Research Article

Design and Evaluation of Ketorolac Tromethamine Drug Loaded Mucilage-Alginate Based Microspheres

Ruturaj P. Jadhav*.
Department of Quality Assurance*. Ashokrao Mane College of Pharmacy, Peth Vadgaon, Kolhapur, Maharashtra, India.
***Corresponding author's E-mail:** jadhavruturaj0760@gmail.com

Received: 16-01-2024; **Revised:** 23-03-2024; **Accepted:** 10-04-2024; **Published on:** 15-04-2024.

ABSTRACT

The present study was started with aim to utilize natural mucilage for sustained delivery of drug. Linum usitatissimum mucilage was selected to formulate drug loaded microspheres. Ketorolac tromethamine (KTM) and Erythriana Indica (EI) microspheres were selected to formulate mucilage-alginate based microspheres. They showed acceptable particle diameter and good stability as predicted from surface charge. The microspheres were formulated, coloaded with drug & evaluated for physical examination, swelling index. The drug content in the microspheres were evaluated using FTIR and DSC. Thus, formulated microspheres could be promising alternative as mucoadhesive novel drug delivery system.

Keywords: Mucilage, Microspheres, FTIR, DSC, Novel Drug Delivery System.

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 required 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.

After oral administration the drug absorbs in systemic circulation and undergoes non-specific distribution in target site as well as off target site. Thus, majority of administered drug undergoes wastage and more amount of drug need to be administered to produce desired pharmacological effect which may precipitates dose dependent side effects. gradually with time. This phase is known as absorption phase where rate of drug absorption is more than rate of elimination.

The therapeutic action of drug starts when concentration of drug in blood plasma reaches in therapeutic window. Once the concentration reaches up to peak level, the descending phase begin. In this phase the concentration declined due to metabolism and excretion thus generally known as elimination phase. During this phase the rate drug elimination is more than its rate of absorption. The therapeutic action of drug is observed until the concentration remains in therapeutic window. The time period during which concentration of drug remains above the MEC is known as duration of action. Once concentration of drug fall below the MEC, the second dose of drug need to be administered to produce desired pharmacological effect. Thus, fluctuations in plasma drug concentration are observed with conventional drug delivery systems. 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.

1.1 Rationale

As mentioned earlier, controlled release drug delivery system was investigated to minimize limitations associated with conventional systems. The controlled release system is defined as the system which releases an encapsulated drug at a predetermined rate so that a constant plasma drug concentration is maintained for extended period of time with minimum side effects. The basic concept behind formulation of controlled release formulations is to alter pharmacokinetics and pharmacodynamics of drugs either by modifying molecular structure or using novel drug delivery principles and physiological parameters. Thus, in depth understanding of pharmacokinetics and pharmacodynamics parameters of drugs is necessary before designing of system. 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.

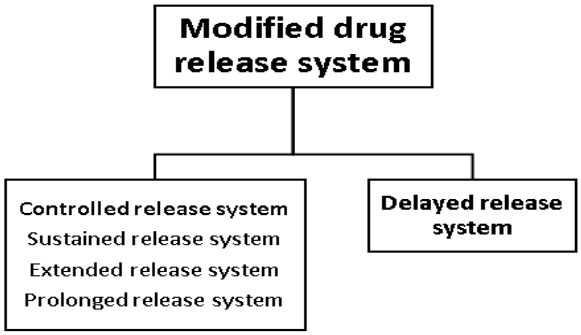
The rationales of controlled release system are highlighted below;

1. To provide controlled release of medicament prolonged duration of drug action.
2. To increase the bioavailability of drug.
3. To provide a location-specific action of drug within the GIT.
4. To reduce dosing frequency and to improve patient compliance.

1.2 Classification of modified release system

Based on the mechanism of drug release control the controlled release system can be classified into following;

1. Diffusion controlled systems
2. Dissolution controlled systems.



1.3 Natural polysaccharides: A promising carrier for oral drug delivery

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.2

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,3 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.

1.3.1 Natural gums

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 results 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.[2]

Many scientific experts have investigated use of natural gums in various drug delivery systems. The gums are commonly used as suspending agent, thickening agent, emulsifying agent, binder, drug release retardant, mucoadhesive agent, gelling agent etc. The commonly used gums and their pharmaceutical applications are represented in below mentioned table.

Table 1: Common natural polysaccharides and their use in drug delivery:

Name of gum	Botanical name	Constituent	Applications in drug delivery
Gum acacia	*Cyamopsis tetragonoloba (Fabaceae)*	Galactose, Mannose	Suspending agent, emulsifier, tablet binder, demulcent and emollient[4]
Gum tragacanth	*Astragalus brachycalyx (Fabaceae)*	Arabino galactans, Pectinaceous	Suspending agent, emulsifier, demulcent and emollient[5]
Almond Gum	*Prunus dulcis (Rosaceae)*	L-arabinose, L-galactose	Adhesive and suspending agent[6]
Tamarind gum	*Tamarindus indica (Fabaceae)*	Glucosyl: Xylosyl: Galactosyl	Drug release retardant[7]
Grewia gum	*Grewia mollis (Malvaceae)*	Galacturonic acid, Rhamnose	Drug release retardant[8]
Khaya gum	*Khaya grandifoliola (*Meliaceae)	L-arabinose, L-galactose	Drug release retardant[9]
Xanthan gum	*Xanthomonas campestris*	D-mannosyl, D-glucosyl, as well as D-glucosyluronic acid	Stabilizer, suspending agent, emulsifier, gelling agent, tablet binder, matrix in controlled release, bioadhesive enhancer[10]
Albizia gum	*Albizia zygia (Fabaceae)*	Mannose, Arabinose	Emulsifier[11]

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.[12]

Some important plants and their parts yielding mucilages are presented below:

Table 2: Botanical sources, constituents and pharmaceutical applications of common mucilages.

Common name	Botanical name	Constituent	Applications in drug delivery
Mimosa mucilage	*Mimosa pudica (Fabaceae)*	D-glucuronic acid, D-xylose	Drug release retardant[13]
Hibiscus rosa-sinensis	*Hibiscus rosa-sinensis (Malvaceae)*	D-glucuronic acid, Rhamnose	Binder and drug release retardant[14]
Asario Mucilage	*Lepidium sativum (Brassicaceae)*	Galactose, Mannose	Emulsifier and suspending agent[14]
Fenugreek Mucilage	*Trigonella foenum-graecum (Fabaceae)*	Galactose, Mannose	Drug release retardant[14]
Aloe Mucilage	*Aloe vera (Xanthorrhoeaceae)*	Galactan, Arabinan, D-glucuronic acid	Drug release retardant[14]
Phoenix Mucilage	*Phoenix dactylifera (Arecaceae)*	Cellulose, Mannose, Pectin	Binder[14]
Cassia tora Mucilage	*Senna tora (Fabaceae)*	Tannins, Cinnamaldehyde	Binder and suspending agent[14]
Cocculus Mucilage	*Cocculus hirsutus (Menispermaceae)*	Carbohydrates	Gelling agent[14]
Cordia Mucilage	*Cordia dichotoma (Boraginaceae)*	Carbohydrates	Binder and emulsifier[14]
Ocimum Mucilage	*Ocimum americanum (Lamiaceae)*	Galacturonic acids, Rhamnose	Disintegrating agent[14]

1.3 Gum-alginate based microspheres for controlled drug delivery:

Microspheres are spherical, micron sized biocompatible carriers utilize for controlled delivery of encapsulated drugs. The drug loaded in matrix of microspheres is release in controlled manner. Microspheres can be prepared using polymers, proteins and lipids. Recently, natural gum and alginate combination has been explored for fabrication of biocompatible matrix of microspheres. Numerous scientific experts working in pharmaceutical field have investigated various natural gums for formulation of biocompatible microspheres.

Prunus armeniaca gum-alginate combination to enhance bioavailability of tramadol. The tramadol loaded microspheres containing *Prunus armeniaca* gum-alginate was fabricated using ionic gelation method.[15] Infrared spectroscopy was used to confirm drug and excipient compatibility. The microspheres showed sustained delivery of drug following Korsmeyer-Peppas model. In addition to this, formulated microspheres were found to be non-toxic in mice model.

Acacia nilotica gum-alginate microspheres for sustained delivery of naringin. The microspheres showed slow drug delivery up to 6 hours.[16]

Gellan gum and alginate combination for entrapment of metronidazole. The gellan gum-alginate microspheres were crosslinked in present investigation using maleic anhydride. The formulated microsphere released the loaded drug in controlled manner.[17] Successfully utilized two gums i.e., Okra and gellan gums for formulation of metformin hydrochloride loaded microspheres. The drug loaded microspheres containing gums and alginate were fabricated using ionic gelation technique. Fabricated microspheres showed enhanced mucoadhesive potential tested using goat intestinal mucosa.[18] The formulated microcarrier showed acceptable encapsulation efficiency of metformin and sustained drug release behaviour for 10 hours. The mucoadhesive potential of natural gums was investigated in present investigation. Thus, natural gums could be viable alternative to synthetic mucoadhesive for sustained gastrointestinal drug delivery.

Formulated Karaya gum-alginate microbeads for sustained release of D-penicillamine. The drug loaded

microbeads showed better swelling index and sustained drug release up to 35 hours. [19]

Formulated famotidine loaded *Acacia nilotica* gum microspheres for controlled gastrointestinal drug delivery. The formulated microspheres showed acceptable physicochemical properties and controlled famotidine delivery in simulated gastric fluid. [20]

Khaya gum extracted from *Khaya senegalensis* for sustained delivery of metformin. The Khaya gum-alginate microspheres formulated using ionic gelation technique. The formulated metformin loaded microspheres showed sustained drug release behaviour following Korsmeyer-Peppas model. [9]

Successfully utilized two gums i.e., Okra and gellan gums for formulation of metformin hydrochloride loaded microspheres. The drug loaded microspheres containing gums and alginate were fabricated using ionic gelation technique. Fabricated microspheres showed enhanced mucoadhesive potential tested using goat intestinal mucosa.[18] The formulated microcarrier showed acceptable encapsulation efficiency of metformin and sustained drug release behaviour for 10 hours. The mucoadhesive potential of natural gums was investigated in present investigation. Thus, natural gums could be viable alternative to synthetic mucoadhesive for sustained gastrointestinal drug delivery.

Figure 1: Overview of preparation and outcomes of natural gum-based microspheres

Table 3: Overview of natural gum-based microspheres.

Gum	Drug	Microcarrier	Outcome
Prunus armeniaca	Tramadol	Microspheres	Sustained drug release and non-toxicity in animal model
Acacia nilotica	Naringin	Microspheres	Sustained drug release
Gellan gum	Metronidazole	Microspheres	Controlled drug release
Okra and gellan gums	Metformin	Microspheres	Better mucoadhesive potential to goat intestinal mucosa
Karaya gum	Penicillamine	Microbeads	Better swelling index and sustained drug release
Acacia nilotica	Famotidine	Microspheres	Controlled drug release
Khaya gum	Metformin	Microspheres	Sustained drug release
Gum Arabic	Bovine serum albumin	Microbeads	Better swelling index
Okra gum	Metformin	Microspheres	Better swelling index
Acacia gum	Diclofenac sodium	Microbeads	Controlled drug release
Locust bean gum	Aceclofenac	Microspheres	Controlled drug release and better reduction of rat hind pow edema induced by carrageenan
Guar gum	Glipizide	Microspheres	Good mucoadhesive potential

1.4 Ionotropic-gelation of natural polysaccharides:

Ionotropic-gelation is process of crosslinking of polysaccharides in presence of ions. When solution of charged polymer (for example negative charged) is added in solution of counter ions (positive charged), the interaction between opposite charged species take place which eventually responsible for crosslinking of polymeric chains into three-dimensional geometry. The crosslinking of polymeric chain at specified conditions of operation like agitation and temperature results in formation micron sized spherical particles like microspheres, microparticles as well as microbeads.[21]

The various factors like type and concentration of polymer, pH of counter ion solution, stirring rate affects the ionic crosslinking process. This process is used by many scientific experts for fabrication of polymeric microspheres, microbeads and microparticles.

The major limitations of this technique are;

i) Reduced entrapment efficiency of drug due to leakage of drug during crosslinking of polymer.

ii) The burst release of drugs from alginate microspheres due to quick biodegradation of crosslinked alginate.

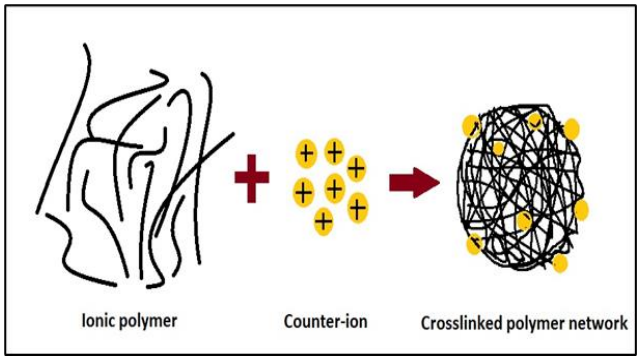


Figure 2: Overview of ionotropic-gelation of natural polysaccharides.

MATERIALS AND METHODS

2.1 Standard plot of ketorolac tromethamine:

Ketorolac tromethamine (10 mg) was weighed accurately on electronic balance, transferred to 10 ml volumetric flask and volume was made up to 10 ml with distilled water, resulting into 1000 µg/ml solution. 2.5 ml of this solution was further diluted to 25 ml with distilled water to obtain 100 µg/ml solution. The 100 µg/ml solution was appropriately diluted with distilled water to obtain solutions having concentrations of 2.5, 5, 10, 15 and 20 µg/ml. Absorbance of all solutions were determined at 294 nm. The experiments were performed in triplicates and mean absorbance readings at each concentration were used to obtain the standard equation and regression coefficient.

2.2 Isolation of *Linum usitatissimum* seed mucilage:

LSM was extracted from ripen and mature *Linum usitatissimum* seeds, 200 g of linseeds were immersed around 1000 mL of distilled water for 4 h at room temperature. After that time, boiled it in an electric water bath until, linseed slurry was shaped. The above clear mixture was then decanted and cooled at room temperature and poured in three parts of ethanol alongside constant mixing. With nonstop blending the precipitates were formed and washed more than once with ethanol and dried for 24 h at room temperature. When they totally dried into hard strong crystals were crushed by utilizing pestle and mortar, afterward passed through sieve # 80.

2.3 Design of ketorolac tromethamine loaded mucilage-alginate microspheres:

Ketorolac tromethamine loaded microspheres were formulated using ionic gelation technique. Briefly appropriate quantities of mucilage and sodium alginate were dissolved in distilled water with continuous stirring to polymeric solution. The weighed quantity of ketorolac tromethamine 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.

2.4 Design of *Erythriana Indica* loaded mucilage-alginate microspheres

Erythriana Indica loaded microspheres were formulated using ionic gelation technique. Briefly appropriate quantities of mucilage and sodium alginate were dissolved in distilled water with continuous stirring to polymeric solution. The weighed quantity of *Erythriana Indica* extract 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.

EVALUATION OF DRUG LOADED MUCILAGE – ALGINATE MICROSPHERES

3.1. Assessment of drug content

The drug content in dried microspheres was measured using UV spectrometric measurement. The dried ketorolac tromethamine loaded microspheres were finely ground using mortar pestle to obtain fine powder. The powder (equivalent to 20 mg of drug) 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 323 nm.

3.2. Assessment of particle size

Particle size distributions of both mucilage-alginate microspheres were assessed by optical microscopy using stage and eyepiece micrometer. Briefly, 50 mg of both microspheres spread over the surface of clean dry glass slide using painting brush and particle diameter 100 random particles was measure in micrometer.

3.3. Determination of swelling index

Swelling studies for each formulation was carried out in phosphate buffer, pH 6.8 with the help of empty tea bags. Accurately weighed 100mg of microspheres were placed in 500ml of respective buffer and kept aside for 24 h at room temperature. These sample bags of swollen microspheres were removed at specific time intervals, dried the surface by tissue paper to absorb the excess of water on surface and then weighed. Swelling index (%) was determined using the following formula.

$$Swelling\ index = \frac{Wt.of\ swollen\ microspheres - Wt.of\ dried\ microspheres}{Wt.of\ dried\ microspheres} \times 100$$

4. RESULT AND DISCUSSION

4.1 Standard plot of ketorolac tromethamine

The standard plot of ketorolac tromethamine was assessed in distilled water. The standard solutions of different concentration of drug were prepared in distilled water and absorbance of solutions were measured using UV spectroscopy. Table 4 gives the absorbance values at 323 nm of different concentrations of ketorolac tromethamine prepared in distilled water. Figure 3 is the graphical representation of the same.

Table 4: Absorbance of various concentrations of ketorolac tromethamine in distilled water.

Concentration (PPM)	Absorbance		
	I	II	III
2.5	0.048	0.051	0.045
5	0.142	0.145	0.135
10	0.265	0.283	0.247
15	0.357	0.374	0.382
20	0.443	0.504	0.453
25	0.635	0.595	0.650

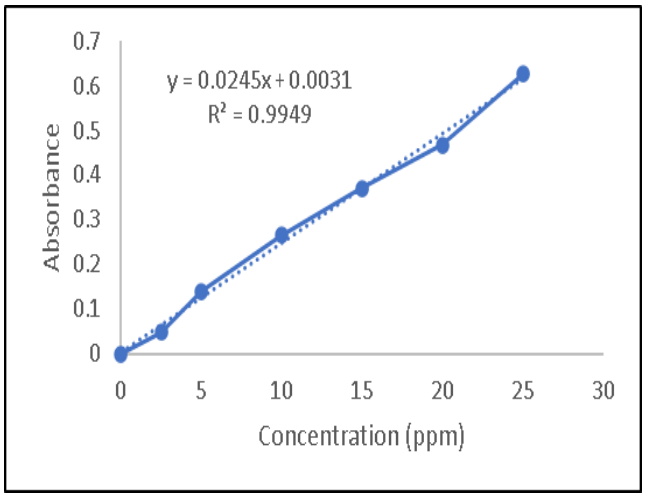


Figure 3: Standard plot of ketorolac tromethamine in distilled water.

4.2 Isolation of *Linum usitatissimum* seed mucilage

The *Linum usitatissimum* seeds were purchased locally. The mucilage from seeds of *Linum usitatissimum* was isolated with distilled water dried. Initially mucilage was checked for organoleptic properties like colour, Odour, taste and texture. The odourless mucilage was brownish in colour. The taste of mucilage was mucilaginous with smooth texture.

After an initial evaluation, the mucilage was subjected to spectroscopic measurement and thermal analysis.

4.2.1 Fourier-transform infrared spectroscopy (FTIR)

FTIR spectrum of dried mucilage was recorded to confirm correctness of mucilage isolation technique. The spectrum showed broad peak at 3305 cm^{-1} which corresponds to stretching of hydroxyl functional group. Two sharp peaks at 2915.2 and 2392.7 cm^{-1} indicated CH_2 stretching vibrations. The broad peak at 3305 cm^{-1} and sharp peaks at 2915.2 as well as 2392.7 cm^{-1} confirmed isolation of mucilage from seeds without impurities.

4.2.2 Differential scanning calorimetry

The thermograms of isolated mucilage exhibited sharp endothermic peak at 131.4^{0}C which corresponds to melting of mucilage. The broad exothermic peak was also observed in thermograms at 239.6^{0}C which may be due to degradation of mucilage.

4.3 Design of ketorolac tromethamine loaded mucilage-alginate microspheres

Ketorolac tromethamine 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 seed mucilage. The crosslinked polymeric microspheres were collected by filtration and dried at 40^{0}C. The microspheres were spherical in shape with light brown colour due to presence of mucilage. The spherical

shape of microspheres was maintained by slow injection of polymeric solution with continuous stirring at fixed rate.

4.4 Design of *Erythriana indica* extract loaded mucilage-alginate microspheres

Erythrina indica extract 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 seed mucilage. 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. The spherical shape of microspheres was maintained by slow injection of polymeric solution with continuous stirring at fixed rate.

4.6 Evaluation of drug loaded mucilage-alginate microspheres

4.6.1. Assessment of particle size

Particle size distributions of both mucilage-alginate microspheres were assessed by optical microscopy using stage and eyepiece micrometer. The particle size distribution was assessed by plotting particle size distribution curve as highlighted in figure 4. The mean particle size of ketorolac tromethamine loaded microspheres was found to be in the range. of 687.4 to 702.8 µm with arithmetic mean diameter of 655.08 µm. The mean particle size of *Erythriana indica* extract loaded microspheres was found to be in the range of 674.8 to 1103.7 micrometer with arithmetic mean diameter of 1097.5 µm.

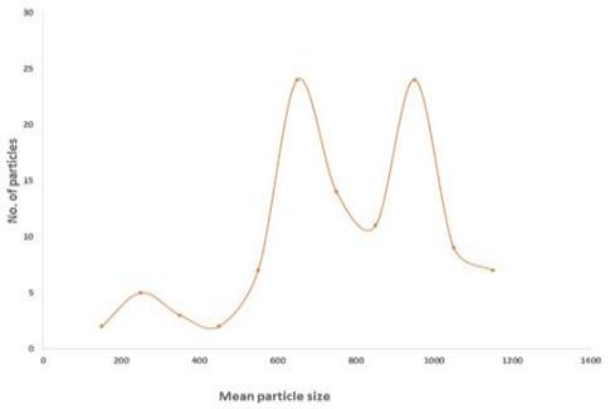


Figure 4: Particle size distribution of *Erythriana indica* extract loaded microspheres.

4.6.2 Assessment of drug content

The absorbance of the solution at wavelength 323 shows the clear presence of the KTM drug in solution.

Name	Absorbance		
	I	II	III
Microsphere Solution	0.048	0.048	0.044

- Theoretical yield- 20 mg of microspheres contains 1.39 mg of KTM drug
- Calculated yield- From standard plot of KTM actual yield of drug were found out and was found to be 0.94 mg in 20mg of microspheres, at 323nm.
- % drug content- The % drug content were found to be 67.62%

4.6.3 Assessment of swelling behaviour:

1. Swelling index of KTM microspheres- 190%

   Initial Weight-100mg

   Final Weight-290mg

2. Swelling index of *Erythriana indica* microsphere- 320%

   Initial Weight-100mg

   Final Weight-420mg.

CONCLUSION

The present study was started with aim to utilize natural mucilage for sustained delivery of drug. The mucilage obtained from linseed has mucoadhesive and drug release retardant properties. Thus, linseed mucilage was selected to formulate drug loaded microspheres.

Ketorolac tromethamine and *Erythriana Indica* extracts were selected for formulation of microspheres. Both microspheres were formulated using ion-gelation technique. Mucilage and Na-Alginate combination was used as matrix for loading of drug and extract. The formulated microspheres evaluated for physical parameters.

Both microspheres reveled acceptable physicochemical characteristics, swelling index, drug content and particle size of both microspheres was found to be quite coarse which can be reduced for ease of drug delivery. Thus, natural mucilage-based microspheres could be viable carrier for delivery of drug.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Natarajan V, Krithica N, Madhan, Sehgal P. Formulation and evaluation of quercetin polycaprolactone microspheres for the treatment of rheumatoid arthritis. Journal of Pharmaceutical Sciences. 2011 Jan;100(1):195–205. doi:10.1002/jps.22266.
2. Amiri M, Mohammadzadeh V, Yazdi M, Barani M, Rahdar A, Kyzas G. Plant-based gums and mucilage applications in pharmacology and nanomedicine: A Review. Molecules. 2021 Mar 22;26(6):1770. doi:10.3390/molecules26061770.
3. Jiménez RA, Millán D, Suesca E, Sosnik A, Fontanilla MR. Controlled release of an extract of calendula officinalis flowers from a system based on the incorporation of gelatin-collagen microparticles into collagen I scaffolds: Design and in vitro performance. Drug Delivery and Translational Research. 2015 Feb 5;5(3):209–218. doi:10.1007/s13346-015-0217-3.
4. Sharma N, Sharma A, Bhatnagar A, Nishad D, Karwasra R, Khanna K, et al. Novel Gum Acacia based macroparticles for colon delivery of mesalazine: Development and Gammascintigraphy study. Journal of Drug Delivery Science and Technology. 2019 Dec;54:101224. doi:10.1016/j.jddst.2019.101224.
5. Verma C, Pathania D, Anjum S, Gupta B. Smart designing of tragacanth gum by graft functionalization for Advanced Materials. Macromolecular Materials and Engineering. 2020 Feb 26;305(4):1900762. doi:10.1002/mame.201900762.
6. Mahfoudhi N, Sessa M, Chouaibi M, Ferrari G, Donsì F, Hamdi S. Assessment of emulsifying ability of Almond Gum in comparison with gum arabic using response surface methodology. Food Hydrocolloids. 2014 Jun; 37:49–59. doi:10.1016/j.foodhyd.2013.10.009.
7. Pal D, Nayak A. Novel tamarind seed polysaccharide-alginate mucoadhesive microspheres for oral gliclazide delivery: *in vitro–in vivo* evaluation. Drug Delivery. 2012 Feb 22;19(3):123–131. doi:10.3109/10717544.2012.657717.
8. Ogaji I, Okafor I, Hoag S. Grewia gum as a potential aqueous film coating agent. I: Some physicochemical characteristics of fractions of Grewia Gum. Journal of Pharmacy And Bioallied Sciences. 2013;5(1):53. doi:10.4103/0975-7406.106575.
9. Ozoude C, Azubuike C, Ologunagba M, Tonuewa S, Igwilo C. Formulation and development of metformin-loaded microspheres using Khaya senegalensis (Meliaceae) gum as co-polymer. Future Journal of Pharmaceutical Sciences. 2020 Dec;6(1):120. doi:10.1186/s43094-020-00139-6.
10. Bhupathyraaj M, Pole S. Study on effect of combination of sodium alginate and xanthan gum on drug release from Tacrolimus microbeads. European Journal of Molecular & Clinical Medicine. 2020;7(11):4584–4596.
11. Odeku O, Fell J. In-vitro evaluation of Khaya and Albizia gums as compression coatings for drug targeting to the colon. Journal of Pharmacy and Pharmacology. 2005 Feb;57(2):163–168. doi:10.1211/0022357055362.
12. Afghah F, Altunbek M, Dikyol C, Koc B. Preparation and characterization of nanoclay-hydrogel composite support-bath for bioprinting of complex structures. Scientific Reports Springer US. 2020 Mar 24;10(1):1–13. doi:10.1038/s41598-020-61606-x.
13. Joseph B, George J, Mohan J. Pharmacology and traditional uses of *Mimosa pudica*. International Journal of Pharmaceutical Sciences and Drug Research. 2013 Apr;5(2):41–44.
14. Beikzadeh S, Khezerlou A, Jafari S, Pilevar Z, Mortazavian A. Seed mucilages as the functional ingredients for biodegradable films and edible coatings in the food industry. Advances in Colloid and Interface Science. 2020 Jun;280:102164. doi:10.1016/j.cis.2020.102164.
15. Noureen S, Noreen S, Ghumman S, Batool F, Hameed H, Hasan S, et al. Prunus armeniaca gum-alginate polymeric microspheres to enhance the bioavailability of tramadol hydrochloride: Formulation and evaluation. Pharmaceutics. 2022 Apr 22;14(5):916. doi:10.3390/pharmaceutics14050916.
16. Sharma A, Kaushik A. FORMULATION, EVALUATION AND CHARACTERIZATION OF NARINIGN LOADED MICROPARTICLES USING ACACIA NILOTICA GUM. World Journal of Pharmaceutical Research. 2022 Sept;11(13):1222–1230. doi:10.20959/wjpr202213-25527.
17. Das S, Pan R, Dey R, Ghosh M. Development and in vitro study of metronidazole loaded cross linked sodium alginate and gellan gum microspheres. Journal of Drug Delivery and Therapeutics. 2022 Feb 15;12(1-S):60–63. doi:10.22270/jddt.v12i1-s.5345.
18. Mady F, Ibrahim S, Abourehab M. Development and evaluation of alginate-gum blend mucoadhesive microspheres for controlled release of metformin hydrochloride. Journal of advanced Biomedical and Pharmaceutical Sciences. 2021 Apr 1;4(2):111–118. doi:10.21608/jabps.2021.60824.1119.
19. Reddy O, Subha M, Jithendra T, Madhavi C, Rao K. Fabrication and characterization of smart Karaya gum/sodium alginate semi-IPN microbeads for controlled release of D-Penicillamine Drug. Polymers and Polymer Composites. 2020 Feb 13;29(3):163–175. doi:10.1177/0967391120904477.
20. Abrar A, Yousuf S, Dasan M. Formulation and evaluation of microsphere of antiulcer drug using

Acacia nilotica gum. International Journal of Health Sciences. 2020 Apr;14(2):10–17.

21. Mazumder R, Pal R, Chakraborty M, Shrestha B, Choudhary P, Maity T, et al. Formulation and in vitro evaluation of natural polymers based microspheres for colonic drug delivery. International Journal of Pharmacy and Pharmaceutical Sciences. 2010;2(1):211–219.