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Research Article

DEVELOPMENT AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF HYDROCORTISONE SODIUM SUCCINATE IN THE TREATMENT OF CHRONIC SINUSITIS

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ABSTRACT

Objective: In the world, chronic sinusitis is one of the most common illness disorders. However, no viable medication has been identified to fully cure it as of yet. Patients are necessitated to use sprays, inhalers, and other devices to treat chronic sinusitis in contrast to all of its dangerous symptoms. However, these dosage forms need for concurrent administration, which cause inconvenient in the long term. An effort has been made to create a controlled release dosage form to increase patient compliance.

Methods: Two polymers Chitosan and HPMC were used to create hydrocortisone sodium succinate microspheres through the orifice-ionic gelation process.

Result and Discussion: It had a yield of about 89.33±2.33% drug entrapment efficiency and 86.65±0.25% percentage yield. The evaluation results for formulation F6 were the best of all the formulations.

Conclusion: It concluded that the most effective and promising dosage form was microspheres made from the drug (hydrocortisone sodium succinate), sodium alginate, and HPMC in the ratio of 1:2:2.

Keywords: Chronic sinusitis, Patient compliance, Orifice-ionic gelation method, Microspheres, HPMC.

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INTRODUCTION

Mucoadhesion is a relatively new and emerging topic. The idea behind mucoadhesion is that it enhances patient compliance by extending the residence duration of the medicine with the mucous membrane. The medicine is released in a controlled manner by these systems while they remain in close contact with the mucosal membrane, increasing the drug's bioavailability. Microspheres are solid, spherical particles with a size range between 1 and 1000 microns. They resemble powders that are composed of biodegradable synthetic polymers or proteins. Because they may generate a specific reaction and have a controlled release mechanism, microspheres are used to deliver drugs [1].

The process of mucoadhesion involves the creation of mucoadhesive connections in three easy steps between the polymer and the mucosal membrane as shown in Fig. 1.

1) Contact Stage: In this stage polymer is wetted and swollen.
2) Interpenetration stage: It occurs between mucous membrane and polymer chains of microspheres.
3) Consolidation stage: The entangled chains develop bonds with one another [2].

Mucoadhesive microspheres for oral, buccal, nasal, ophthalmic, rectal, and vaginal routes have recently been developed. However, a potent dose form that guarantees the highest level of safety and the least amount of toxicity is needed to treat a variety of nasal issues. There are numerous disadvantages to the use of conventional and traditional dosage forms to treat infections of the nasal cavity. In comparison to traditional drug delivery methods, mucoadhesive microspheres have various benefit including greater efficacy, reduced toxicity, and increased bioavailability [3].

Sinusitis is most common illness disorder. Mucous membrane that lines the sinuses which is severely inflamed is the condition known as sinusitis. Severe facial pain, a runny nose, fever, a bad sense of smell, etc., are symptoms of sinusitis. Infection, allergies, air pollution, bacterial or viral infections, nasal abnormalities, and other conditions are only a few of the many causes of sinusitis. While sinusitis often resolves within few weeks, in certain cases it can continue up to 12 weeks [4]. Sinusitis is of different types 1) Acute sinusitis 2) chronic sinusitis. Acute sinusitis happens when the inflammation subsides within 10–14 days of when it first appears. Chronic sinusitis can last longer than 12 weeks makes it awful. This study is a minor first step toward the treatment of chronic sinusitis using hydrocortisone sodium succinate microspheres. An anti-inflammatory corticosteroid is hydrocortisone sodium succinate. It is frequently given to treat rhinitis. The stimulation of glucocorticoid receptors is an aspect of its mechanism of action [5,6].

METHODS

Hydrocortisone sodium succinate was procured from Combiotic Global Caplet Pvt. Ltd. Sonipat. Chitosan were obtained from Central Drug House Ltd. Bombay, New Delhi. Hydroxypropylmethyl cellulose and sodium alginate were obtained from Loba Chemie Pvt. Ltd. Mumbai, India. Calcium chloride was obtained from Nice Chemicals Pvt. Ltd. Kerala, India. All the chemicals used were of fine grade [7-9].

Preformulation studies

FTIR compatibility studies

The compatibility of the API (Hydrocortisone sodium succinate) with polymers was examined by using FTIR spectroscopy (chitosan, HPMC). The findings of FTIR studies on the pure drug and drug-excipient combinations were analyzed. The graph below shows how the study's findings were interpreted as shown in Figs. 2-4 and Table 9.

Preparation of mucoadhesive microspheres

Hydrocortisone sodium succinate mucoadhesive microspheres were developed using the orifice ionic gelation process. Table 1 provides the optimized formulation for hydrocortisone sodium succinate microspheres as well as the components of each formulation. The method for creating mucoadhesive microspheres is as follows:

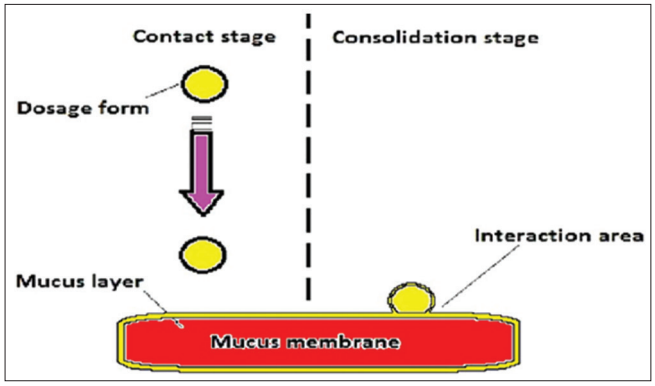

Fig. 1: Mechanism of mucoadhesion

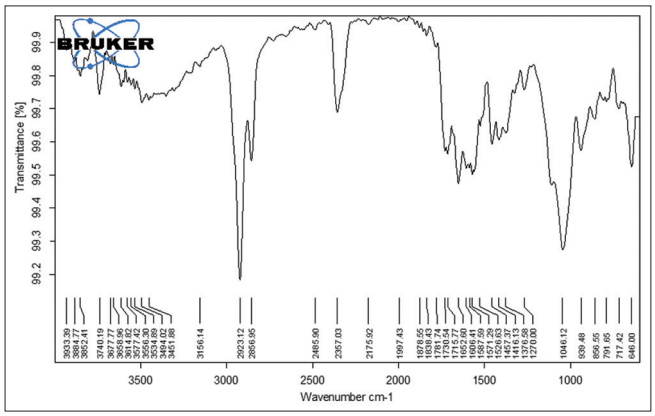

Fig. 2: FTIR spectrum of hydrocortisone sodium succinate and HPMC

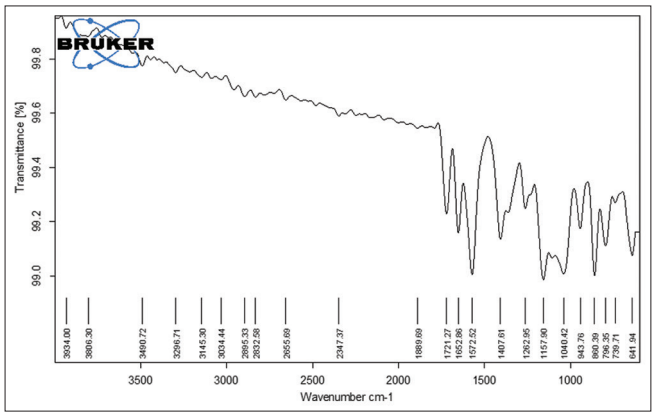

Fig. 3: FITR spectrum of hydrocortisone sodium succinate

1) To achieve consistent particle size, the medication hydrocortisone sodium succinate and polymers such chitosan, HPMC, and sodium alginate were passed through sieve no. 40.
2) A 5% calcium chloride solution was made in distilled water and set aside in one beaker.
3) Sodium alginate, chitosan, and HPMC were placed in a separate beaker with 25 ml of distilled water in various ratios in accordance with the formula shown in Table 1.
4) To create uniform slurry, the drug was gradually added to the beaker containing the polymers and sodium alginate while being constantly stirred.
5) In a syringe, a homogenous mixture of the medication, sodium alginate, and mucoadhesive polymer was added dropwise to a solution containing 5% calcium chloride solution while being stirred at 50 revolutions/min.

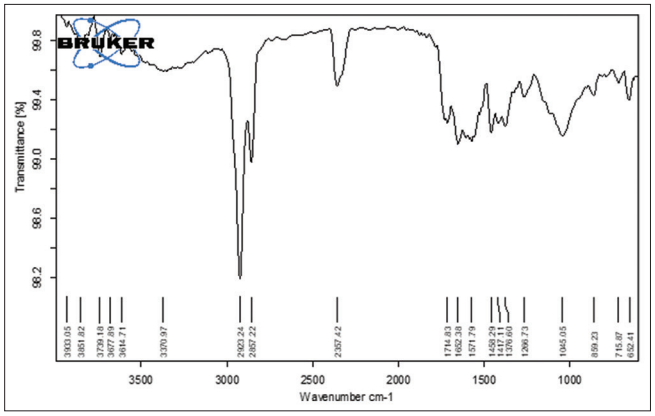

Fig. 4: FTIR spectrum of hydrocortisone sodium succinate and Chitosan

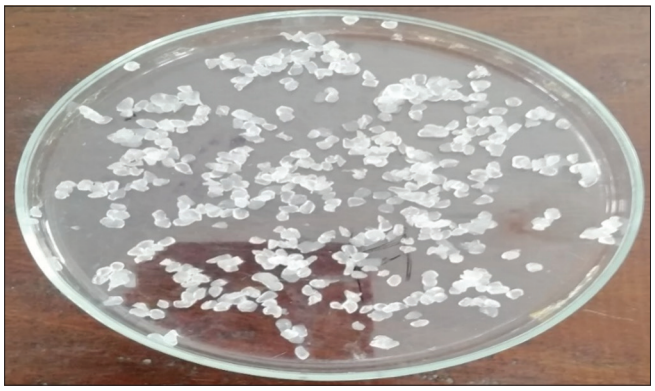

Fig. 5: Image of formed microspheres by ionotropic gelation technique

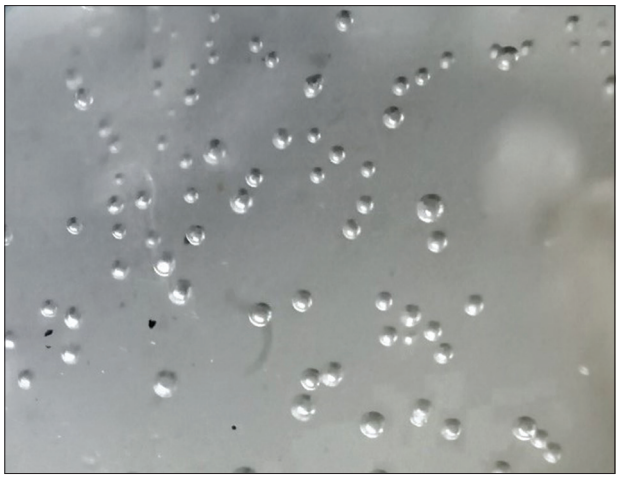

Fig. 6: Microscopic view of hydrocortisone sodium succinate microspheres

6) The resulting microspheres were then allowed to react in calcium chloride solution for 30 min. Decanted microspheres were shaped into mucoadhesive microspheres, which were then rinsed with distilled water and allowed to air dry over the course of one night at room temperature as shown in Fig. 5.

Evaluation of microspheres

Particle size and shape analysis

100 microspheres were chosen at random from each formulation and examined with a calibrated oculometer and stage micrometer

Table 1: Compositions of mucoadhesive microspheres of hydrocortisone sodium succinate

S. No	Formula code	Sodium alginate (mg)	Chitosan (mg)	HPMC (mg)	Distilled water (ml)	Calcium chloride (%)	Drug: Sodium alginate: Polymer
1.	F1	100	100	-	25	5	1:1:1
2.	F2	100	-	100	25	5	1:1:1
3.	F3	200	100	-	25	5	1:2:1
4.	F4	200	-	100	25	5	1:2:1
5.	F5	200	200	-	25	5	1:2:2
6.	F6	200	-	200	25	5	1:2:2

Table 2: Particle size distribution of microspheres

S. No.	Formulation code	Particle size (μm)±SD
1.	F1	247±0.5
2.	F2	237±1.29
3.	F3	355±0.38
4.	F4	372±0.28
5.	F5	488±4.2
6.	F6	510±3.4

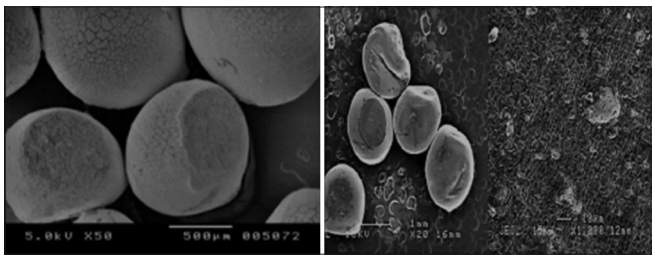

Fig. 7: Scanning electron microscopy of optimized formula (F6)

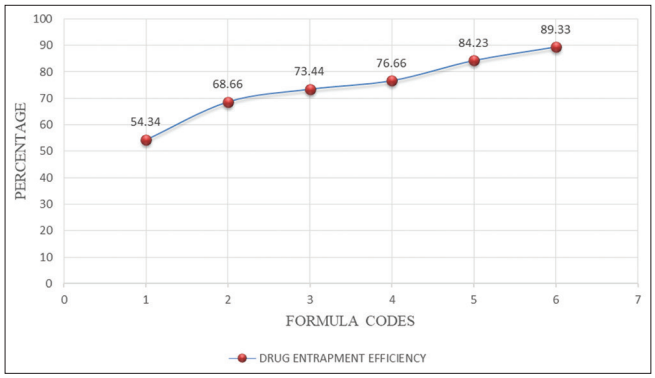

Fig. 8: Graphical representation of drug entrapment efficiency

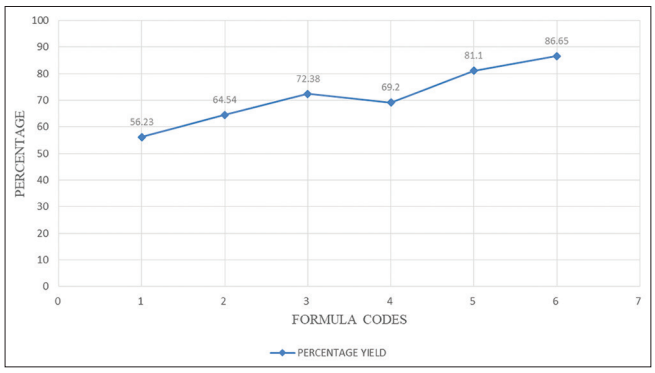

Fig. 9: Graphical representation of percentage yield

to determine their size and shape. Visual observations enabled the observation of shape and size [10].

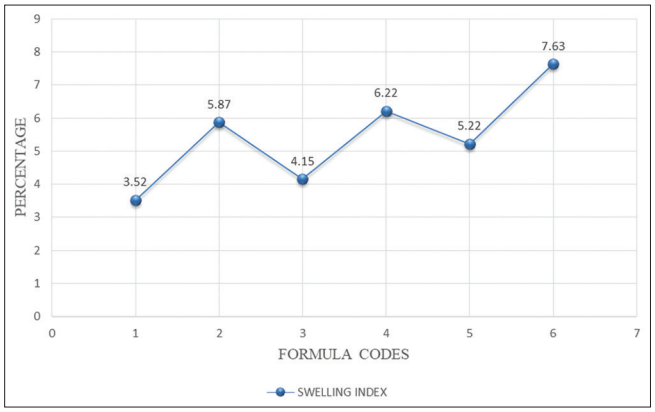

Fig. 10: Graphical representation of swelling index

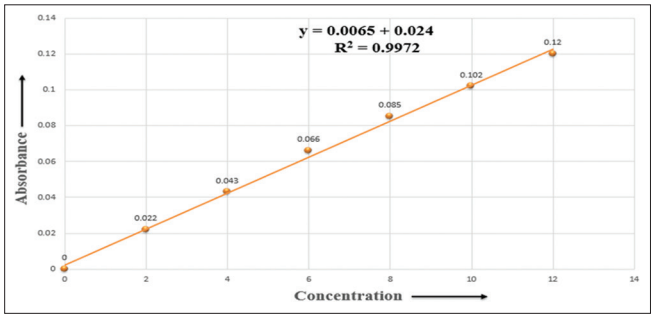

Fig. 11: Standard curve of hydrocortisone sodium succinate

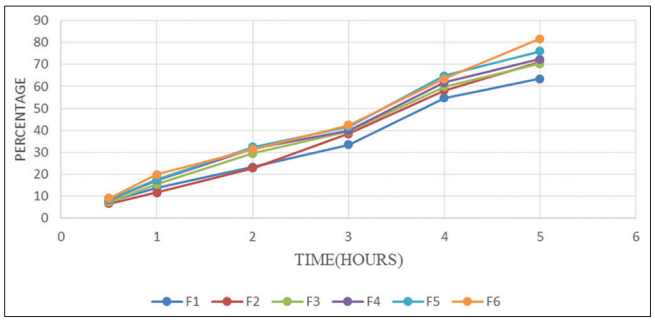

Fig. 12: Graphical representation of percentage drug release

Surface morphology

Scanning electron microscope (SEM, Philips XL20, and Holland) images of the internal cross section and surface morphology of an optimized batch (F6) of microspheres were acquired in a vacuum. Under reduced pressure and vacuum, gold film was applied to the dry microspheres as they were placed on the SEM stub. Later, photomicrography was performed using a 10 Kv voltage [11].

Drug entrapment efficiency

Using the formula shown below, the hydrocortisone sodium succinate microspheres entrapment efficiency was determined. From each formulation, 10 mg of dried hydrocortisone sodium succinate microspheres were crushed and dissolved in 100 ml of acetone solution. The solution was rapidly shaken and then filtered after interacting for 24 h. The aliquots were obtained, diluted (2, 4, 6, 8, 10, and 12 g/ml), and examined using a UV spectrophotometer at 290 nm to determine the degree of drug entrapment [12].

$$\text{Drug entrapment efficiency}(\%) = \frac{A.C}{T.C} \times 100$$

Where, A.C = Actual content of drug

T.C = Theoretical content of drug.

Percentage yield

The dried weight of the microspheres that had been formed was divided by the total of the original weights of the medication and polymer that had been used in each formulation to determine the percentage yield for each batch of microspheres [13].

$$\text{Percentage yield} = \frac{\text{Weight of dried microspheres}}{\text{Weight of drug} + \text{Weight of polymer}} \times 100$$

Swelling index

We measured the swelling capacity of hydrocortisone sodium succinate microspheres by dissolving approximately 100 mg of dried microspheres from each batch in phosphate buffer solution (pH 6.8). The microspheres were checked at intervals of 1 h, and if any weight gain was reported [14].

$$\text{Swelling index} = \left(\text{mass of swollen microsphere} - \text{mass of dried microsphere} \times 100\right)$$

In-Vitro test

To study *in-vitro* experiments, a USP dissolution test device was used. A weighed quantity of microspheres was added to 900 ml of phosphate buffer dissolving media (pH 6.8) that was kept at 37±0.5°C throughout the investigation. 5 ml of the sample was taken out and put back in at regular intervals, along with new dissolving medium, into the flask. The medication concentration in the samples was evaluated spectrophotometrically at 290 nm after the proper dilutions. The *in vitro* drug release experiments took place in ideal sink conditions [15].

In-vitro wash off test (mucoadhesive test)

An *in-vitro* wash off test was used to examine the hydrocortisone sodium succinate microspheres ability to adhere to mucous membranes. A freshly removed piece of goat intestinal mucosa (4×5 cm) was put on glass slides, wrapped with thread, and then suspended on to the arm of a device used to evaluate the USP tablet disintegrating test apparatus. The tissue sample was given a gradual, regular up and down movement in the dissolve fluid (500 ml) maintained at 37°C in a 1000 ml vessel of the disintegrating test apparatus while it was in operation. The equipment was ceased every hour and counted how many microspheres were still adhered to the tissue. Repeatedly performing this method took roughly 7 h [16].

Accelerated stability studies

Stability testing was done for the improved formula in accordance with ICH recommendations (Q1A). For 30, 60, and 90 days, the optimized formula was maintained at 40±2°C, 75±5 RH. Particle size, drug entrapment effectiveness, a mucoadhesive test, and *in vitro* drug release were later evaluated for this formulation. The outcomes are listed below [17].

RESULTS AND DISCUSSION

Particle shape and size analysis

Under a microscope, the generated microspheres shape could be seen. Microspheres of hydrocortisone sodium succinate had an apparent spherical form. This test was carried out to evaluate how the microscope will look after drying. With an increase in sodium alginate and mucoadhesive polymer concentration, it was discovered that average particle size was increasing. Particle sizes for Formulation F6 were the biggest as shown in Table 2 and Fig. 6.

Surface morphology

Under a SEM, the hydrocortisone sodium succinate microspheres of optimized formula F6 were examined. On one side of an adhesive stub, the sample was scattered. Under the SEM, the microspheres' size and surface shape were evaluated. The SEM of the F6 formulation revealed a spherical shape with a smooth exterior and a rough, pore-filled interior as shown in Fig. 7. Drug transport from the core is accelerated by the presence of a rough surface.

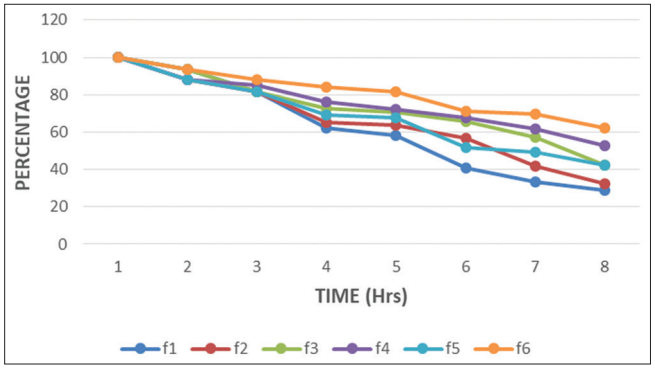

Fig. 13: Graphical representation of mucoadhesive strength

Table 3: Percentage drug entrapment efficiency

S. No.	Formula code	Drug entrapment efficiency (%) ±SD
1.	F1	54.34±2.09
2.	F2	68.66±2.43
3.	F3	73.44±2.32
4.	F4	76.66±2.54
5.	F5	84.23±2.83
6.	F6	89.33±2.33

Table 4: Percentage yield

S. No.	Formula code	Percentage yield (%) ±SD
1.	F1	56.23±2.10
2.	F2	64.54±3.22
3.	F3	72.38±0.65
4.	F4	69.20±1.90
5.	F5	81.10±2.95
6.	F6	86.65±0.25

Table 5: Swelling index

S. No.	Formula code	Swelling index (%) ±SD
1.	F1	3.52±0.05
2.	F2	5.87±0.08
3.	F3	4.15±0.12
4.	F4	6.22±0.90
5.	F5	5.22±1.90
6.	F6	7.63±0.07

Table 6: Data of *in vitro* test

Time (hours)	F1 (%) ±SD	F2 (%) ±SD	F3 (%) ±SD	F4 (%) ±SD	F5 (%) ±SD	F6 (%) ±SD
0.5	7.5±0.16	6.62±0.90	7.39±0.18	8.32±0.14	8.72±0.14	9.14±0.07
1	13.89±0.11	11.58±1.54	15.46±1.56	17.29±0.61	17.42±1.04	19.84±1.54
2	23.36±1.23	22.76±0.55	29.56±1.55	31.56±1.53	32.46±1.65	31.36±1.52
3	33.45±1.55	38.43±0.01	39.45±0.56	39.78±1.01	41.68±0.51	42.34±0.57
4	54.81±0.61	58.16±0.54	59.89±0.07	61.87±0.54	64.87±1.26	63.47±0.52
5	63.46±1.54	71.08±0.50	70.45±0.21	72.38±0.65	76.12±1.16	81.76±0.55

Table 7: Data of *in vitro* wash off test

Time (hrs.)	F1	F2	F3	F4	F5	F6
0	100±0.25	100±0.25	100±0.25	100±0.25	100±0.25	100±0.25
1	93.67±1.12	87.93±1.34	93.67±1.12	87.93±1.34	87.93±1.34	93.67±1.12
2	81.41±1.64	81.41±1.64	81.41±1.64	85.12±1.08	81.41±1.64	87.93±1.34
3	61.96±1.45	65.08±1.54	72.58±0.92	76.32±1.76	69.26±0.54	84.23±2.83
4	58.43±1.26	63.45±1.73	70.45±0.21	72.38±0.65	67.69±1.34	81.76±0.55
5	40.56±0.61	56.89±1.55	65.56±0.07	67.89±0.91	51.87±1.21	71.08±0.50
6	33.45±1.55	41.68±0.51	57.14±0.54	61.87±0.54	49.07±0.23	69.90±0.16
7	29.07±1.54	32.46±1.65	42.34±0.57	52.98±0.07	42.34±0.57	61.96±1.45

Table 8: Stability studies data

Evaluation parameters	Formula code	0 day±SD	30 days±SD	60 days±SD	90 days±SD
Particle size (μm)	F6	510±3.4	510±3.4	501±0.75	497±0.90
Percentage drug entrapped	F6	89.33±2.33	88.90±0.17	86.92±0.67	86.22±0.43
Percentage *in vitro* drug release	F6	81.76±3.4	81.76±3.4	80±0.75	79±0.25

Table 9: FITR spectrum of hydrocortisone sodium succinate, HPMC, Chitosan and physical mixture of hydrocortisone sodium succinate, HPMC, Chitosan

Sample	Infrared peaks (cm^{-1})	Functional groups
Hydrocortisone sodium succinate	860.39	C-H out of plane bending
	1040.42	C-H in plane bending
	1157.90	C-O stretching
	1262.95	C-C stretching
	1407.61	CH_3 asymmetrical bending
	1652.86	Aromatic C=C stretching
	1721.27	C=O stretching
	3490.72	O-H stretching
HPMC	1062.62	C-O bonds
	1377.19	O-H bending
	3073.19	C-H stretching
	3241.78	N-H of amide group
	3456.58	O-H stretching frequency
Chitosan	1043.59	C-O stretching
	1119.56	Asymmetric stretching of C- O-C bridge
	1378.92-1412.49	C-N of stretching of amide III
	1434.85	CH_3 symmetrical deformations
	1558.96	CH_2 bending
	1601.66	N-H bending of amide II
	1654.16	N-H bending of primary amine
	2930.09	C=O stretching of amide
	2884.55	C-H symmetric stretching
	3294.83-3410.49	C-H asymmetric stretching corresponds to N-H,O-H stretching as well as intramolecular –H bonds
Physical mixture of hydrocortisone sodium succinate and HPMC	1270.00	C=O stretching
	2357.03	C-H stretching
	2856.90	N-H stretching
	2923.12	O-H stretching
Physical mixture of hydrocortisone sodium succinate and Chitosan	1652.38	C=O stretching
	2357.42	C-H stretching
	2857.22	N-H bending
	2923.24	O-H stretching

Drug entrapment efficiency

Table 3 and Fig. 8 contains a list of all the microspheres' drug entrapment effectiveness. According to the findings, of all the formulations tested, F6 has the highest drug entrapment efficiency. It is most heavily drug-entrapped. In addition, it suggests that a higher sodium alginate concentration effectively entraps the medication.

Percentage yield

In comparison to other formulations, formulation F6 displayed a superior percentage yield, or approximately 86.65±0.25% as shown in Table 4 and Fig. 9.

Swelling index

It shows how much water each type of polymer can hold. As time went on, it was discovered that the hydrophilic property of the polymers caused them to absorb water and expand up when microspheres were surrounded by water. As the amount of mucoadhesive polymer increases, swelling index rises. At a concentration of 2:1 more than the medication, HPMC (F6) had a swelling index that was higher than that of chitosan as shown in Table 5 and Fig. 10.

***In vitro* test**

As shown in Table 6 and Fig.12 and the Fig. 11 shows the standard curve of hydrocortisone sodium succinate in ethanol.

In vitro wash off test (mucoadhesive test)

The mucoadhesive properties of microspheres containing sodium alginate and HPMC are well-observed. Due to the hydrophilic linkages that develop between the polymers when the polymer concentration rises, adhesion between the polymers and mucosal surfaces occurs. Due to this, the drug's residence time increases. In addition, mucoadhesion also rises with an increase in sodium alginate concentration, as seen in formula F6 as shown in Table 7 and Fig. 13.

Accelerated stability studies

Stability tests were performed on the improved formulation (F6). The table below displays the results. The Table 8 given below displays the results.

FTIR study

To comprehend the relationship between the medication and excipients, a comparative FTIR analysis was conducted. The peaks in hydrocortisone sodium succinate, HPMC, and sodium alginate may be seen between 400 and 2000 cm^{-1}. The FTIR measurements revealed little detectable change, demonstrating high compatibility between the medication and excipients as shown in Figs. 2-4 and Table 9.

CONCLUSION

In this study, an effort was made to create mucoadhesive hydrocortisone sodium succinate microspheres with the goal of treating and managing chronic sinusitis. Utilizing the polymers HPMC, chitosan, and sodium alginate, orifice ionic gelation technique was used. Cross-linking agent employed was calcium chloride. The primary goals were to increase the drug's residence time and mucoadhesive properties to improve patient compliance. The formula (F6) was found to be a promising dosage form for nasal medication delivery after passing all evaluation criteria. This study makes a modest contribution to the field of nasal medicine delivery and intends to help chronic sinusitis patients with frequent administration issues.

AUTHORS' CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Nikita SD. Microsphere: A complete. World J Pharm Pharm Sci 2018;7:786-817.
2. Vyas SP, Khar RK. Controlled Drug Delivery Concept and Advances. 1st ed. New Delhi: Vallabh Prakashan; 2002. p. 419-24.
3. Tripathi KD. Essential of Medical Pharmacology. 6th ed. New Delhi: JP Brother and Medical Publisher and Pvt Ltd.; 2008. p. 254-74.
4. Jain NK. Progress in Controlled and Novel Drug Delivery System. 1st ed. New Delhi: CBS Publisher and Distributers; 2004. p. 353-76.
5. Sedaghat AR. Chronic rhinosinusitis. Am Fam Physician 2017;96:500-6.
6. Rudmik L, Soler ZM. Medical therapies for adult chronic sinusitis: A systematic review. JAMA 2015;314:926-39.
7. Rao DS, Reddy SH, Ramu S, Rambabu E. Preparation and evaluation of mucoadhesive microspheres of simvastatin by ionic gelation technique. Am J Adv Drug Deliv 2014;2:594-608.
8. Roy S, Pal K, Anis A, Pramanik K, Prabhakar B. Polymers in mucoadhesive drug delivery systems: A brief note. Des Monomers Polym 2009;12:483-95.
9. Jithendra T, Reddy OS, Subha MC, Madhavi C, Rao KC. Xanthan gum graft copolymer/sodium alginate micro beads coated with chitosan for controlled release of chlorthalidone drug. Int J Pharm Sci Res 2020;11:1132-45.
10. Parmar H, Bakliwal S, Gujarathi N, Rane B, Pawar S. Different methods of formulation and evaluation of mucoadhesive microsphere. Int J Appl Biol Pharm 2010;I:1157-67.
11. Kumar AS, Nair SS. Formulation and evaluation of colon targeted microspheres of glipizide. Int J Pharm Sci Res 2020;11:1183-9.
12. Khan A, Umadevi SK, Reddy BV, Navaneetha K, Reddy RS, Ravi M, *et al*. Formulation and evaluation of mucoadhesive microspheres of valsartan. Indo Am J Pharm 2014;4:3634-540.
13. Kushwaha SK, Keshari RK, Rai AK. Advances in nasal transmucosal drug delivery. J Appl Pharm Sci 2011;1:21-8.
14. Pandey J, Tripathi PK. Mucoadhesive microspheres of anti-allergic agent for nasal delivery. AJPTI 2016;4:48-58.
15. Albu S. Chronic rhinosinusitis-an update on epidemiology, pathogenesis and management. J Clin Med 2020;9:2285.
16. Kashyap N, Mishra A, Pathak AK. Preparation and evaluation of mucoadhasive microspheres of Propranolol HCl for nasal delivery. Int J Adv Pharm 2015;4:49-54.
17. Pandey J, Tripathi PK. Formulation and evaluation of levocetirizine loaded mucoadhesive microspheres for nasal delivery. Int J Pharm Sci Res 2016;7:2242-51.