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Design and Evaluation of Natural Mucilage Microspheres of Sesamol for Gastroretentive Drug Delivery

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Abstract: The mucilages are polysaccharide obtained from various seeds. The mucilage have good swelling and water holding capacity. The mucoadhesive potential of mucilage is recently explored area. Thus, present study aimed to formulate *Mimosa pudica* mucilage based microspheres for gastroretentive delivery of sesamol. 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 good particle size and drug entrapment. The good swelling ability, mucoadhesive potential coupled with sustained drug release could be promising for gastroretentive drug delivery. Thus, natural mucilage could be alternative carrier for preparation of mucoadhesive microspheres of drug.

Keywords: Sesamol, Natural mucilage, *Mimosa pudica*, Microspheres, Gastroretentive drug delivery

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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. 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 (Nalawade *et al.*, 2023).

Extensive researches have been conducted to minimize the limitations associated with conventional drug delivery systems (Rai *et al.*, 2023). The fruitful outcome of these researches is developed modified drug release systems (Gupta *et al.*, 2022b). 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 (Gupta *et al.*, 2022a). The controlled release is possibly achieved by combining drug with the release modifying polymer. The polymer used to control release of drug from system (Sansare *et al.*, 2019). 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 (Gupta *et al.*, 2021). This could be ensured by controlling plasma drug concentration and reducing dosing frequency (Sansare *et al.*, 2020).

Gastroretentive drug delivery system is a novel 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 (Boddupalli *et al.*, 2012). Another important approach to prolonged gastric residence time of drug delivery system is the use of bioadhesive/mucoadhesive polymers.

The surface epithelium of stomach is constantly exposed 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 ($pK_a=2.6$) and glycoproteins which are capable to neutralize HCl which 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 contained 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 micro-sized 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. 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, gelatin, silk fibroin, fibrin and 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 are 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. 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. 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.

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. The mucilage act as an emulsifier as well as foaming agent. It also acts as thickening agent because of its high molecular weight. Akram *et al.* (2022) 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. Ghuman

et al. (2019) utilized Taro corn mucilage for fabrication of alginate beads. Taro corn is *Colocasia esculenta*, 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 aimed to formulate *Mimosa pudica* based microspheres of sesamol for prolonged gastroretention.

Materials and Methods

Sodium alginate and calcium carbonate were purchased from S. D. Fine Chemicals Ltd., India. *Mimosa pudica* seeds were purchased locally. All other reagents, chemicals and solvent were laboratory grade and purchased locally.

Design of drug loaded microspheres:

Sesamol loaded microspheres were formulated using ionic gelation technique as illustrated in Figure 1. 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 sesamol 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 min for crosslinking of alginate in presence of calcium ions. After continuous stirring for

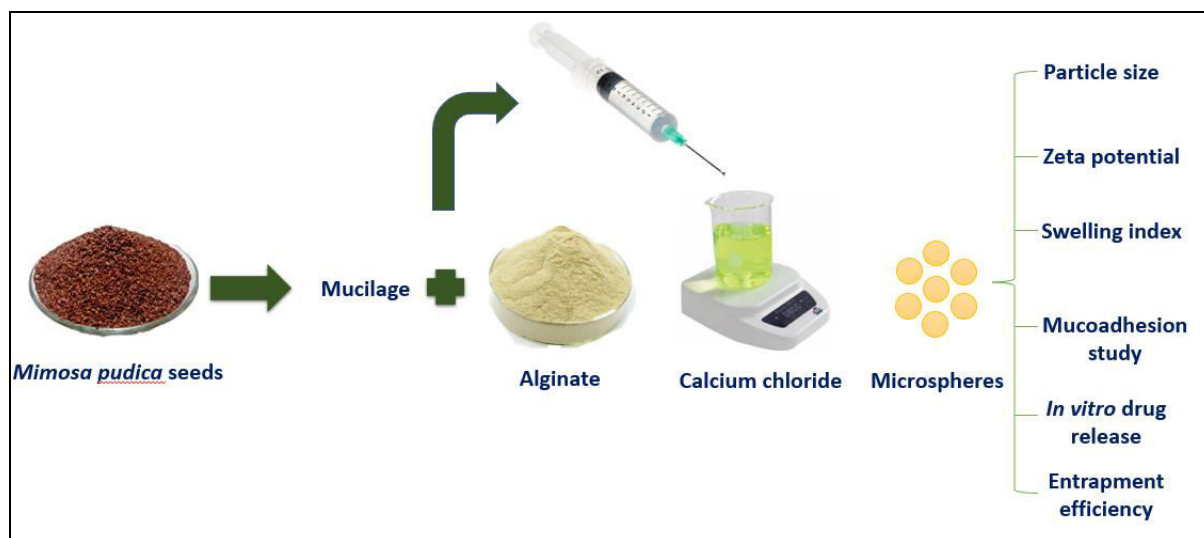


Fig. 1: Overview of preparation and evaluation of microspheres.

specified time, the dispersion was kept in standing for 1 h for complete cross-linking of polymer. After 1 h the microspheres were collected by filtration, washed with double distilled water and finally dried in hot air oven at 40°C for 10 h.

Evaluation of mucilage-alginate microspheres:

Assessment of particle size:

Particle size of sesamol loaded mucilage-alginate microspheres was assessed by photon correlation spectroscopy principal using Zetasizer Nano ZS (Malvern instruments, UK). Briefly, 50 mg of drug loaded microspheres was dispersed in 5 ml double distilled water and resulting dispersion was subjected to particle size measurement at 24 °C.

Measurement of entrapment efficiency:

The entrapment of sesamol 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 40 mg of powder (equivalent to 20 mg of metformin) was weighed and dispersed in phosphate buffer pH 6.8. The resulting dispersion was stirred on 12 h and filtered. The filtrate was diluted ten times

using phosphate buffer and subjected to spectrometric measurement. The entrapment efficiency of sesamol in microspheres was then calculated using equation:

$$\text{Per cent entrapment of sesamol} = \frac{W_p}{W_t} \times 100$$

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

Assessment of drug release behavior:

The dialysis membrane drug diffusion method was used to assess sesamol release. Dialysis membrane (Mol. weight: 12–14 kDa) was soaked in distilled water overnight. The sesamol encapsulated microspheres were dispersed 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 sesamol 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 0.1 N HCl for first 2 h. After 2 h the release medium was changed to phosphate buffer pH 6.8 for next 8 h. The

temperature of the both release mediums was adjusted to $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. 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 sesamol release in medium.

In vitro mucoadhesive behavior:

The mucoadhesion potential of formulated microspheres was assessed on goat intestinal mucosa. The intestine was obtained from a local slaughter house. 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° .

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 min for hydration and swelling of microspheres. After hydration, 50 ml of isotonic saline (37°C) 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:

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

Results and Discussion

Design of drug loaded microspheres:

Sesamol 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. The crosslinked polymeric microspheres were collected by filtration and dried at 40°C . The microspheres were spherical in shape with white colour due to presence of mucilage as illustrated in Figure 2 (Abrar, 2020).



Fig. 2: Formulated *Mimosa pudica* mucilage-Alginate microspheres.

Evaluation of mucilage-alginate microspheres:

Assessment 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 (Donato *et al.*, 2016).

The particle size distribution was assessed by plotting particle size distribution curve (Fig. 3). The mean particle size was found to be 695.94 micrometer.

Measurement of entrapment efficiency:

Per cent entrapment of metformin in dried microspheres was assessed using UV spectrometric measurement. All batches of formulated microspheres showed per cent entrapment in the range of 71.473%.

Assessment of drug release behavior:

In vitro sesamol release behavior from mucilage-alginate microspheres was assessed using dialysis

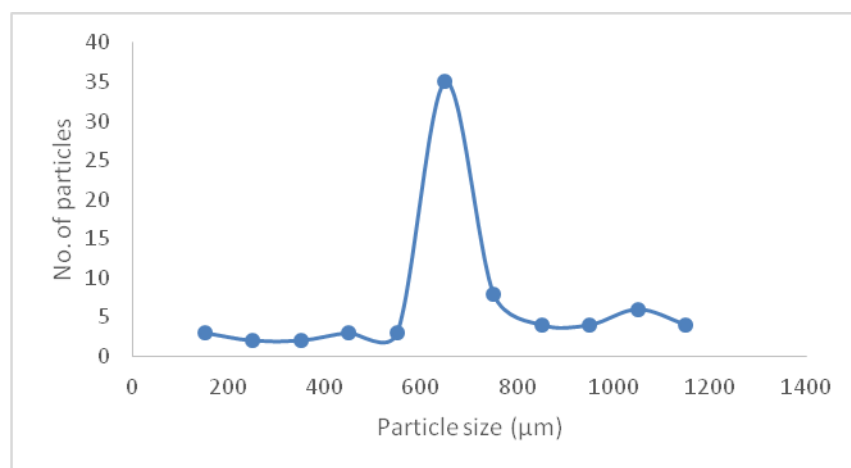


Fig. 3: Particle size distribution of formulated microspheres.

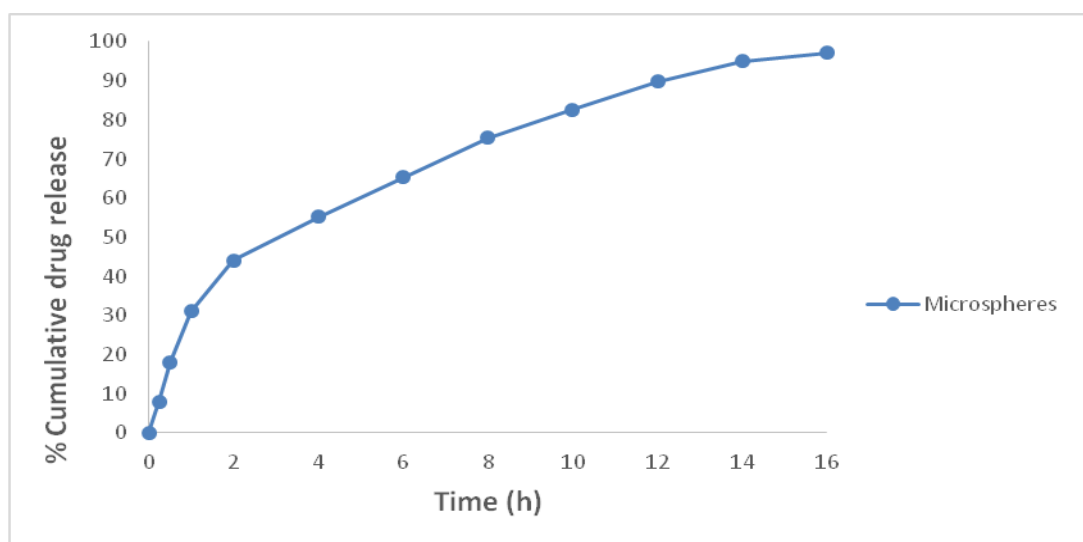


Fig. 4: Drug release profile of *Mimosa pudica* mucilage-alginate based microspheres.

diffusion technique. The release study was performed in both acidic as well as basic buffers. 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. The drug release profile is highlighted in Figure 4. The initial burst release of sesamol was observed in first two hours, with almost 43.16 % of drug release. The initial burst release of drug could be due initial release of drug loaded at the surface of microsphere matrix. After 2h, the sustained drug release was observed for next 14 h. The sustained drug could be due to slow penetration of drug

across mucilage-alginate microsphere matrix. (Gourishetti *et al.*, 2020).

In vitro swelling and mucoadhesive behavior:

The swelling behavior of microsphere in presence of phosphate buffer pH 6.8 is represented in Figure 5. The microspheres showed increased swelling capability up to 8 h with almost 74.17 % swelling index. After 8 h swelling behavior of microspheres was progressively declined. This could be due to breakdown of mucilage. The reduction in swelling of microspheres after 8 h could be due to slow erosion of polymer. The per cent mucoadhesion of mucilage-alginate

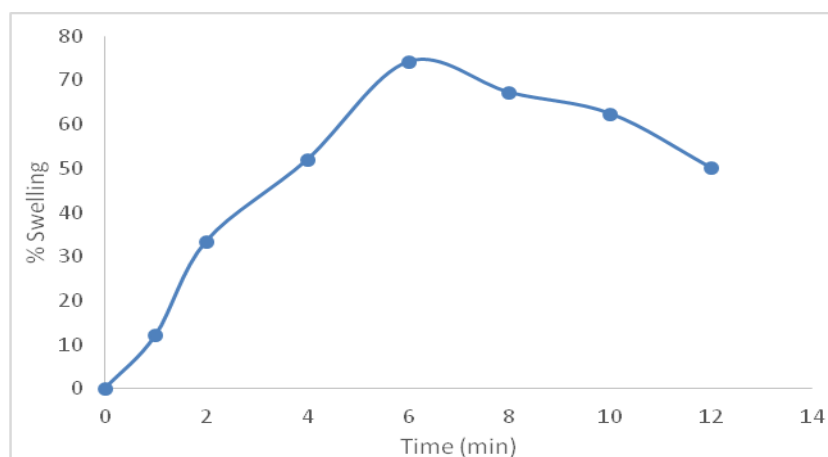


Fig. 5: Swelling behavior of *Mimosa pudica* mucilage-alginate based microspheres.

microspheres on goat intestinal mucosa was found to be $66.16 \pm 1.31\%$. The formulated microspheres showed acceptable swelling and mucoadhesion capabilities.

Conclusion

Many scientific investigators have proved mucoadhesion capability and swelling potential of gum and mucilage. These gum and mucilage can interact with mucin by forming weak bonding and stay in contact with gastrointestinal mucosa for prolonged period of time. Thus, present study was initiated to utilize natural mucilage for controlled mucoadhesive delivery of sesamol. Drug 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 mucilage. The formulated microspheres showed good mucoadhesion and swelling capabilities with sustained drug release profile. The above results showed effectiveness of mucilage for sustained oral drug delivery.

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