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PREPARATION AND EVALUATION OF MARAVIROC MUCOADHESIVE MICROSPHERES FOR GASTRO RETENTIVE DRUG DELIVERY

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ABSTRACT

Objective: The objective of this research was to formulate and evaluate pectin and HPMC different grades mucoadhesive microspheres in combination with sodium alginate for controlled release of maraviroc.

Methods: The maraviroc mucoadhesive microspheres was successfully developed by Ionotropic gelation technique, using sodium alginate, pectin, HPMC K4, K15, and K100 as mucoadhesive polymer in various proportions in combination. Further, the prepared maraviroc mucoadhesive microspheres were characterized for particle size, morphology, micrometric studies, entrapment efficiency, mucoadhesion, *in vitro* drug release, release kinetics, compatibility studies (FTIR) and stability studies.

Results: The maraviroc Microspheres was discrete and free-flowing. The mean particle size ranged from 646.3±10.2 µm to 910.0±6.56 µm and the entrapment efficiency ranged from 50.80% to 91.43%. Entrapment efficiency of maraviroc microspheres was increased by increasing drug to mucoadhesive polymer ratio. Scanning electron microscopy revealed the rough surface morphology and no visible cracks of best formulation F16. The FTIR study confirmed the stable nature of maraviroc in the drug-loaded mucoadhesive microspheres. All the maraviroc microspheres showed good mucoadhesive property ranging from 04-73 % in the *in-vitro* wash off test after 8 hours. The Crystallinity of maraviroc was found to be reduced in prepared mucoadhesive microspheres, which were confirmed by XRD studies. The mechanism of maraviroc release from the mucoadhesive microsphere was found to be anomalous and super case-II transport type. Stability studies were carried out for the best formulation F16 indicates that there is no change in entrapment efficiency and percentage mucoadhesion of the formulation.

Conclusion: The results obtained in this research work clearly indicated a promising potential of control release maraviroc mucoadhesive microspheres containing HPMC K100 as a rate controlling polymer for the effective treatment of AIDS/HIV patients.

Keywords: Pectin, HPMC K4, HPMC K15M, HPMC K100, Maraviroc, Mucoadhesive microspheres.

INTRODUCTION

Oral controlled 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 reduction of frequency of administration [1]. The problem commonly encountered with the controlled release delivery system is the inability to restrain and localize the dosage form at the gastrointestinal tract, due to the rapid gastrointestinal transit phenomenon [2]. In order to overcome this limitation, it has been proposed, to coupling the bioactives to microparticulate systems an important part of novel drug delivery [3]. However, the success of microparticulate carrier system is limited due to their limited residence time at the site of absorption [4].

It can be executed by coupling mucoadhesion characteristics to microparticulate by using mucoadhesive polymers and developing mucoadhesive microspheres [5]. Mucoadhesive microspheres have advantages like efficient absorption and improved bioavailability of the bioactives due to high surface to volume ratio, an intimate contact with the mucus membrane and drug targeting to the absorption site [6].

Maraviroc is a new class of anti HIV drug known as CCR5 antagonists and only oral entry inhibitor appr oved for the treatment of HIV 1infection [7]. Maraviroc poorly absorbed from lower gastrointestinal tract and the oral bioavailability after a single 300-mg oral dose is reported to be 33% with biological half life of 10.6±2.7 h. Administration of conventional dosage form suffers from certain drawbacks like first pass metabolism, variation of absorption and fluctuation in the plasma drug level [8].

In our previous investigation [9], sodium alginate mucoadhesive microspheres of maraviroc controlled the drug release for 8 hrs. To prolong the maraviroc release, improve mucoadhesion, bioavailability and to reduce dosing frequency, a suitable formulation was required with a controlled rate to treat anti HIV patients. In the present study, mucoadhesive microspheres were developed using a hydrophilic polymer, Hydroxypropyl methylcellulose (HPMC K4M, K15M and K100) and pectin in combination with sodium alginate.

MATERIALS AND METHODS

Materials

Maraviroc was a gift sample from Hetro Pharma Ltd, Hyderabad. Sodium alginate, HPMC different grades, pectin polymers were received as the gift sample from Cadila Pharma, Ahmedabad, India. All other ingredients used were of analytical grade.

Formulation of Maraviroc mucoadhesive microspheres

The Maraviroc mucoadhesive microspheres were prepared by Ionotropic external gelation technique [10, 11], the composition of various formulations was mentioned in Table1. Maraviroc and mucoadhesive polymers were individually passed through sieve number 60. The required quantities of mucoadhesive polymers were dissolved in purified water to form a homogenous polymer solution. Maraviroc was added to the polymer solution and mixed thoroughly with stirrer at 400 rpm to form a homogeneous dispersion. The resulting homogeneous dispersion was sonicated for 30 min to remove any air bubbles. For the formation of microspheres the dispersion was then extruded manually drop wise into aluminum sulphate solution (10%) using a polyethylene syringe (needle size 24 G). The extruded droplets were retained in the aluminium sulphate solution for 30 min to complete the curing reaction and to produce spherical rigid maraviroc microspheres [9]. The obtained microspheres were collected by decantation, washed repeatedly with distilled water to remove excess aluminum impurity and dried at 45 °C for12 h.

Table 1: Composition of Maraviroc mucoadhesive microspheres

Formulation code	Drug: polymer ratio	Polymer ratio
F1	1:0.5	0.25:0.25 (Sodium alginate: Pectin)
F2	1:1	0.5:0.5 (Sodium alginate: Pectin)
F3	1:1.5	0.75:0.75 (Sodium alginate: Pectin)
F4	1:2	1:1 (Sodium alginate: Pectin)
F5	1:0.5	0.25:0.25 (Sodium alginate: HPMC K4)
F6	1:1	0.5:0.5 (Sodium alginate: HPMC K4)
F7	1:1.5	0.75:0.75 (Sodium alginate: HPMC K4)
F8	1:2	1:1 (Sodium alginate: HPMC K4)
F9	1:0.5	0.25:0.25 (Sodium alginate: HPMC K15)
F10	1:1	0.5:0.5 (Sodium alginate: HPMC K15)
F11	1:1.5	0.75:0.75 (Sodium alginate: HPMC K15)
F12	1:2	1:1 (Sodium alginate: HPMC K15)

F13	1:0.5	0.25:0.25 (Sodium alginate: HPMC K100)
F14	1:1	0.5:0.5 (Sodium alginate: HPMC K100)
F15	1:1.5	0.75:0.75 (Sodium alginate: HPMC K100)
F16	1:2	1:1 (Sodium alginate: HPMC K100)

Particle size

Particle size and size distribution of the maraviroc microspheres was measured by sieve analysis method [12]. The maraviroc microspheres were separated into different size fractions (% mass fraction) by sieving for 5 min using standard sieves having a nominal mesh opening of 1.0 mm, 0.85 mm, 0.71 mm, 0.60 mm and 0.50 mm and the mean particle size of the maraviroc microspheres was determined.

Mucoadhesive test

The mucoadhesive property of Maraviroc microspheres was evaluated by *in vitro* wash off test. The freshly excised piece of the goat intestinal mucosa was mounted on the glass slide using cyanoacrylate glue. About 100 microspheres were spread onto each wet rinsed tissue specimen and immediately thereafter the support was hang onto the arm of the USP disintegration machine. Now operating the disintegration test apparatus, the intestinal mucosa was given a slow, regular up and down movement in the test fluid (0.1N HCl buffer) at 37±0.5 °C. At predetermined time intervals up to 8 h the equipment was stopped and the number of Maraviroc mucoadhesive microspheres still sticking onto the intestinal mucosa was counted and percent mucoadhesion was calculated [15].

***In vitro* dissolution**

The *in vitro* dissolution studies of prepared Maraviroc microspheres were carried out using USP type II (paddle) dissolution test apparatus. Microspheres containing equivalent to 100 mg of Maraviroc were introduced into 900 ml dissolution medium of 0.1N HCl for 12 hrs at 37±0.5 °C at a rotation speed of 50 rpm. 5 ml of the aliquots was withdrawn through a filter (0.45 µ) at the regular interval of every 1h and replaced with an equal volume of fresh 0.1N HCl buffer. The samples were analyzed at 210 nm for maraviroc content using a UV spectrophotometer. The maraviroc release experiments were carried out in three replicate [16].

Release kinetics and mechanism of maraviroc release

The rate and the mechanism of release of maraviroc from the prepared mucoadhesive microspheres were analyzed by fitting the dissolution data into various kinetic models like zero order; first order, korsemeyer peppas, Higuchi's model and Coefficient of determination r2 values were calculated for the liner curves by regression analysis of the above plots [17].

X-ray diffraction study (XRD)

The crystallinities of Maraviroc and Maraviroc loaded mucoadhesive microspheres were evaluated by XRD measurement using an X-ray diffractometer. XRD studies were performed on the prepared samples by exposing them to Cuk α1 radiation (40 KV, 30 MA) and the scanning rate was 5 °/min over a range of 4-90 ° and with an interval of 0.1 [20].

Stability study

Stability studies were carried out for maraviroc formulation as per ICH guidelines. The best mucoadhesive microspheres formulation (F16) was sealed in high density polyethylene bottles and stored at 4±1 °C/Ambient, 25±2 °C/60±5 % RH %, 40±2 °C/75±5 % RH for 90 d. The samples were periodically evaluated for entrapment efficiency and percentage mucoadhesion [21, 22].

RESULTS AND DISCUSSION

Percentage yield and micromeritics studies

The prepared maraviroc microsphere by ionotropic gelation method was found to be spherical shape and free flowing in nature. The production yields of maraviroc microspheres formulations were found to be between 82 to 95% as shown in table 2.

Table 2: Physicochemical properties of maraviroc mucoadhesive microspheres

Formulation code	Percentage yield [a]	Theoretical drug content (mg)	Practical drug content (mg) [a]	Entrapment efficiency (%) [a]	Particle size [µm] [a]
F1	90.96±3.56	66.60	33.84±0.14	50.81±0.22	652.02±5.35
F2	91.93±2.79	50.00	27.97±0.06	55.95±0.12	676.29±2.31
F3	94.56±2.31	40.00	25.44±0.08	63.60±0.20	711.88±2.25
F4	97.83±2.01	33.00	22.99±0.08	69.66±0.25	748.75±3.13
F5	86.50±3.87	66.60	42.80±1.20	64.26±1.80	712.29±4.77
F6	89.43±3.02	50.00	35.92±0.91	71.84±1.81	737.92±1.57
F7	93.11±2.61	40.00	31.75±0.02	79.37±0.06	764.38±3.13
F8	95.15±2.09	33.00	27.91±0.09	84.57±0.28	809.73±2.61
F9	89.40±3.73	66.60	46.13±1.01	69.27±1.51	758.13±3.13
F10	93.33±3.07	50.00	38.19±0.53	76.37±1.06	790.39±2.93
F11	94.18±2.64	40.00	33.83±0.02	84.57±0.06	827.13±3.63
F12	95.91±2.39	33.00	29.45±0.16	89.25±0.49	858.54±5.54
F13	91.64±3.93	66.60	48.93±0.61	73.47±0.92	790.39±2.93
F14	93.92±3.20	50.00	41.07±0.61	82.13±1.22	824.71±5.54
F15	92.51±2.75	40.00	35.43±0.06	88.57±0.15	870.63±3.63
F16	93.63±2.69	33.00	30.17±0.06	91.43±0.19	910.50±7.25

[a]mean±SD, *n* = 3.

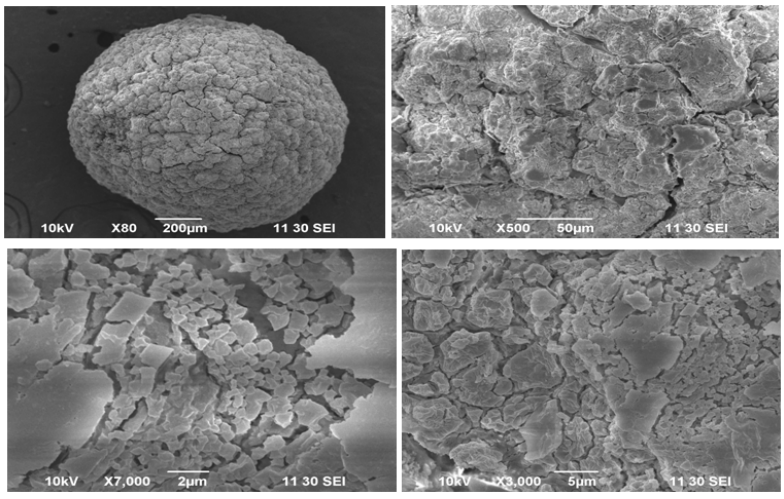

Fig. 1: Scanning electron photomicrographs of the Formulation F16, A): 80 X, B): 500 X, C): 7000X, D): 3000X

Morphology of microspheres

The SEM photographs revealed that obtained maraviroc microspheres were discrete and spherical shape with a rough surface morphology (fig.1) which could be due to the surface association of the Maraviroc with mucoadhesive polymer [24].

Entrapment efficiency

Maraviroc microspheres were characterized for percentage entrapment efficiency. The percentage entrapment efficiency ranged from 50.80 to 91.43%. (table 2).

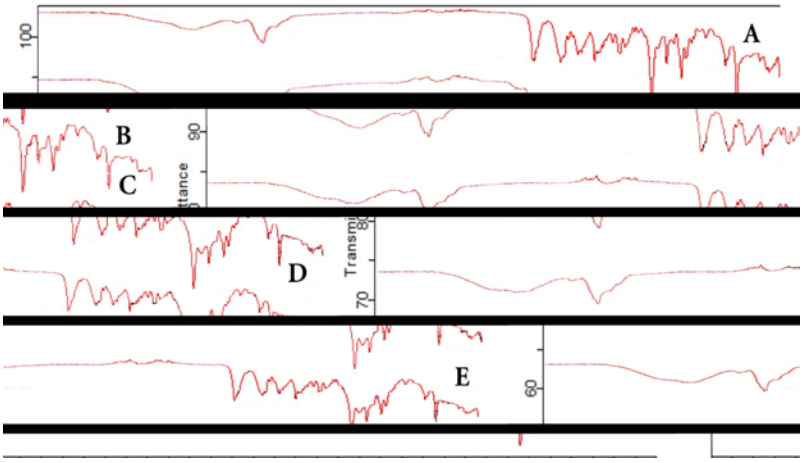

Fig. 2: FTIR spectra of, (A): Pure Maraviroc; (B): Formulation containing Pectin; (C): Formulation containing HPMC K4; (D): Formulation containing HPMC K15; (E): Formulation containing HPMC K100 (F16)

Stability study

After 3 months, storage of F16 formulation at 4±1 °C/Ambient, 25±2 °C/60±5 % RH, 40±2 °C/75±5 % RH, percentage entrapment efficiency, percentage mucoadhesion were checked and found to be almost similar to the initial values. There was no substantial alteration in any value and also the physical appearance. So it can be said that maraviroc mucoadhesive microspheres prepared with HPMC K100 is stable.

CONCLUSION

The HPMC K100 mucoadhesive microspheres containing maraviroc can be successfully prepared by ionotropic gelation technique. The prepared Maraviroc mucoadhesive microspheres were spherical and free flowing. The entrapment efficiencies ranged from 50.80 to 91.43% and mean size was in the range of 646.3±10.2 µm to 910.0±6.56 µm. Concentration of mucoadhesive polymer ratio influences the entrapment efficiency and maraviroc release profile of microspheres. Thus the investigation clearly indicated a promising potential of control release maraviroc mucoadhesive microspheres containing HPMC K100 as rate controlling polymer for the effective treatment of AIDS/HIV patients.

CONFLICTS OF INTERESTS

All authors have none to declare

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