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Herbal Simvastatin Mucoadhesive Microspheres: Development, Characterization, and Investigation of Drug Release Mechanisms

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Abstract

Background and Objective: The primary objective of this research was to develop and evaluate mucoadhesive microspheres of simvastatin using herbal gums by ionic gelation method. This approach aimed to enhance the gastrointestinal residence time of the drug, thereby improving its bioavailability. Simvastatin, characterized by a short half-life, necessitates frequent administration, which can lead to patient non-compliance and fluctuating drug levels. To address these challenges, the study focused on formulating a sustained release system to ensure a more consistent therapeutic effect and reduce dosing frequency.

Methods: Mucoadhesive microspheres were prepared using combination of natural polymers, such as katira gum and sodium alginate, in different ratios using the ionic gelation method. All the formulated microspheres were evaluated for percentage yield, angle of repose, swelling index, assay, and in-vitro dissolution studies.

Results: Results revealed that the formulated microspheres were discrete, spherical, free flowing and % drug content of up to 84% was achieved. Invitro drug release studies showed all the batch formulations with drug release for at least 8 hrs. Formulation F2 demonstrated the highest swelling index of 52, particle size 701µm, angle of repose 20, % yield was found to be 93, drug content of 81%, carr's index of 14 and 81.99% drug release upto 8 hrs.

Conclusion: Formulation F2 was identified as the most effective. The release kinetics data suggested that the release mechanism for all formulations followed a non-Fickian diffusion process. The developed Simvastatin microspheres have the potential for clinical use, offering prolonged drug release for up to 8 hours, which could enhance bioavailability and improve patient compliance.

Keywords: Controlled Release; Ionic Gelation Method; Simvastatin; Sodium Alginate; Katira Gum

Abbreviations

SR: Swelling Ratio; CI: Carr's Index

Introduction

The term "Drug Delivery" encompasses a wide variety of methods designed to introduce therapeutic agents into the

human body. These delivery systems are intended to treat or manage medical conditions by effectively administering medications to address specific health issues [1].

Drugs are rarely administered in their pure form; instead, they are prepared in appropriate formulations to regulate their onset, intensity, and overall duration of action. Various terms such as sustained release, sustained action, prolonged action, controlled release, extended-release, and depot release describe drug delivery systems specifically designed to provide a prolonged therapeutic effect. These systems work by continuously releasing medication over an extended period following a single dose administration [2,3].

The primary objective of designing a sustained release drug delivery system is to minimize dosing frequency while enhancing the drug's effectiveness. This can be achieved by targeting the drug's action to a specific site, reducing the required dosage, or ensuring a consistent drug release [4,5].

Microspheres

Microspheres are solid, spherical particles ranging in size from 1 to 1000 μm, composed of proteins or synthetic polymers. They are typically free-flowing and characterized by uniform shape and size, ensuring consistency [6].

Types of microspheres:

1. Bioadhesive microspheres
2. Floating microspheres
3. Radioactive microspheres
4. Magnetic microspheres
5. Mucoadhesive microspheres
6. Polymeric microspheres
7. Biodegradable polymeric microspheres

- Synthetic polymeric microspheres

Methods of Preparation of Microspheres

The various methods of preparations are [7-10]:

- Emulsion solvent evaporation technique
- Emulsion cross linking method
- Co-acervation method
- Spray drying method
- Emulsion solvent diffusion technique
- Multiple emulsion method
- Ionic gelation method

In the present study, microspheres were prepared using the ionic gelation method. Mucoadhesive microspheres, with diameters ranging from 1 to 1000 nm, are designed either entirely from mucoadhesive polymers or with an outer coating of such materials, imparting adhesive properties. These microspheres are capable of attaching to a variety of mucosal tissues, including those located in the eyes, nasal cavity, and gastrointestinal tract. This characteristic enables both localized and systemic controlled drug release.

Gum katira, a natural polysaccharide derived from the stem bark of *Cochlospermum reliogosum* Linn., is biocompatible and non-toxic. It possesses antioxidant, antimicrobial, and immunomodulatory properties. Traditionally, it has been used in the treatment of ailments such as jaundice, gonorrhoea, syphilis, stomach disorders, and as a sedative [11-16].

Simvastatin has a very low oral bioavailability of 5% due to high first-pass metabolism. Mucoadhesive microspheres with sustained release of simvastatin aid in increasing bioavailability with the synergistic effect of gum katira as an antihyperlipidemic agent. Present work of preparation of simvastatin mucoadhesive microspheres by ionic gelation method avoids deterioration of product due to heat, oxidation and radiation. Thus, an attempt is made to prepare simvastatin microspheres to improve bioavailability.

Materials

Simvastatin was received as a gift sample from Quest Pharma, Hyderabad. Sodium alginate, Katira gum and Calcium chloride were purchased from sigma Aldrich.

Methodology

Standard calibration curve

Simvastatin was analyzed through a spectrophotometric study, with its maximum absorbance (λmax) identified at 238 nm using 0.1 N sodium hydroxide as the solvent.

100 mg of simvastatin was transferred to 100 ml volumetric flask and dissolved in 100 ml of at 0.1N sodium hydroxide. Then 5 ml from the above solution was taken into another 50ml volumetric Bask and volume was made up to 50 ml with 0.1 N sodium hydroxide Volumes of 1ml 1.5ml. 2 ml. 2.5 ml. 3 ml and 3.5 ml were taken in 10 ml volumetric flask. The above solution was diluted up to 10ml with 0.1N NaOH. The absorbance of above solution was Scanned in UV region and found that simvastatin showed absorbance at 238 nm (Table 1, Figure 1).

S. No	Concentration	Absorbance
1	10	0.685
2	15	0.864
3	20	0.87
4	25	1.078
5	30	1.277
6	35	1.23

Table 1: Standard calibration curve.

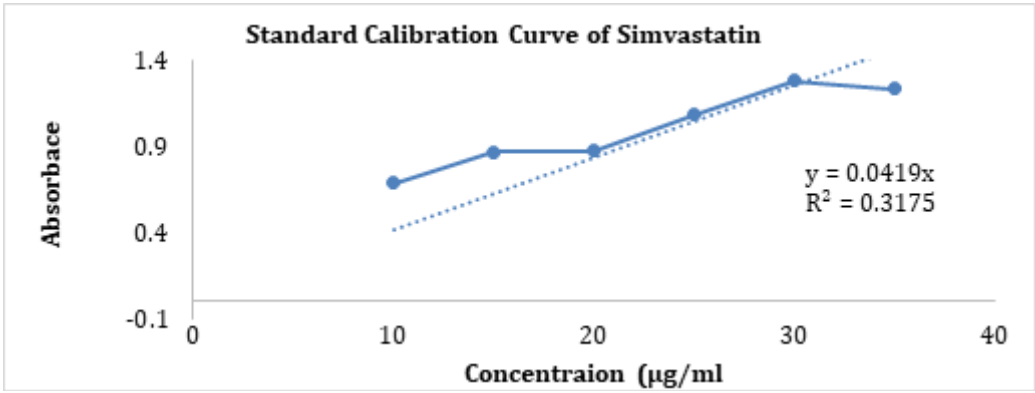

Figure 1: Standard calibration curve.

It was found to be linear with in the concentration range of 2-50 mcg/ml with regression co-efficient of 0.9706 by absorbance ratio method. A straight-line equation was generated, which was further used for assay and drug release Method of Preparation of Simvastatin Microsphere

Ionic Gelation Method

Microspheres were prepared using the ionic gelation method. Sodium alginate was added to 25 mL of distilled water and was stirred in a beaker until completely dissolved. In a separate beaker, 25 mL of distilled water was used to dissolve the mucoadhesive polymer, katira gum, by stirring with a overhead mechanical stirrer for 1.5 hours. Drug was dissolved in 2ml of dimethyl sulfoxide. The three solutions were then combined in a single beaker. The mixture was stirred for 10 minutes using a overhead mechanical stirrer.

A 5% w/v calcium chloride solution was prepared in a 100 mL beaker. The drug-polymeric mixture was added dropwise into the calcium chloride solution using a 22 G needle. The droplets were allowed to solidify in the calcium chloride solution for 1 hour. The resulting microspheres were then filtered, washed with distilled water, and air-dried for 24 hours [17,18] (Table 2).

S. No	Ingredients (g)	F1	F2	F3	F4	F5
1	Simavastatin	0.05	0.05	0.05	0.05	-
2	Sodium alginate	1	1	1	1	1
3	Katira gum	0.2	0.5	0.7	1	-
4	Calcium chloride (%w/v)	5	5	5	5	5

Table 2: Formulation of mucoadhesive microspheres.

Evaluation of Microspheres

Particle Size Analysis: The particle size of microspheres was determined using optical microscopy. The microscope was first calibrated using a stage micrometre to establish the relationship between the divisions on the eyepiece micrometre and the actual distance in micrometres (e.g., 1 division = X µm). A small quantity of the microspheres was placed on a clean glass slide, and if necessary, dispersed in a drop of distilled water to separate clumps. The sample was then covered with a cover slip to prevent movement. Under appropriate magnification, individual microspheres were observed, and the diameters of at least 100 randomly selected particles were measured using the calibrated eyepiece micrometre. The measurements were recorded, and the average particle size was calculated [19,20].

Percentage Yield: The percent yield of each of the samples was calculated from the expression.

% yield = (Actual weight of the product /Total weight of excipients and drug) x 100

Angle of Repose: The fixed funnel method was used for estimating the angle of repose for different formulations (n = 3) Angle of repose was defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan q = h / r$

$q = \tan^{-1} h/ r$

Where h= height of pile, r = radius of the base of the pile, q=angle of repose.

Swelling Index: 100 mg of microspheres were placed in glass vials containing pH 7.4 phosphate buffer with occasional shaking and kept aside for 4 hours. The microspheres were periodically removed, and blotted with filter paper and their weight changes were measured during the swelling until equilibrium was attained. Finally, the weight of swollen microspheres was recorded after 4 hrs and the swelling ratio (SR) was then calculated using the formula [21-24].

$SR = W_R - W_0 / W_0$

W_0 Initial weight of drug microspheres, W_R= Weight of swollen microspheres at equilibrium

Carr's Index: Carrs index was calculated using the formula:

C= Bulk density –Tapped density/Tapped density×100
The Bulk density of a sample is a ratio of the mass of an untapped sample and its volume including the contribution of the interparticulate void volume.

The tapped density is an increased bulk density attained after mechanically tapping a container containing the sample. The tapped density is obtained by mechanically tapping a graduating measuring cylinder containing the sample [25-27].

In-Vitro dissolution studies: *In-Vitro* drug release study was carried out using USP type-II dissolution test apparatus. The dissolution medium 900ml of pH 7.4 phosphate buffer was maintained at 37 ±1°C and stirred at 50 rpm for 8 hours. The samples were analyzed for simvastatin content by UV-Visible spectrophotometer at 238nm [28].

Kineties of Drug Release: Kinetic models helps to determine how a drug is released over time from the prepared herbal simavastin mucoadhesive microspheres. The drug release was investigated by studying the release data with zero-order, first-order kinetics, the Higuchi equation, and the Korsmeyer Peppas model.

Zero Order Kinetics: When the drug release data is plotted as cumulative % drug release versus time, if the plot is linear then the data obeys zero- order release Kinetics, with a slope equal to K_0
The following equation would predict zero order release:
$A_t = A_0 - K_0 t$
Where,
A_t Drug release at time t
A_0 = Initial drug concentration. K_0= Zero order rate constant (hr^{-1})
First Order Kinetics: When the drug release data is plotted as the logarithm of the cumulative percentage of drug remaining versus time, a straight-line relationship indicates that the drug release follows first-order kinetics. The release rate constant (K) can be calculated by multiplying the slope of the line by 2.303
The following equation would predict first order release:
$\log C = \log C_0 - K t / 2.303$
Where,
C= of drug remained at time 't'.
C_0 = concentration of drug.
K-First-order rate constant (hr)
Higuchi's Model: When the drug release data is plotted as cumulative drug release versus the square root of time, a straight-line relationship indicates that the drug release follows a diffusion-controlled mechanism. The slope of this line corresponds to the release rate constant, "K." Drug release by diffusion is described by Higuchi's classical diffusion equation.
$Q_t = K t^{1/2}$
Where,
Q amount of drug released at time 't'
K-Higuchi constant (hr)
Korsmeyer equation/Peppa's model: When the drug release data is plotted as log of drug released versus time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y- intercept. To study the mechanism of drug release, the release data were also fitted to the well-known exponential equation (Korsmeyer equation/ Peppa's law equation), which is often used to describe the drug release behaviour from polymeric systems.
$M_t / M_a = Kt^n$
Where,
M_t / M_a the fraction of drug released at time t
K = 1 Constant incorporating the structural and geometrical characteristics of the drug/polymer.
N = Diffusion exponent related to the mechanism of the release.
Above equation can be simplified by applying log on both sides,
$\log M_t / M_a = \log K + n * \log(t)$
For Fickian release n = 0.5 while for anomalous (non-Fickian) transport n ranges between 0.5 and 1.0.

Results and Discussion

Solubility Analysis

Simvastatin sample were white to off-white, non-hygroscopic, crystalline powder that was practically insoluble in water and freely soluble in dichloromethane, chloroform, methanol and ethanol.

Standard Calibration Curve of Simvastatin

It was found that the estimation of Simvastatin by UV spectrophotometric method at λ_{max} 238 nm in 0.1 N NaOH had good reproducibility and this method was used in the study. The concentration range was taken from 2-50 mcg/ml. The R^2 value was found to be 0.9899

Particle Size

The particle size of the prepared simvastatin microspheres was determined using the optical microscopy method and the particle size was in the range of 682.5 mm to 729.8 mm. Based on the polymer ratio the particle size was less in the case of 0.5:1, 1:1 ratio and was bigger in case of 1.5:1 ratio.

Considering this we could say that to increase in polymer ratio increased the particle size. The microscopic image of the prepared microspheres showed that they were spherical and discrete in shape.

Angle of Repose

The Angle of repose of all 5 formulations of microspheres was in the range of 20° to 35°. The value of the angle of repose for the formulations F1, F2, F3, F4 and F5, indicated good flowability.

Percentage Yield

The percentage yield ranged from 70% to 90%, with higher polymer concentrations enhancing the yield. The highest yield was observed in the formulation F4 containing the highest concentrations of both polymers, sodium alginate and gum katira.

Swelling Index

The microspheres demonstrated a swelling index, swelling two to three times their original weight. This aligns with literature emphasizing the swelling capacity of polymers like gum katira, which also aids in adhesion to mucosal surfaces. Achieving optimal matrix density is crucial for maximizing swelling. The highest swelling was observed in formulation F2, which contained gum katira at 50% of the sodium alginate weight. The matrix structure of F2 was less dense compared to F4, providing more space for polymer chain relaxation, thereby facilitating greater swelling.

Drug content

The drug content of all five formulations was determined and ranged from 67% to 83.5%. Formulation F5 showed the highest drug content among all, attributed to its lower polymer concentration relative to the drug. F2 also exhibited high drug content.

Carr's Index

Microspheres with a lower CI value (14) demonstrated better flowability, which is crucial for uniformity in filling capsules or tablets. Conversely, microspheres with a higher CI (closer to 35) exhibited poorer flow properties, which could potentially affect their uniformity in drug delivery and processing. This variation in flowability is attributed to differences in the polymer concentration and particle size, which can influence the packing density and cohesiveness of the microspheres.

Overall, the Carr's Index results indicate that the formulations demonstrate acceptable flow characteristics.

In-Vitro Dissolution Studies

All the prepared formulations of simvastatin microspheres (F1–F5) were subjected to in vitro drug release studies. The release data for each formulation was tabulated, and cumulative percentage drug release was plotted as a function of time over a 8-hour period. Among the formulations, F5 exhibited the maximum drug release, as it did not contain gum katira. Conversely, F4 showed the lowest drug release, which can be attributed to its highest concentration of gum katira, highlighting the gum katira's role in controlling drug release (Table 3).

S. No	Formulation Code	Particle Size (µm)	Angle of Repose (^{0})	Percentage Yield (%)	Swelling Index	Drug Content (%)	Carr's Index	Drug Release at 8hr (%)
1	F1	682.5±1.86	22±0.53	91±1.09	15±0.9	67±0.65	16±0.87	82.68±0.98
2	F2	701±0.76	20±0.45	93±0.84	52±0.7	81±0.44	14±0.65	81.99±0.44
3	F3	720±1.43	35±0.97	87±1.22	30±0.87	76±0.76	20±0.78	71.16±0.67
4	F4	730±0.75	30±0.57	95±0.78	35±0.83	72±0.87	35±0.83	70.11±0.73
5	F5	608±0.95	25±0.66	70±0.54	15±0.93	83.5±0.97	24±0.75	90.26±0.65

Source: Kinetic Release study of Simvastatin Microsphere.
Table 3: Evaluation of microspheres.

Drug release was studied by fitting into various kinetic models. The model that best fits the experimental data is typically identified by the coefficient of determination (R^2) value. The higher the R^2 value, the better the model describes the drug release mechanism. The range of R^2 value for F1 to F5 is given below for the various models studied.

Zero order release: Regression values were found within the range from 0.8609-0.9755 near to 1 that followed zero order.

First order release: Regression values were found within the range from 0.4225 to 0.5763, it below 0.6, so these formulations did not follow first order.

Higuchi release: Regression values were found within the range from 0.9313 to 0.988, was highly linear and followed Higuchi release.
Higuchi constant was found within the range from 0.518 to 0.7534.

Korsmeyer Peppas Model: In korsmeyer peppas model n value means diffusion constant from was found within the range from 0.9427 to 1.0803.

Here n value was found more than 0.89, and all formulations were found super case II transport.

Super Case II transport is characterized by an anomalous mechanism where the drug release rate is governed by the relaxation of polymer chains under swelling conditions, rather than by simple diffusion or erosion. In the case of gum katira, a hydrophilic polymer, swelling occurs upon water absorption, leading to polymer chain relaxation. This relaxation facilitates drug release primarily through polymer swelling and chain relaxation, highlighting the role of gum katira in controlling the release mechanism

Conclusion

This study focused on the development and evaluation of a mucoadhesive drug delivery system for Simvastatin using natural gums.. Microspheres were prepared using sodium alginate and katira gum through the ionic gelation method, aiming for sustained and controlled drug release over 8 hours. The influence of polymer concentration on particle size was investigated, resulting in an optimal particle size distribution and consistent drug content across formulations. Evaluated parameters such as angle of repose, swelling index, drug content, particle size, and in vitro drug release were within acceptable ranges. Formulation F2 demonstrated the highest swelling index, suggesting superior mucoadhesion. Drug release kinetics adhered to the Korsmeyer-Peppas model, with n-values greater than 0.89 for all formulations, indicating a Super Case II transport mechanism. In conclusion, the study successfully formulated mucoadhesive microspheres of Simvastatin with promising sustained and controlled release characteristics, highlighting their potential for effective drug delivery on a laboratory scale.

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