BioGecko

Vol 12 Issue 03 2023

ISSN NO: 2230-5807

Design and evaluation of *Mimosa pudica*seed mucilage based microspheres of metformin hydrochloride: *In-vitro* characterization

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Abstract

The metabolic disorder type 2 diabetes mellitus continuously increasing in the world. This disorder affecting all age groups. Thus, this disorder is now creating burden on healthcare sector, especially in case of underdeveloped countries. Nowadays many conventional drug delivery systems are available for management of diabetes mellitus. The mucilages are polysaccharide obtained from various seeds. Thus, present study is started with aim to formulate *Mimosa pudica*seed mucilage based microspheres for gastroretentive delivery of metformin hydrochloride. The drug loaded microspheres were formulated using ionic gelation method and evaluated for physicochemical properties, mucoadhesive potential, swelling index and *in vitro* drug release study. The microspheres showed acceptable physicochemical properties, good swelling ability, mucoadhesive potential and sustained drug release. Thus, *Mimosa pudica*mucilage could be promising alternative for fabrication of gastroretentive drug delivery system.

Keywords: Metformin hydrochloride, *Mimosa pudica*, Natural Mucilage, Microspheres

1. Introduction

The oral route is most common, safe and convenient route of drug administration. The solid oral dosage form like tablet is most popular oral dosage form because of ease of handling, large scale production and stability[1]. About 80% oral dosage forms are available in the form of tablet. However these dosage forms suffer with number of limitations like;the daily administration of dosage form is require which is difficult to monitor and greater chance of missing dose. The dosage form like tablet is available with fixed strength thus careful calculation is required to prevent overdosing. It is difficult to calculate exact dose of drug required for a child and geriatric patients.

Extensive researches have been conducted to minimize the limitations associated with conventional drug delivery systems. The fruitful outcome of these researches is developed modified drug release systems. The desirable characteristic of such system is the duration of drug action. The controlled release system should provide therapeutic drug concentration for prolonged period of time. This can be achieved by controlled release of drug from system. The controlled release is possibly achieved by combining drug with the release modifying polymer. The polymer used to control release of drug from system. This could possibly prolong the duration of drug action. The objective behind formulation of such system is to improve patient compliance by ensuring safety and enhanced efficacy of drug. This could be ensured by controlling plasma drug concentration and reducing dosing frequency.

Gastroretentive drug delivery systemis anovel approach to prolong gastric residence time, these dosage forms can retain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs[2].Another important approach to prolonged gastric residence time of drug delivery system is the use of bioadhesive/mucoadhesive polymers [3].

The surface epithelium of stomach constantly exposes to gastric fluid which contains highly concentrated hydrochloric acid (approximately 0.16 N) and protein digesting enzyme, pepsin. Thus in order to maintain integrity, the surface epithelium has self-protective mechanism i.e. mucus. Mucus contains mucin i.e.

oligosaccharides with sialic acid (pKa=2.6) and glycoproteins which are capable to neutralize HCl thus protects the epithelium.

The adhesive properties of mucus layer have been recognized and used for development of gastroretentive system. The drug delivery system consists of drug core coated with mucoadhesive polymer. Thus, after ingestion of such system, the mucoadhesive polymer hydrates and bind/adhere to mucin molecules in mucus lining of stomach. This enables the device to retain in stomach for extended period of time by resisting gastric emptying. The drug molecules contain in core are constantly released in stomach for absorption. A bio/mucoadhesive polymer is a natural or synthetic polymer capable of adhere to biological membrane, which is then called a bioadhesive polymer or with the mucus lining of the GIT, which is then called a mucoadhesive polymer. Several approaches have been utilized for incorporation of drug in mucoadhesive polymer for preparation of gastroretentive system. For water soluble polymer it is possible to use polymer to coat the surface of microsized capsule shape drug core. The duration of gastric retention of such system is controlled by dissolution of mucoadhesive polymer.

The use of natural excipients as carriers in drug delivery systems is recent trend of oral drug delivery. At present, socio-economic condition of the modern world has elevated the interest of natural polymers. Environmental concerns are also playing considerable role and contributing to the growing interest in natural polymers due to their biocompatibility, biodegradability and low processing cost[4].Naturally obtaining polymers are diverse class of macromolecules with a wide range of pharmaceutical applications. Various natural polymers can be classified as proteins-based natural polymers like collagen[5], gelatin, silk fibroin, fibrinand natural polysaccharides like chitosan, starch, alginate, gellan gum, pectin, gum acacia, gum tragacanth, guar gum. These polysaccharides have some excellent water solubility as well as swelling potential, which eventually useful for oral controlled drug delivery.

Natural gums obtained from different parts of the plant. Chemically these are polysaccharides containing monosaccharides blocks joined in linear as well as branched fashion. Thus, hydrolysis of gums result in formation of various sugar units. Gum acacia and tragacanth are most common gums used in pharmaceutical formulations since long period of time. These gums are produced by the plant as part of protection mechanisms on injury to the plant. The process of formation of gum is termed as gummosis, which indicates breakdown of cell walls [4]. Many scientific experts have investigated use of natural gums in various drug delivery systems.

The term mucilage indicates substances which have high water absorbing and swelling capability on contact with water. Several species of mucilaginous species of plants have been used in traditional system of medicine in the world since last 4000 year.Mucilage found in seed endosperms, roots and rhizomes may act primarily as energy reserves [4]. Chemically these are high molecular weight (approx. 200,000 Da) compounds consisting of sugar and uronic acid units. These are generally sulphuric acid esters and have a complex structure of polysaccharide. The high-water absorbing capability of mucilage is due to presence of hydroxyl groups in sugar structure of mucilages. However, upon addition of alcohol, mucilages are precipitated in the form of amorphous or granular mass [6].

Many scientific investigators have utilized plant derived mucilage for development of nano and microcarrier based systems. Mucilage obtained from Quince seeds mainly contains glucuronic acid[7]. The mucilage act as an emulsifier as well as foaming agent[8]. It also acts as thickening agent because of its high molecularweight.Akram et al. 2022 [9] formulated cefixime loaded Quince seeds mucilage-sodium alginate microspheres for sustained oral drug delivery. Formulated microcarrier based systems showed sustained drug release behavior with non-Fickian type of drug release pattern. In addition to this, the formulated microspheres showed enhanced antibacterial potential with minimum toxicity. The slow drug release is due to controlled release of cefixime across gum-alginate matrix. Ghumman et al. 2019 utilized [10] Taro corn mucilage for fabrication of alginate beads. Taro corn is *Colocasiaesculenta*, which is normally cultivated in Asia. Taro corn contains rich percentage of mucilage which is generally used as

binder in tablets and emulsifier. In addition to this, it has good swelling ability in aqueous medium and mucoadhesive potential. The pregabalin loaded Taro corn-alginate microspheres were formulated using ionic gelation technique. The formulated microspheres showed acceptable particle size and surface characteristics. The drug release pattern was sustained following Korsmeyer-Peppas model. In addition to this, the microspheres showed better bioavailability of drug compared to free drug. Thus, natural mucilages are viable mucoadhesive agent for sustained delivery of drug.

Thus present study has started with aim to formulate *Mimosa pudica*seed mucilage based microspheres of metformin hydrochloride for prolonged gastroretention.

2. Materials and methods

Metformin hydrochloride was purchased from Zenvito Healthcare, India. *Mimosa pudica*seeds were purchased from VR Enterprises, India. Sodium alginate and calcium carbonate were purchased from S. D. Fine Chemicals Ltd., India. All other regents, chemicals and solvent were laboratory grade and purchased locally.

2.1 Isolation and characterization of *Mimosa pudica* mucilage

Mucilage of M. pudica was isolated according to method reported by Singh et al., 2009 [67]. Briefly, 100 gram of M. pudica seeds were soaked in 500 ml of water for 10 hours for hydration of seeds. The hydrated mucilage along with seeds were dried in hot air oven at 50◦C. The dried mucilages were sieved through sieve 18 for separation from seeds. The isolated mucilage from seeds was characterized with respect to following parameter.

2.1.1 Assessment of liquid uptake

A modified volumetric glass apparatus was used to assess the liquid uptake of isolated mucilage [68]. Two pipettes of 1 ml capacity were used in present study. The two pipettes were hold vertically on stand and lower end was connected using curved plastic tube to form U shaped glass apparats as represented in figure. The pipettes were filled with appropriate volume of water and height of water was adjusted in both pipettes. The 100 mg of mucilage was taken on piece of absorptive filter paper and placed on top end of the first pipette as highlighted in below figure. As result of water absorption by the mucilage, height of water in second pipette reduces. This reduction in water level from second pipette was recorded at various time intervals. The experiments were performed in triplicate and mean
uptake was calculated.

2.2 Design of *Mimosa pudica* mucilage-alginate microspheres

Metformin hydrochloride loaded microspheres were formulated using ionic gelation technique [54]. Briefly appropriate quantities of *Mimosa pudica* mucilage and sodium alginate were dissolved in distilled water with continuous stirring to polymeric solution. The weighed quantity of metformin hydrochloride was dissolved in polymeric solution with continuous stirring. The ratio of polymer to drug was maintained as 2:1. The resulting medicated polymeric solution was injected in 100 ml of 7% w/v calcium chloride solution using 24-G needle with continuous stirring at 500 rpm using magnetic stirrer. The resulting polymeric dispersion was stirred for 30 minutes for crosslinking of alginate in presence of calcium ions. After stirring continuous stirring for specified time, the dispersion was kept in standing for 1 hour for complete crosslinking of polymer. After 1 hour the microspheres were collected by filtration, washed with double distilled water and finally dried in hot air oven at 40°C for 10 hours.

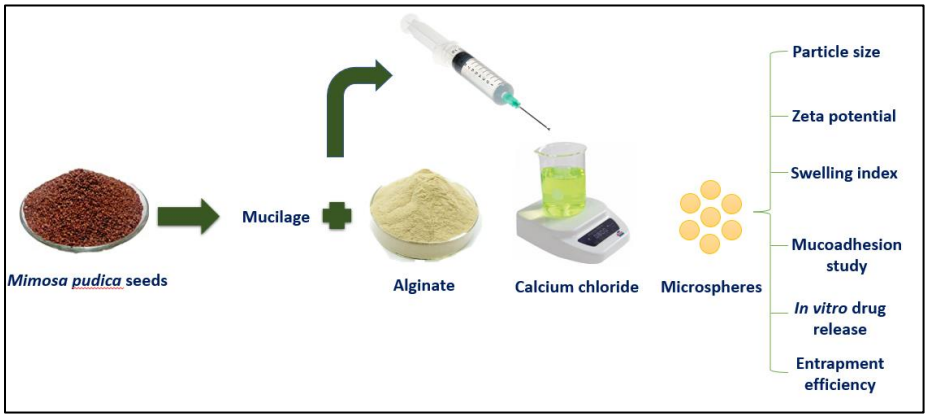

Figure 1 Overview of preparation and evaluation of microspheres

2.3 Evaluation of *Mimosa pudica* mucilage-alginate microspheres

2.3.1Assessment of particle size

Particle size of metformin hydrochloride loaded mucilage-alginate microspheres was assessed by optical microscopy using calibrated eyepiece and stage micrometers. Briefly, 50 mg of drug loaded microspheres spread over the surface of glass slide and particle diameter of 100 particles was measured.

2.3.2 Measurement of entrapment efficiency

The entrapment of metformin hydrochloride in mucilage-alginate micromatrix was quantitatively measured in percentage using UV spectrometric measurement. The dried drug loaded microspheres were finely ground using mortar pestle to obtain fine powder. The powder (equivalent to 20 mg of metformin) was weighed and dispersed in phosphate buffer pH 6.8. The resulting dispersion was stirred on 12 hours and filtered. The filtrate was diluted ten times using phosphate buffer and subjected to spectrometric measurement at 233 nm [42]. The entrapment efficiency of metformin hydrochloride in microspheres was then calculated using following equation.

$$\text{Percent entrapment of metformin hydrochloride} = \frac{W_p}{W_t} \times 100$$

Where, W_p is practical content ofmetformin hydrochloride in dispersion and W_t is theoretical content of metformin hydrochloride in microspheres (20 mg).

2.3.3 Assessment of metformin hydrochloride release behavior

The dialysis membrane drug diffusion method was used for assessment of metformin hydrochloride release [84]. Dialysis membrane (Mol. weight: 12–14 kDa) was soaked in distilled water overnight. The metformin hydrochloride encapsulated microspheres weredispersed in 5 ml of distilled water. The resulting dispersion was filled in membrane and closed at both ends using dialysis bag locks. The microspheres equivalent to 10 mg of metformin hydrochloride was taken for drug release study. The weight of dried microspheres required was calculated based on entrapment efficiency study. The resulting dialysis membrane was fixed on USP type II dissolution apparatus. The drug release study was carried out in 500 ml of 0.1N HCl for first 2 hours. After 2 hours the release medium was change to phosphate buffer pH 6.8 for next 14 hours. The temperature of the both release mediums was adjusted to 37°C ± 0.5 °C. The rotational speed of the paddle was fixed at 50 rpm. At fixed time intervals from start of study, the 2 mL of release medium was withdrawn and subjected to UV-spectrophotometry for assessment of extent of metformin hydrochloride release in medium.

2.3.4 In vitro mucoadhesive behavior

The mucoadhesion potential of formulated microspheres was assessed on porcine intestinal mucosa. The intestine was obtained from a local slaughterhouse. The isotonic saline solution was used to wash the intestine and pieces of dimension 2×4 cm were made. The piece of intestine was mounted on a glass slide separately and slide was fixed at an angle of 45°[11].

The 50 mg of dried microspheres were accurately weighed and sprinkled over the surface of each piece of intestinal mucosa. The isotonic solution was sprinkled over the microspheres and kept for 15 minutes for hydration and swelling of microspheres. After hydration, the 50 ml of isotonic saline (37^0C) was passed through the mucosa at a flow rate of 5 ml/ min and collected in pre-weighed petri plate. Finally, the collected saline solution was subjected to evaporation and weight of petri plate was recorded after complete evaporation of saline solution. Based on initial weight of microspheres applied on mucosa and weight of dried microspheres collected in petri plate, the weight of microspheres adhere to mucosa was calculated. The percentage mucoadhesion was calculated using following equation.

$$\% \text{ Mucoadhesion} = \frac{\text{Wt. of microspheres adhere to mucosa}}{\text{Wt. of microspheres initially added}} \times 100$$

3. Results and Discussion

3.1 Isolation and characterization of *Mimosa pudica* mucilage

The mucilage from *Mimosa pudica*seeds were isolated with distilled water as highlighted in figure 2. The extracted mucilage was dried in hot air oven at 50^0C [12]. The resulting dried mucilage was transferred through sieve to obtain dried free flowing powdered mucilage [13]. Initially mucilage was checked for organoleptic properties like colour, odor, taste and texture. The results are highlighted in table 1. The odorless mucilage was brownish in colour. The taste of mucilage was mucilaginous with smooth texture. After initial evaluation, the mucilage was subjected to spectroscopic measurement and thermal analysis.

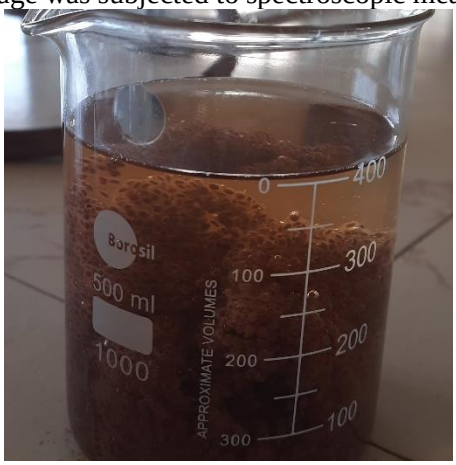

Figure 2 Isolation of mucilage from *Mimosa pudica*seed

Table 1 Organoleptic properties of *Mimosa pudica*mucilage

Colour	Odour	Taste	Texture
Brownish	None	Mucilaginous	Smooth

3.1.1 Assessment of liquid uptake

The water uptake characteristic of isolated mucilage was assessed using specially fabricated 'U' shaped glass water uptake study apparatus. The water absorption characteristic mucilage governs its mucoadhesive performance. Prior to the mucoadhesion, the mucilage must hydrate by absorption of water from biological fluid. Thus, initially water uptake characteristic of mucilage was assessed. The isolated mucilage showed good water uptake capability with maximum 0.137 ml of water absorption over the period of 7000 seconds as highlighted in figure 3. Thus, isolated mucilage could be good for formulation of drug loaded microspheres [14].

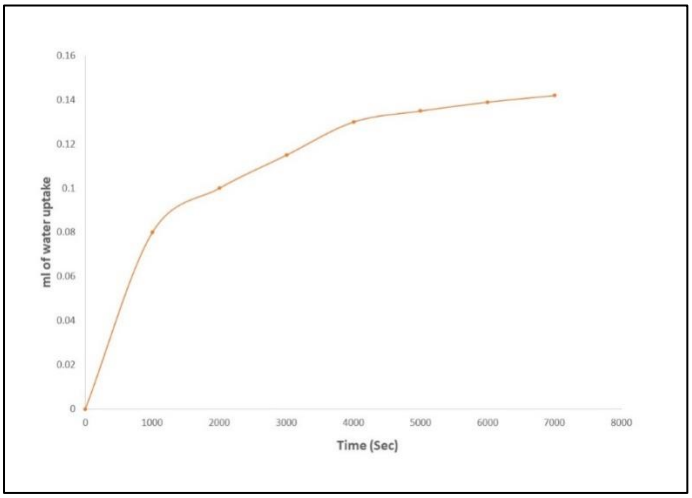

Figure 3 Water uptake characteristic of isolated mucilage

3.2 Design of *Mimosa pudica* mucilage-alginate microspheres

Metformin hydrochloride loaded microspheres were formulated using ionic gelation technique. The gelation of sodium alginate in presence of divalent calcium ions was used for fabrication of micron sized particles. The matrix of microsphere was prepared by combination of sodium alginate and *Mimosa pudica*mucilage [15]. The crosslinked polymeric microspheres were collected by filtration and dried at 40^0C. The microspheres were spherical in shape with light brown colour due to presence of mucilage as highlighted in figure 4. The spherical shape of microspheres was maintained by slow injection of polymeric solution with continuous stirring at fixed rate.

Figure 4 Metformin loaded *Mimosa pudica*mucilage containing microspheres of sodium alginate

3.3 Evaluation of *Mimosa pudica* mucilage-alginate microspheres

3.3.1Assessment of particle size

The particle size of formulated mucilage-alginate based microspheres was measured using optical microscopy. The dried microspheres were spread on the clean glass slide and subjected to particle size measurement using compound microscope and calibrated eyepiece micrometer. The particle diameter of 100 particle was randomly measured and mean particle size was calculated [16]. The particle size distribution was assessed by plotting particle size distribution curve as highlighted in figure 5. The mean particle size was found to be in the range of 687.4 to 702.8 micrometer.

3.3.2 Measurement of entrapment efficiency

Percent entrapment of metformin in dried microspheres was assessed using UV spectrometric measurement. All batches of formulated microspheres showed percent entrapment in the range of 71 to 75%.

3.3.3 Assessment of metformin hydrochloride release behavior

In vitro metformin release behavior from formulated mucilage-alginate microspheres was assessed using dialysis diffusion technique. The release study was performed in both acidic as well as basic buffers. The 0.1 N HCl was selected as an acidic medium and Phosphate buffer pH 6.8 was selected as basic medium for assessment of drug release behavior [17]. The drug release profile has highlighted in figure 6. The initial burst release of metformin was observed in first two hours, with almost 40 % of drug release. The initial burst release of drug could be due initial release of drug loaded at the surface of microsphere matrix. After two hours, the sustained drug release was observed for next 14 hours. The sustained drug release could be due to slow penetration of drug across mucilage-alginate microsphere matrix.

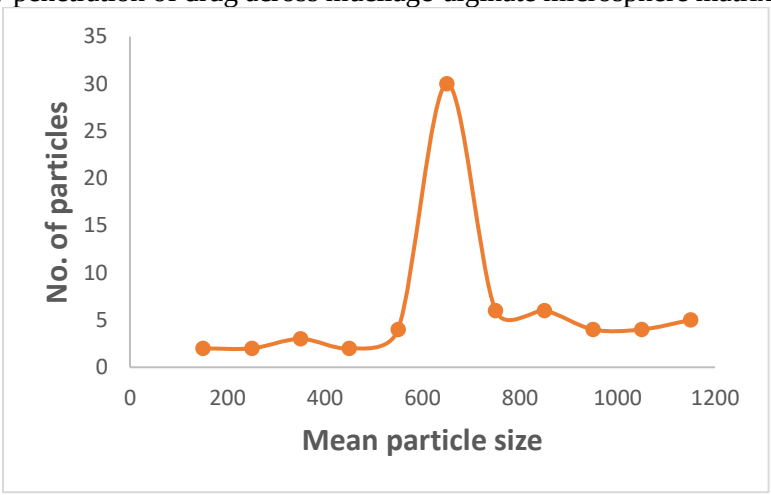

Figure 5 Particle size distribution of mucilage-alginate microspheres.

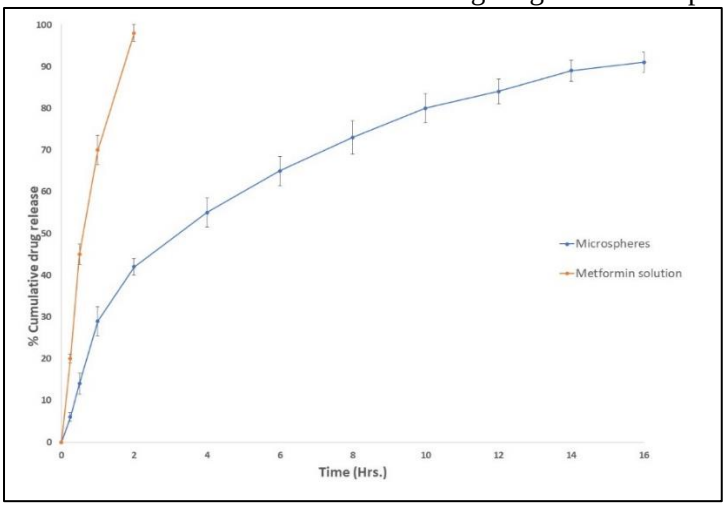

Figure 6 *In vitro* drug release profile of mucilage-alginate microspheres.

3.3.4 In vitro mucoadhesive behavior

Assessment of mucoadhesion potential and swelling ability of microspheres is essential evaluation parameter governing *in vivo* performance of microspheres based systems. The swelling behavior of microsphere in presence of phosphate buffer pH 6.8 has represented in figure 7. The microspheres showed increase swelling capability up to 8 hours with almost 79 % swelling index. After the 8 hours

swelling behavior of microspheres was progressively decline up to 12 hours [18]. The reduction in swelling of microspheres after 8 hours could be due to slow erosion of polymer. The percent mucoadhesion of mucilage-alginate microspheres on porcine intestinal mucosa was found to be 72.19 ± 1.8%. The formulated microspheres showed acceptable swelling and mucoadhesion capabilities.

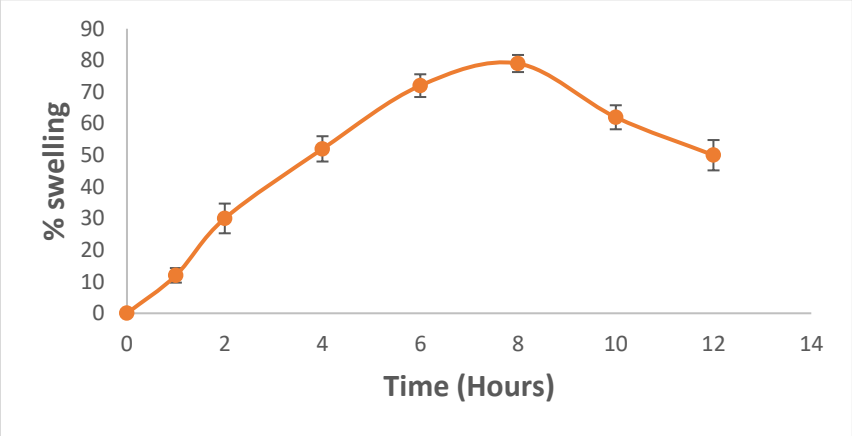

Figure 7 Swelling behavior of mucilage-alginate microspheres.

4. Conclusion

The metabolic disorder type 2 diabetes mellitus continuously increasing in the world. This disorder affecting all age groups. Thus, this disorder is now creating burden on healthcare sector, especially in case of underdeveloped countries. Nowadays many conventional drug delivery systems are available for management of diabetes mellitus. However, theses drug delivery systems are suffers with many limitations like poor bioavailability, short biological half-life and off target distribution. Metformin is oral antihyperglycemic drug normally use for management of type 2 diabetes mellitus. The mucilages are polysaccharide obtained from various seeds. Many scientific investigators have proved mucoadhesion capability and swelling potential of mucilage. These natural polysaccharides can be interacted with mucin by forming weak bonding and stay in contact with gastrointestinal mucosa for prolonged period of time. Thus, mucilage based microspheres can retain in stomach for prolonged period of time and eventually enhance gastric retention time of loaded drug. Thus, present investigation was initiated to utilize natural mucilage for controlled mucoadhesive delivery of metformin. The mucilage extracted from *Mimosa pudica*seeds was used in present investigation. The mucilage was extracted from *Mimosa pudica*seeds and evaluated. The mucilage showed acceptable organoleptic properties and water uptake capability. The FTIR spectroscopy and DSC confirmed isolation of mucilage in pure form without impurities. Metformin hydrochloride loaded microspheres were formulated using ionic gelation technique. The gelation of sodium alginate in presence of divalent calcium ions was used for fabrication of micron sized particles. The matrix of microsphere was prepared by combination of sodium alginate and *Mimosa pudica*mucilage. 3^3 Box Behnken Study design was used for optimization. Polymer concentration, polymer/drug ratio and calcium chloride concentrationare three variables selected at three concentration for optimization. The mean particle size was found to be in the range of 687.4 to 702.8 micrometer. All batches of formulated microspheres showed percent entrapment in the range of 71 to 75%. The sustained drug release pattern was observed for 16 hours. The FTIR spectroscopy and DSC confirmed loading of drug in microspheres matrix. In addition to this, the percent mucoadhesion of mucilage-alginate microspheres on porcine intestinal mucosa was found to be 72.19 ± 1.8%. The above results shows usefulness of *Mimosa pudica*-alginate microspheres for sustained oral delivery of metformin hydrochloride.

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