PREPARATION, EVALUATION AND STABILITY OF LAMIVUDINE LOADED ALGINATE-TAMARIND MUCILAGE MICROSPHERES

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ABSTRACT

Objective: The objective of the present study was to investigate the possibility of obtaining a controlled, relatively constant effective level of lamivudine microspheres.

Methods: Lamivudine loaded sodium alginate (SA) and tamarind mucilage(TM) mucoadhesive microspheres were prepared by ionic gelation technique with three different proportions of SA and TM with different concentrations of CaCl2. The prepared microspheres were evaluated for drug loading, particle size distribution, surface morphology, FTIR, in vitro wash off, in vitro release and stability studies.

Results: The microspheres were found to be free flowing having diameter ranging from 769.22 to 978.56 µm, drug encapsulation efficiency (DEE) was found to be 65.28 to 92.33%. Percent drug release after 12 h were ranging from 85±1.51 to 97±1.44. In vitro release profile of all formulations shows slow controlled release up to 12 h. In vitro wash off studies shown fairly good mucoadhesivity with 20% microspheres adhered after 6h. Stability studies showed that no significant change in particle size and maximum DEE in comparison to the formulation stored at room temperature.

Results: The lamivudine loaded SA-TM mucoadhesive microspheres can be conveniently prepared which showed result and it may be used full for controlling the drug release and improve the bioavailability.

Keywords: Microspheres, Mucoadhesive, Tamarind, Muclilage, In vitro, Lamivudine

INTRODUCTION

Oral drug delivery systems continue to be the most accepted and popular one among all the drug delivery systems as it offers several advantages over the conventional drug delivery systems like improving patient’s compliance and convenience due to the reduction of frequency of administration [1]. The formulation of controlled drug delivery systems is important to achieve better clinical efficacy and patient compliance [2]. Such systems are highly desirable for drugs that have a short half-life to avoid unnecessary side effects, burst effect or overdose [3, 4]. In addition, controlled release dosage forms ensure optimum and uniform supply of the drug, reduce the frequency of intakes [5, 6], enhance stability [7] and increase absorption of some drugs [8].

Microspheres possess important features among the controlled drug delivery systems by virtue of their small size and efficient carrier characteristics [9], but the success of dosage form is limited due to its residence time. Hence mucoadhesive microsphere drug delivery systems are used to extend the residence time at the site of application, maintain therapeutically effective plasma drug concentration levels for a longer duration, reducing the dosing frequency and minimize fluctuations in the plasma drug concentration at the steady state in the controlled and reproducible manner [10-12].

Recently, the mucoadhesive polymers have drawn great interest in the designing of oral drug delivery systems to prolong the gastric residence time for the dosage forms as well as to facilitate the intimate contact with an underlying absorptive surface to enhance the oral bioavailability of drugs [13, 14].

Amongst various natural polymers, alginates have been found extensively used, as the matrix in various drug delivery applications due to its hydrogel-forming properties [15]. Alginates are polysaccharides obtained from marine brown algae (Laminaria hyperborea, Ascophyllum nodosum, Macrocystis pyrifera etc.) [16], which are the monovalent form of alginic acid belonging to the family of linear copolymers, composed of two monomeric units, β-D-mannuronic acid (M) and α-L-guluronic acid (G). These residues are arranged in homopolymeric blocks (GG and MM) and heteropolymeric blocks (MG) [17]. Alginates undergo ionotropic gelation in aqueous solution in the presence of divalent cations like Ca2+, Ba2+, Pb2+, Cu2+, Cd2+, Zn2+, and the like and trivalent cation like Al3+ due to the ionic interaction and intermolecular bonding between the carboxylic acid groups located on the polymer backbone and cations [18]. Though alginates have mucoadhesive property, but, the cross-linked alginic beads are usually fragile [19, 20]. Therefore, to overcome this fragile character, blending of different mucoadhesive polymers is done. Blending with suitable polymers may improve the drug encapsulation efficiency (DEE), which is usually lower in only alginate microspheres prepared by ionotropic gelation method.

One cheap and naturally derived polymer is tamarind mucilage (TM) obtained from the seeds of Tamarindus indica L., a common tree of India and South East Asia. Tamarind is composed of (1 → 4)-β-D-glucan backbone substituted with side chains of α-D-xylopyranose and β-D-galactopyranosyl (1 → 2)-α-D-xylopyranose linked (1 → 6) to glucose residues [21, 22]. It is used as a binder, gelling, thickening, emulsifying, and suspending agent in different pharmaceutical formulations and acts as a stabilizer in food and pharmaceutical industries [23, 24]. Tamarind mucilage has been described as a viscosity enhancer showing mucomimetic, and mucoadhesive property [25]. Again, due to its hydrophilic and mucoadhesive property, it finds its use in the development of mucoadhesive drug delivery systems [26].

Lamivudine is an anti-retroviral agent which is chemically designated as 4-amino-1-[2R,5S]-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropropimidin-2-one, used in the treatment of HIV [27]. Lamivudine (3TC), 2-deoxy-3-thiacytidine, is a potent nucleoside analog reverse transcriptase inhibitor with very low cellular cytotoxicity. Moreover, lamivudine is active against zidovudine-resistant human immunodeficiency virus (HIV) [28, 29]. Lamivudine has approximately 80% oral bioavailability in human with the usual dosage of 150 mg twice daily in combination with other antiretroviral agents [30]. Conventional oral formulations of lamivudine are administered multiple times a day because of its...
Isolation of tamarind mucilage

Method
Distilled water was used throughout the studies. with distilled water to remove any extra pulp. Two hundred fifty grams of cleaned seeds were broken into small pieces and ground into fine powder. Powders were taken in 1000 ml beaker loaded 500 ml water and boiled on water bath at 80–100 °C with a constant stirring till a viscous solution was obtained and kept aside for 2 h for the release of mucilage, then filtered. The filtrate was precipitated out with ethanol in crude form. The precipitated material was filtered through a muslin bag into conical flask and marc is squeezed well in order to remove the mucilage completely, in between hot distilled water (25 ml) was added through the sides of muslin bag. The aqueous filtrate is concentrated to 1/3rd of its volume. The obtained precipitate is settled by keeping in a refrigerator for overnight. After complete settling of the precipitate, it was filtered and dried the residue at 37 °C. The obtained dried powder was reduced to a fine powder and passes through 21 gauze needles into 100 ml CaCl₂ solution. The thin stream droplets were retained in the CaCl₂ solution for 15 min to complete the curing reaction and to produce rigid spheres. The microspheres were collected by filtration and washed repeatedly with water. The obtained microspheres were then air-dried and stored for further characterization [36]. Formulation was shown in table 1.

Materials
The pure drug Lamivudine was obtained by Hetero Drugs Pvt ltd, Hyderabad (Telangana, India). Sodium alginate and Calcium chloride were procured from Yarrow chemicals and SD fine chemicals Mumbai respectively. Tamarind seeds were procured from the local market. All other reagents used were of analytical grades and double distilled water was used throughout the studies.

Method
Isolation of tamarind mucilage
Raw seeds of tamarind seeds (Tamarindus indica L.) were cleaned with distilled water to remove any extra pulp. Two hundred fifty grams of cleaned seeds were broken into small pieces and ground into fine powder. Powders were taken in a 1000 ml beaker loaded 500 ml water and boiled on water bath at 80–100 °C with a constant stirring till a viscous solution was obtained and kept aside for 2 h for the release of mucilage, then filtered. The filtrate was precipitated out with ethanol in crude form. The precipitated material was filtered through a muslin bag into conical flask and marc is squeezed well in order to remove the mucilage completely, in between hot distilled water (25 ml) was added through the sides of muslin bag. The aqueous filtrate is concentrated to 1/3rd of its volume. The obtained precipitate is settled by keeping in a refrigerator for overnight. After complete settling of the precipitate, it was filtered and dried the residue at 37 °C. The obtained dried powder was reduced to a fine powder and passes through 21 gauze needles into 100 ml CaCl₂ solution. The thin stream droplets were retained in the CaCl₂ solution for 15 min to complete the curing reaction and to produce rigid spheres. The microspheres were collected by filtration and washed repeatedly with water. The obtained microspheres were then air-dried and stored for further characterization [36]. Formulation was shown in table 1.

**Table 1: Formulation and processing parameters of lamivudine based SA-TM mucoadhesive microspheres**

| Formulation code | SA: TM | CaCl₂ (%) | DEE* | PS* |
|------------------|--------|-----------|------|-----|
| FT-1             | 1:1    | 5         | 65.28±3.81 | 978.56±12.58 |
| FT-2             | 1:1    | 7.5       | 73.85±2.66 | 928.21±15.68 |
| FT-3             | 2:1    | 10        | 79.96±4.06 | 873.13±16.26 |
| FT-4             | 2:1    | 5         | 70.65±3.95 | 919.24±19.47 |
| FT-5             | 2:1    | 7.5       | 78.35±3.26 | 874.48±15.12 |
| FT-6             | 2:1    | 10        | 86.35±3.98 | 823.47±13.28 |
| FT-7             | 3:1    | 5         | 77.86±4.17 | 851.28±14.54 |
| FT-8             | 3:1    | 7.5       | 85.89±3.68 | 806.53±18.65 |
| FT-9             | 3:1    | 10        | 92.33±4.42 | 769.22±10.19 |

Where, Xᵢ = Mean size range;
f. Percentage microspheres retained on the smaller sieve range.

Surface morphology studies

The external morphology of the microspheres was studied using scanning electron microscopy (SEM). Mucoadhesive microspheres of lamivudine loaded SA-TM were fixed on aluminium studs and coated with gold using a sputter coater SC 502, under vacuum [0.1 mm Hg] and are analyzed using-Model [SM-840 A], Joel Japan. The samples were then randomly scanned, and photomicrographs were taken [40].

In vitro wash off test for mucoadhesion

The mucoadhesivity of lamivudine loaded SA-TM mucoadhesive microspheres were evaluated by in vitro wash-off method. Freshly excised pieces of goat intestinal mucosa (2 x 2 cm) (collected from the slaughterhouse) were mounted on a glass slide (7.5 x 2.5 cm) using cyanoacrylate glue. About 50 microspheres were spread onto the wet tissue specimen, and the prepared slide was hung onto a groove of the disintegration test apparatus. The tissue specimen was given a regular up and down movement at 37 ± 0.5 °C loaded 900 ml of phosphate buffer (pH 7.4). After regular time intervals, the machine was stopped and the number of microspheres still adhering to the tissue was counted [41].

Stability studies

All the formulations were studied for stability profile at 40 °C/75%±5% RH for 6 mo (Climatic zone IV condition for accelerated testing) to assess their stability. The protocol of stability studies was in compliance with the WHO recommended ICH guidelines for stability testing intended for the global market. After intervals of 30, 60, 90, 120 and 180 d, samples were withdrawn and retested for DEE (Drug Content) and Particle size [42].

In vitro drug release studies

To study the in vitro dissolution profile, microspheres equivalent to 50 mg of lamivudine were filled in hard gelatin capsules. Dissolution studies were performed using the dissolution test apparatus USP-II with paddle (Electrolab, Mumbai, India). The phosphate buffer pH 7.4 (900 ml) was used as dissolution medium at 37 ± 1 °C. The paddle was rotated at 50 rpm. The 5 ml of samples were withdrawn on definite time intervals using pipette and immediately replaced with an equal quantity of phosphate buffer pH 7.4. The amount of drug released was determined using (collected aliquots were filtered and suitably diluted) UV-VIS spectrophotometer (Shimadzu, Japan) at 271 nm against a blank (phosphate buffer, pH 7.4). In order to predict and correlate the in vitro release behaviour of lamivudine from SA-TM mucoadhesive microspheres and marketed tablet Lamivir, data were fitted into a suitable mathematical model. The studies were carried out in triplicate. The in vitro dissolution data were tabulated and computed by using dissolution software viz., PCP DISSO V3.0.

RESULTS AND DISCUSSION

Isolation of tamarind mucilage and preparation of lamivudine loaded SA-TM mucoadhesive microspheres

Mucilage was isolated from tamarind seeds (Tamarindus indica L.) and the average yield of mucilage was found to be 16.32% w/w. The lamivudine loaded different ratio of isolated TM and SA blend (1:1, 1:2 and 1:3) with different concentrations of CaCl₂ were prepared, as shown in table 1. Rigid and discrete lamivudine loaded SA-TM mucoadhesive microspheres were obtained when dispersion mixture of SA, TM and core material lamivudine added in a solution containing calcium ions.

Encapsulation efficiency

The DEE in lamivudine loaded SA-TM mucoadhesive microspheres were within the range between 65.28±3.14 and 92.33±3.93 % w/w (table 1). The higher DEE in lamivudine loaded SA-TM mucoadhesive microspheres was seen in formulation FT9, where TM to SA blend ratio as 1:3 and the concentration of cross-linking material, CaCl₂ was 10 % w/w. The DEE was increased with decreasing TM to SA blend ratios and increasing cross-linking concentrations. This may be due to the high degree of cross-linking as the amount of SA in the polymer blend, and concentration of crosslinking material (i.e. CaCl₂) solution was increased [43].

When drug-loaded polymer blend (SA-TM) was added into a solution of CaCl₂, the calcium ions replaces the sodium ions of SA to form calcium alginate, which provides cross-linking to form the cross-linked microspheres. Again, at a lower concentration of CaCl₂, the microspheres might have larger pores due to insufficient cross-linking that resulted in lower drug encapsulation [44].

Particle size and surface morphological characteristics

The particle size of lamivudine loaded SA-TM microspheres for each formulation was carried out by sieve analysis method. The diameters of these microspheres were within the size range of 769.2±7.42 to 978.49±18.72 μm (table 1). Increases in the diameter of these microspheres were found with the increasing proportion of TM into formulations. This is may be due to the increase in viscosity of polymer blend solution with the incorporation of TM in an increasing ratio that in turn increased the size of the droplet. Again, the reduction in the size of the particle of these formulated SA-TM mucoadhesive microspheres was observed when there is an increase in the concentration of CaCl₂ in solution. This may due to shrinkage of the polymeric gel by a higher degree of cross-linking with the high concentration of crosslinker (i.e. CaCl₂) [45]. It was also observed that the DEE of lamivudine loaded SA-TM mucoadhesive microspheres were appeared to decrease with increasing diameter. The morphological analysis of microspheres was done by SEM and presented in fig. 1. The SEM photograph indicated that microspheres were spherical particles of rough surfaces with no tendency to aggregate. Their surface morphologies appeared to have a rough surface with characteristic pores, large wrinkles, and cracks. These pores, cracks, and wrinkles may be due to polymeric gel collapsing during the drying process of microspheres.

FTIR spectroscopic analysis

FTIR spectrometric analysis was performed to confirm the compatibility of lamivudine with polymers used to prepare microspheres formulation. The FTIR spectra of lamivudine, SA, TM, and lamivudine loaded SA-TM mucoadhesive microspheres were shown in fig. 2. In the FTIR spectra of lamivudine loaded SA-TM mucoadhesive microspheres, various characteristic peaks of sodium alginate, tamarind, and lamivudine were appeared without any significant shifting of peaks. Suggesting, there were no interactions between the lamivudine and the polymers (TM, and SA) used.
In vitro drug release

Lamivudine release from various SA-TM microspheres was studied in simulated intestinal pH (phosphate buffer, pH 7.4). Various lamivudine loaded SA-TM microspheres showed the controlled release of lamivudine over 12 h. The lamivudine release from SA-TM microspheres was slow and dependent on both the proportion of the polymer (TM, and SA) and the percentage of cross-linking agent CaCl₂. The release of lamivudine from SA-TM mucoadhesive microspheres was observed 85.16±1.51 to 97.37±2.44 in phosphate buffer, pH 7.4 after 12 h (fig. 3). It can be observed that comparatively higher proportion of TM in formulations, the more hydrophilic property of the TM combined better with water to form a viscous gel structure, which might block the pores on the surface of microspheres and controlled the release profile of the drug, lamivudine. Also, the release of lamivudine from SA-TM microspheres formulated with a higher concentration of CaCl₂ comparatively controlled than the microspheres prepared with a lower concentration of CaCl₂ [46].

Mucoadhesive (in vitro wash-off test)

The in vitro wash-off test to know mucoadhesivity of these SA-TM microspheres loaded lamivudine was carried out at simulated intestinal pH (phosphate buffer, pH 7.4) for 6 h. The percentage of microspheres adhering to the goat intestinal mucosal tissue varied from 15.55±0.58 to 19.60±3.25% in phosphate buffer after 6 h (fig. 4). The results of the wash-off test indicated that the lamivudine loaded SA-TM microspheres had fairly good mucoadhesive properties.

Stability studies

The stability study of the microspheres was carried out at accelerated temperatures. The percentage of drug content was estimated as a part of storage stability studies considering initial drug content as 100%. The thermal degradation of optimized formulation were studied by keeping the formulations at accelerated temperatures of 40 °C ±2 °C/75% RH ±5% RH. The physical observations of samples, particle size, DEE given in table 2 and 3. The product retained its spherical geometry and did not show shrivelling tendency during the 6-month storage period. The results of the stability studies indicated that the lamivudine containing SA-TM microspheres were stable at all conditions but most stable at room temperature.
Fig. 4: *In vitro* wash off test to know mucoadhesiveness of lamivudine loaded SA-TM microspheres

Table 2: Stability study of particle size for optimized batches of lamivudine loaded SA-TM mucoadhesive microspheres

| Formulation code | Parameter | Observation during accelerated stability studies* |
|------------------|-----------|---------------------------------------------------|
|                  |           | Initial | 3 Mo   | 6 Mo   |
| FT-3             | Particle Size | 873.13±16.26 | 878.05±15.91 | 879.23±13.85 |
| FT-6             | 823.47±13.28 | 831.24±12.67 | 831.68±14.25 |
| FT-9             | 769.22±10.19 | 776.35±16.38 | 780.35±11.98 |

*Avg of three determinations

Table 3: Stability study of DEE for optimized batches of lamivudine-containing SA-TM mucoadhesive microspheres

| Formulation code | Parameter | Observation during accelerated stability studies* |
|------------------|-----------|---------------------------------------------------|
|                  | DEE       | Initial | 3 Mo   | 6 Mo   |
| FT-3             | 79.96±4.06 | 79.02±3.86 | 78.05±2.67 |
| FT-6             | 86.35±3.98 | 85.92±2.94 | 84.83±3.89 |
| FT-9             | 92.33±4.42 | 91.12±4.08 | 90.73±2.96 |

*Avg of three determinations

CONCLUSION

The lamivudine loaded SA-TM mucoadhesive microspheres by ionotropic gelation technique was developed and evaluated. The DEE of these microspheres were within the range. The prepared microspheres were of spherical shape with rough surfaces, and their average particle size varied with coat ratio and calcium chloride concentration FTIR analysis suggested that there were no interactions between the lamivudine and the polymers (TM, and SA) used. All these SA-TM mucoadhesive microspheres exhibited fairly good mucoadhesivity. The method of preparation for SA-TM mucoadhesive microspheres for oral lamivudine delivery was found to be very simple and reproducible. Finally, it can be said that this lamivudine loaded SA-TM mucoadhesive microspheres are very much suitable for controlled systemic administration of lamivudine through controlled drug release, increase bioavailability their by improving patient compliance.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

The authors report no conflicts of interest

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