C in mechanical shaker. The samples were then filtered to obtain clear solution and analysed for the drug content spectrophotometrically at 233 nm, it gives drug content for 100 mg of beads from that calculate drug content for total quantity of beads, from actual drug content, the value of encapsulation efficiency was determined using the formula given below.

$$\text{Encapsulated efficiency} = \frac{\text{Calculated \%age drug content} \times 100}{\text{Theoretical percentage drug content}}$$

Shape and size of microcapsules

The average diameters of microcapsules were determined using a caliper (Mitutoyo, Japan) in triplicate and the surface morphology was studied by scanning electron microscope (SEM) (JSM-5310LV Scanning Microscope, Tokyo, Japan).^[13, 14]

In vitro Mucoadhesion study

The sheep stomach mucosa was used for in vitro mucoadhesion evaluation. The mucosa was removed and cut into pieces 2 cm long and 2 cm wide and were rinsed with 2 ml of 0.1 N HCl (pH 1.2). Fifty microcapsules of each were scattered uniformly on the surface of the stomach mucosa. Then, the mucosa with the microcapsules was placed in a chamber maintained at 93% relative humidity and room temperature. After 20 minutes, the tissue were taken out and fixed on a polyethylene support at an angle 45°. The stomach was rinsed with pH 1.2 hydrochloric acid buffer for 5 minutes at a rate of 22 ml/ minutes. The microcapsules adhered on to the surface of mucosa was counted, and the percentage of the adhered microcapsules was calculated.^[15, 16]

In vitro release studies

In vitro release studies were carried in pH 1.2 HCl buffer medium. Drug released rate was tested on all prepared formulations. The test conditions as follows^[17]: microcapsules containing 10 mg of drug were placed in baskets in a vessel containing 900 mL of pH 1.2 HCl buffer medium with the temperature maintained at 37±0.5°C. The rotating rate of the basket was adjusted to 50 rpm. With intervals, 5 mL of samples were withdrawn and filtered through a whatman's filter paper. The equivalent volume of the medium with the same temperature was added to the dissolution vessel. The absorbance values of the filtrate at the wavelength of 233 nm were determined after suitable dilution. To analyze the mechanism and order of drug release

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RESULTS AND DISCUSSION

Microcapsules of Metformin with coat consisting of various concentration alginate and mucoadhesive natural and synthetic polymer in ratio of 1:1, 5:1, 9:2 and 9:1 (Alginate: Mucoadhesive polymer) could be prepared by Orifice-Ionic Gelation technique. The microcapsules were found to be discrete, almost spherical, free flowing and of the monolithic matrix type. The microcapsules were completely covered with coat polymer.

Yields of production

The production yields of prepared formulations were in the range of 72.6 % - 84.7%. This high yield of production is may be due to all the polymer is available for gelation into cross linking agent.

Drug content and Entrapment efficiency

Percentage drug content indicated uniformity of drug content in each batch of microcapsules. Encapsulation efficiency of the microcapsules was dependent on mainly the concentration of sodium alginate; it was found that by increasing the concentration of sodium alginate, the encapsulation efficiency of the microcapsules also increases. The entrapment efficiency was in the range of 57.08±1.04 to 88.26±1.9, as shown in Table 1.

Shape and size of microcapsules

The microcapsules were uniform in size, with a size range of 900.8 -1118.3 µm. Surface morphology of microcapsules is presented in Fig. 1. The difference in the shape of microcapsules is observed, representing that microcapsules containing higher amount of alginate (M13-M16) are more spherical and regular as compared to that of microcapsules having lower percent of alginate (M1-M4). Such

results may be due to as the polymer (alginate) concentration increases the spherical nature of microcapsules also increases.

Table 1: Composition, Percentage yield (%), Drug content (% w/w) and Entrapment efficiency (%) of prepared Mucoadhesive Metformin Microcapsules.

Formulation Code	Composition	Percentage yield (%)	Drug content (%w/w) Mean ± (S.D.)	Entrapment efficiency (%) Mean ± (S.D.)
M1	Alginate: HPMC (1:1)	72.46	29.14±1.05	58.28±1.2
M2	Alginate: Carbopol 934P (1:1)	74.12	33.16±1.4	66.32±1.7
M3	Alginate: Chitosan (1:1)	69.98	28.96±0.9	57.92±0.4
M4	Alginate: Gelatine (1:1)	68.5	28.54±1.02	57.08±1.04
M5	Alginate:HPMC (5:1)	75.8	29.21±1.1	58.42±1.2
M6	Alginate: Carbopol 934P (5:1)	77.46	39.76±1.4	79.52±1.5
M7	Alginate: Chitosan (5:1)	71.49	31.02±1.8	62.04±1.5
M8	Alginate: Gelatine (5:1)	70.78	31.12±1.9	62.24±1.2
M9	Alginate:HPMC (9:2)	82.26	43.97±0.56	87.94±0.7
M10	Alginate: Carbopol 934P (9:2)	86.35	44.13±1.7	88.26±1.9
M11	Alginate: Chitosan (9:2)	79.22	39.67±1.8	79.34±1.2
M12	Alginate: Gelatine (9:2)	75.61	38.12±1.2	76.24±1.9
M13	Alginate:HPMC (9:1)	79.96	38.13±1.47	76.26±1.1
M14	Alginate: Carbopol 934P (9:1)	81.25	41.09±1.7	82.18±1.04
M15	Alginate: Chitosan (9:1)	74.84	37.45± 0.8	74.90±1.01
M16	Alginate: Gelatine (9:1)	71.94	37.94±0.7	75.88±0.6

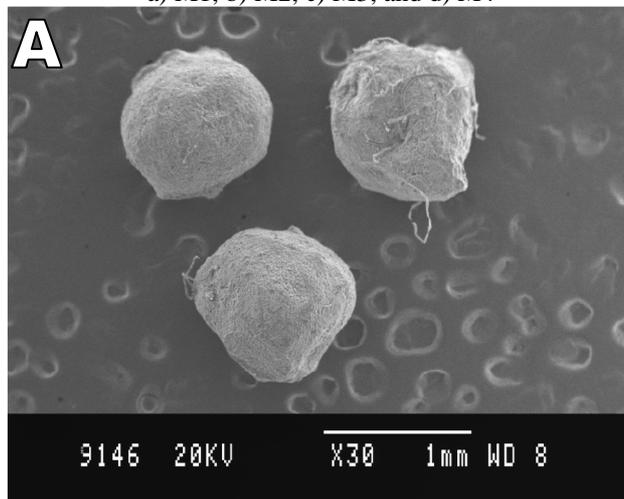
± S.D- Standard deviation for (n=3)

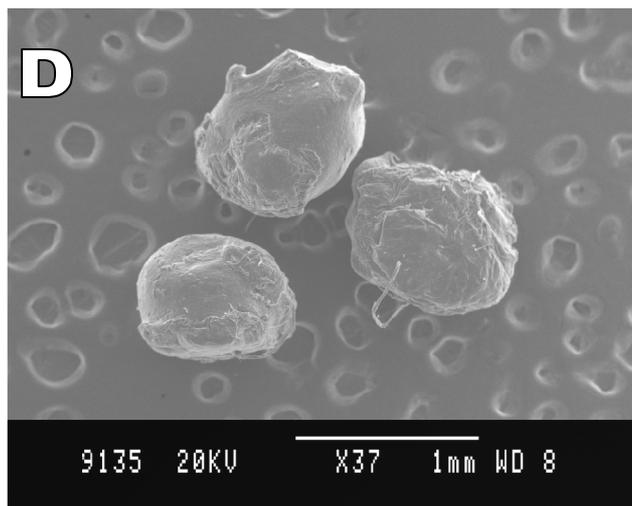
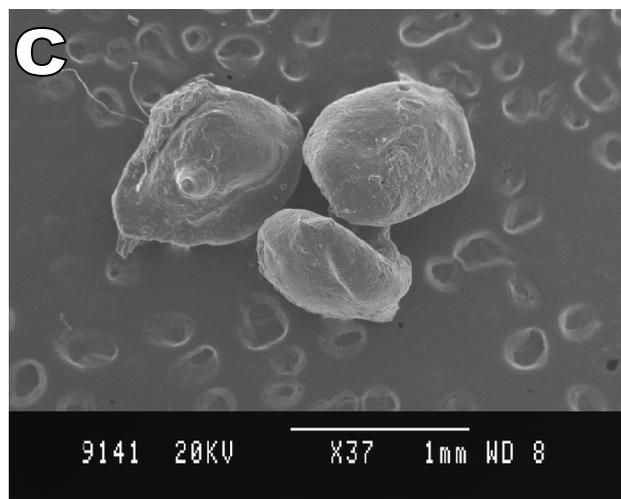
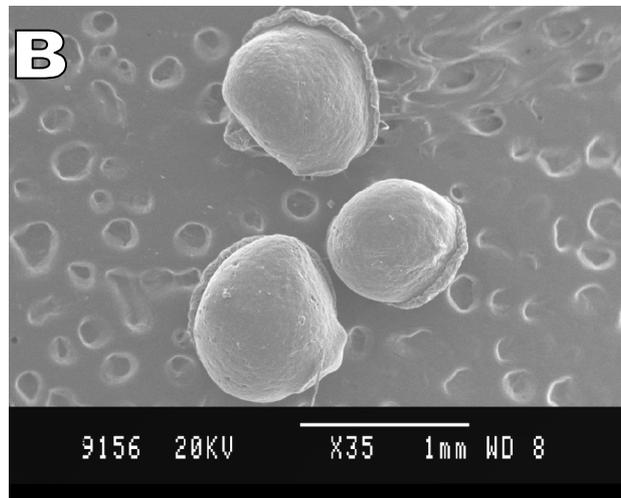
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Figure 1: Scanning electron microscopy of prepared Metformin mucoadhesive microcapsules: a) M1, b) M2, c) M3, and d) M4





In vitro Mucoadhesion

Microcapsules with a coat consisting of alginate and a mucoadhesive polymer exhibited good mucoadhesive properties (Fig. 2). The formulations containing higher ratio of alginate showed less

mucoadhesion (M13-M16) compared to that of microcapsules having lower percent of alginate (M1-M4). The results (Table 2) indicating that formulations containing carbopol as coating layer showing more mucoadhesion than HPMC,

Chitosan, Gelatine coating formulations. The mucoadhesion of all formulations are as follows

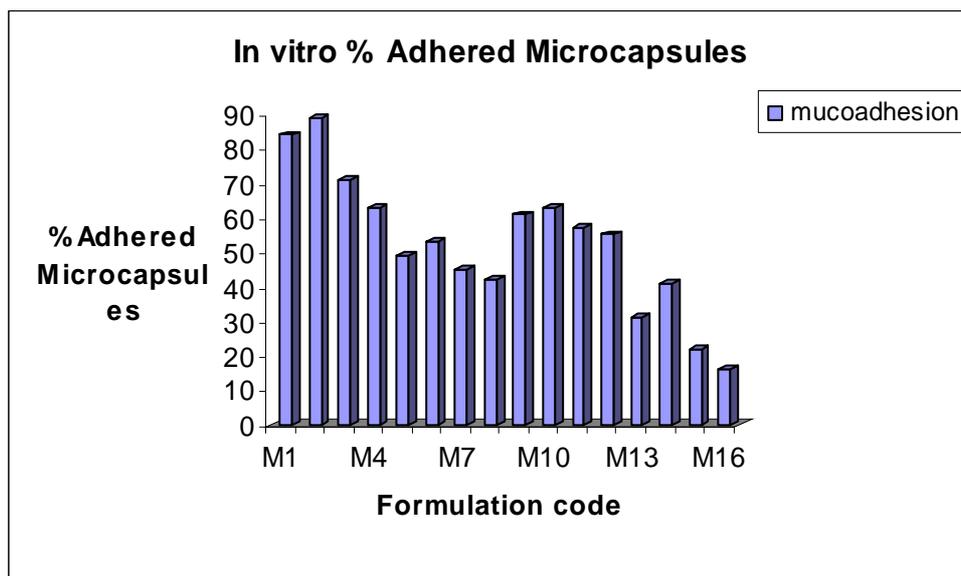
M2>M1>M3>M4>M10>M9>M11>M12>M6>M5>M7>M8>M14>M13>M15>M16.

Table 2: In vitro adhered Microcapsules (%) and Cumulative drug Released (%).

Formulation Code	In vitro % Adhered Microcapsules Mean±(S.D.)	Cumulative % Drug Released Mean±(S.D.)
M1	84±3	94.7
M2	89±4	91.05
M3	71±2	98.24
M4	63±1	98.84
M5	49±1	87.7
M6	53±2	84.7
M7	45±3	89.6
M8	42±2	90.9
M9	61±1	63.7
M10	63±2	59.6
M11	57±3	68.9
M12	55±2	69.7
M13	31±2	74.88
M14	41±3	70.14
M15	22±2	78.7
M16	16±1	80.7

± S.D- Standard deviation for (n=3)

Figure 2: In vitro % Adhered Microcapsules.



In vitro release studies

The *in vitro* release profile of Metformin from microcapsules is shown in Fig. 3a-3d. It was observed that with the increase in the concentration of sodium alginate the release of the Metformin

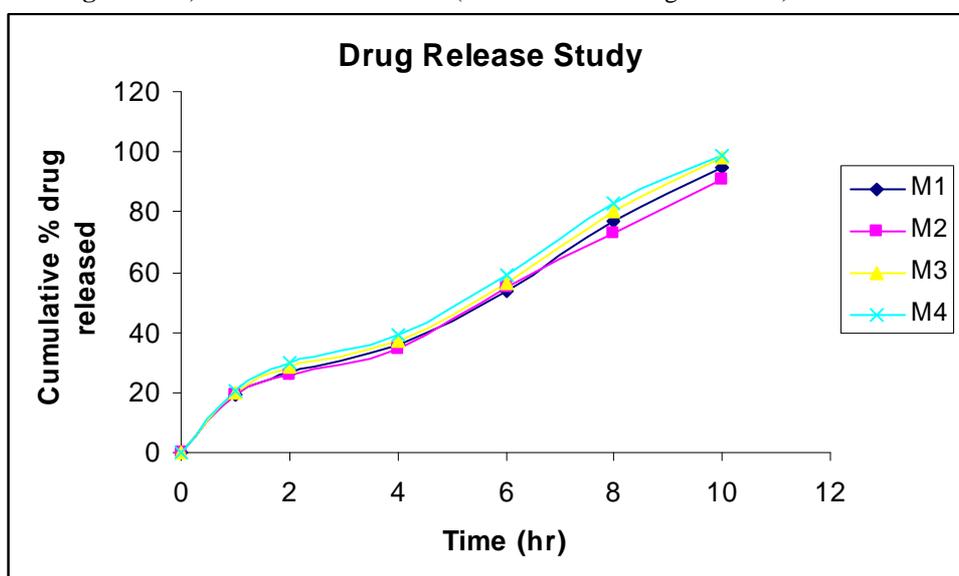
from the polymer matrix was retarded. Hence all polymers show retardation of drug release up to 10 h with nine parts of sodium alginate. In case of carbopol containing formulation, containing one or two parts of carbopol and nine parts of alginate,

showed controlled drug release up to 10 h where as Gelatine containing formulations (one part of Gelatine and one part of alginate) were showed more drug release. Metformin release from the microcapsules was slow and depended on the composition of the coat. Release followed zero-order kinetics after a lag period of 1 hour. Microcapsules of alginate-Gelatine gave relatively fast release when compared to others. The order of increasing release rate observed with various

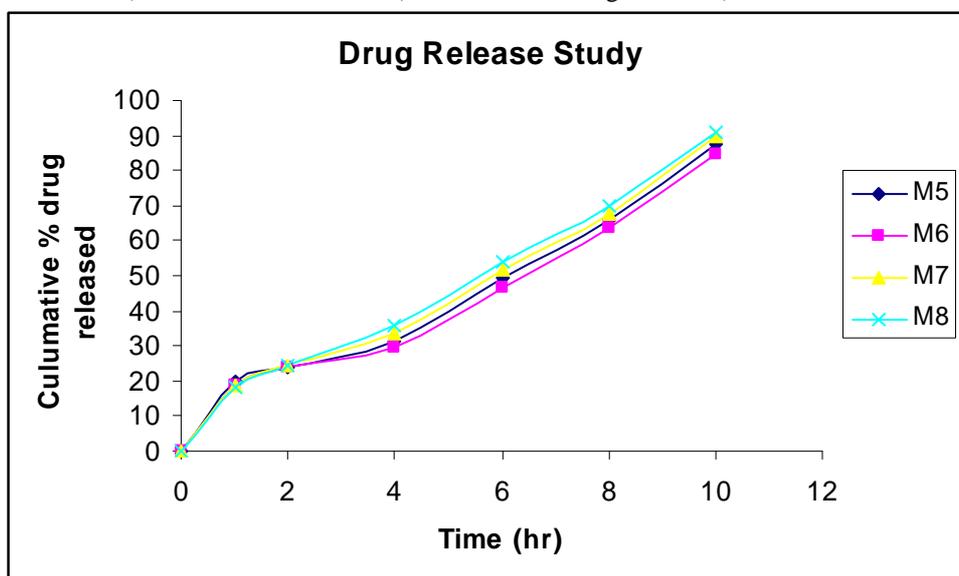
microcapsules was alginate-Carbopol < alginate-HPMC < alginate-Chitosan < alginate-Gelatine.

In comparison (natural polymers to synthetic polymers) alginate:synthetic polymer microcapsules showed more mucoadhesion and prolonged drug release. The drug release was more for M4 mucoadhesive microcapsules than other formulations. M10 microcapsules showed controlled release up to 10 h.

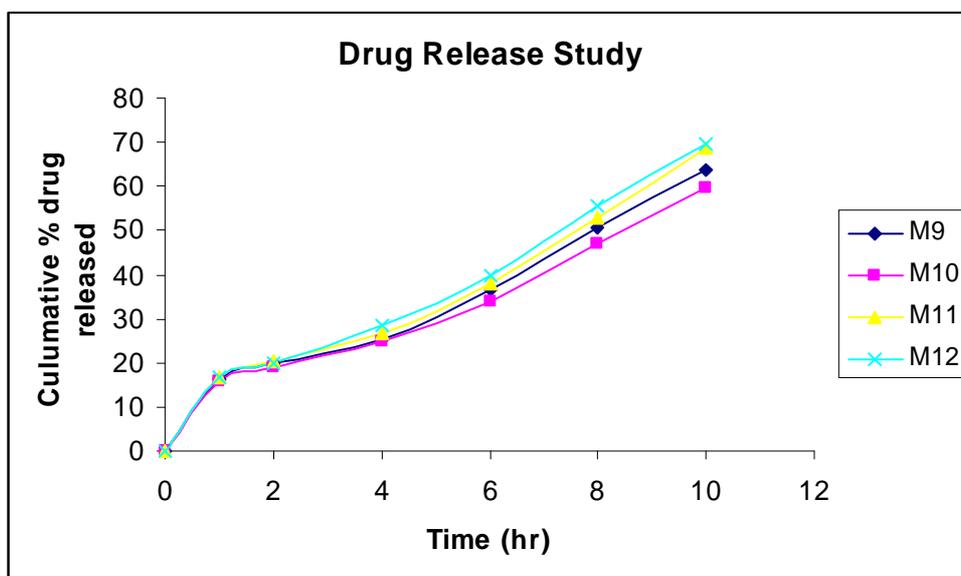
Figure 3: a) In vitro release studies (Cumulative % Drug Released) for M1-M4.



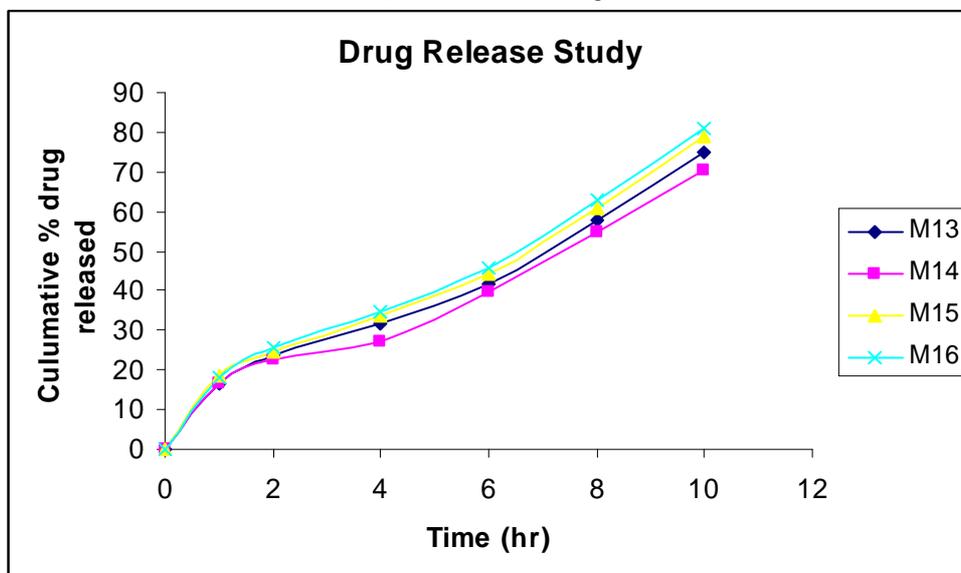
b) In vitro release studies (Cumulative % Drug Released) for M5-M8.



c) In vitro release studies (Cumulative % Drug Released) for M9-M12.



d) In vitro release studies (Cumulative % Drug Released) for M13-M16.



CONCLUSIONS

A successful attempt has been made to formulate mucoadhesive alginate microcapsules of Metformin using alginate and a mucoadhesive polymer (Carbopol, HPMC, Chitosan, or Gelatine) could be prepared by an orifice-ionic gelation process. The microcapsules exhibit good mucoadhesive property in an *in-vitro* mucoadhesion test. Metformin release from these mucoadhesive microcapsules was slow and extended over longer period of time and depends on the composition of coat. Drug release

was diffusion control and followed zero order kinetics. These mucoadhesive microcapsules are thus suitable for oral control release of Metformin.

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