NATURALISTA CAMPANO
ISSN: 1827-7160
Volume 28 Issue 1, 2024

Fabrication, Characterization and in Vitro Assessment of Gastroretentive Mucoadhesive Microspheres of Boswellic Acid Isolated from Boswelliaserrata Resin

Kunal Arora[1], P. Manikandan[2], Payal Dasgupta[3*], SoniyaR[4], Fahim Ansari[5], CharulataTushar Nemade[6], Hitesh Vishwanath Shahare[7], Sonali A. Bhagat[8]

[1]Faculty of Pharmacy, Swami VivekanandSubharti University, Meerut, Pin Code- 250005, Uttar Pradesh, India.
[2]Senghundhar College of pharmacy, Tiruchengode -637205.Tamilnadu, India.
[3]Royal School of Pharmacy, The Assam Royal Global University, Betkuchi, Guwahati, Assam 781035.
[4]Department of Microbiology, SRM Dental College, Ramapuram,Chennai– 89.
[5]Department of Pharmaceutics, R PInstitute of Pharmacy, Bastara, Karnal 132114(Haryana).
[6]SNJB's ShrimanSureshdada Jain College of Pharmacy Chandwad Nashik Maharashtra IndiaPin code:-423101.
[7]SNJB's ShrimanSureshdada Jain College of Pharmacy Chandwad Nashik Maharashtra IndiaPin code:-423101.
[8]Department of Pharmaceutics, Indira College of Pharmacy, Vishnupuri, Nanded-431606 (Maharashtra)

Corresponding Author
Payal Dasgupta[3*]
[3]Royal School of Pharmacy, The Assam Royal Global University, Betkuchi, Guwahati, Assam 781035.

Abstract: The purpose of this study is to design and evaluate formulations of gastroretentive mucoadhesive microspheres that loads boswellic acid. Heat stabilisation and single-phase emulsification were used to prepare the mucoadhesive microspheres. The process of chemical stabilisation emerged as a quick and easy way to fabricate microspheres loaded with Boswellic acid. This approach generated microspheres with a high drug encapsulation efficiency, adequate manufacturing yield, and batch-to-batch repeatability. The best and optimized formulation among all might be regarded as microspheres with a drug and polymer ratio of 1:2 (MC2) as it has the greatest mucoadhesive and drug release properties.

Keywords: Microspheres, Mucoadhesive, Boswellic acid, Chemical stabilization, Gastroretentive

1. Introduction

Any drug delivery system's objective is to sustain the intended drug concentration while delivering a therapeutic dose of the active ingredient to the target spot in the body. Following the injection of a standard dosage, the medication spreads freely throughout the body, interacting with both the target and healthy cells in the process, frequently leading to harmful consequences (Khan et al. 2015; Shadab et al. 2012). The drug must be delivered to the target tissue in the ideal amount and at the ideal timing to achieve optimum therapeutic efficacy with the least degree of toxicity and adverse effects.Target-oriented drug delivery systems may be the most effective in delivering the medication to the intended site of action with maximum therapeutic activity (by means of regulated and pre-established drug release kinetics) while shielding the body from unfavourable reactions resulting from improper disposal. Therapeutic substances can be delivered to the target location in a number of ways using prolonged, controlled release techniques. Using biologically inert carrier systems to deliver medications to a particular location within the body is one such method (Jain et al. 2012; Shivanand 2010). Up till now, a variety of drug carriers have been investigated; the most commonly used are colloidal and cellular drug carriers.Cellular carriers include leukocytes, platelets, and erythrocytes; colloidal carriers include liposomes, niosomes, nanoparticles, and microspheres. Targeting is the process of directing a drug to a particular organ or tissue by either altering the drug carrier's natural distribution pattern through various means (polymer coating, attachment with particular ligands, etc.) or by taking advantage of the carrier's natural distribution pattern, known as passive targeting. We refer to this as active targeting. Another tool for this kind of targeting is the microsphere (Mohan et al. 2014).

Mucoadhesive microspheres are made up of either an exterior coating or a complete mucoadhesive polymer. They can be microparticles or microcapsules (with a drug core) with a diameter of 1-1000µm. 1 In general, microspheres hold promise for targeted and controlled release medication administration; however, adding mucoadhesive qualities to microspheres confers further benefits. For example, effective absorption increased the drugs' bioavailability because of a high surface to volume ratio, a closer interaction with the mucous layer, and the ability to target drugs specifically to the absorption site by attaching plant lectins, bacterial adhesion, antibodies, and other materials to the surface of microspheres (Shadab et al. 2012).Mucoadhesive microspheres have the ability to stick to any mucosal tissue, such as that in the eye, nose, urinary tract, and gastrointestinal tract. This means that controlled medication release can occur both locally and systemically (Patil and Sawant 2008; Shadab et al. 2012).

Recently, there has been a lot of interest in innovative dosage forms that can target the active drug molecule to a specific spot and manage the release rate. One of the innovative medication delivery technologies, microspheres are composed of several polymers and have multiple uses. Often measuring between 1 µm and 1000 µm in diameter, microspheres are also known as microparticles. The polymers used to make the microspheres might be synthetic or natural.In general, microspheres have the potential to be used for targeted, controlled, or prolonged drug release; however, adding mucoadhesive qualities to microspheres will also enhance the medications' bioavailability and absorption. Mucoadhesive microspheres enhance tight contact between the drug targeting the absorption location and the mucus layer by attaching bacterial adhesions, plant lectins, antibodies, and other substances. Customized mucoadhesive microspheres can stick to any mucosal tissue found in the GI system, nose, eyes, or urine tract, allowing for both localised and regulated medication release (Shukla and Tiwari 2012; Sinha et al. 2004; Sivadas et al. 2008). Because mucoadhesive microspheres have a high surface to volume ratio, make much closer contact with the mucus layer, and specifically target the absorption site for the medications, they have effective absorption and increased bioavailability of the pharmaceuticals. The most common use of mucoadhesion is in innovative medication delivery systems. The phrase mucoadhesion, which characterises the sticky contacts that happen between polymer surface and mucus membrane or mucosal faces, combines the phrases muco and adhesion. Put another way, it describes the situation when two surfaces, at least one of which is biological in origin, are kept together in close proximity over a prolonged period of time by interfacial forces (ChunCho et al. 2005; ChunSah et al. 2005; Soane et al. 1999; Sun et al. 2009).

Pharmaceutical experts have lately become interested in mucoadhesive polymers as a way to enhance drug administration by lengthening the dosage form's residency and contact times with the mucous membranes. Mucoadhesion is the process by which synthetic and natural polymers adhere to the mucosal surfaces of the body. The medicine may be delivered at the location for a longer amount of time or mucosal cells may absorb the drug more readily if these ingredients are added to pharmaceutical formulations.Additional advantages of the mucoadhesive qualities combined with microspheres include a far closer interaction with the mucus layer, effective absorption, and increased drug bioavailability because of the high surface to volume ratio. Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery(Hall 2010).

Because of their anti-inflammatory and analgesic properties, non-steroidal anti-inflammatory medications (NSAIDs) make up 8% of prescriptions globally, with those over 65 using them most frequently. In addition, there has been a rise in over-the-counter usage, with 26% of users exceeding the suggested dosage and many of them being unreported to medical experts. 1,2 NSAID-related side effects that are most commonly recognised include bleeding and symptomatic upper gastrointestinal (GI) peptic ulcer disease. But NSAID-related side effects can happen with or without symptoms, in the event of mucosal damage, and in the upper, mid, and lower gastrointestinal (GI) tracts (up to the second half of the duodenum, or D2) (Tai and McAlindon 2021).

Peptic ulcers are mostly treated with two major methods. The first focuses on lowering stomach acid production, while the second supports the preservation of the stomach mucosa (Goodman et al. 2011). Proton pump inhibitors, cytoprotectants, and H2 receptor antagonists are examples of widely used anti-ulcer medications with drawbacks and adverse effects (Brenner and Stevens 2009; Tripathi 2008). Thus, natural compounds with ulcer-preventing qualities are favoured. Many herbs and plants have been used to cure stomach ulcers and other gastrointestinal issues. Boswellic acid, one of the phytocompounds, Resin *Boswellia serrata*, which was isolated from an indigenous plant, has been shown to have anti-peptic ulcer properties (Khare 2007; Mukherjee et al. 2010; N and Chopra 2006).Pentacyclic triterpene molecule Boswellicacid has a variety of properties, including anti-inflammatory, anti-fungal, anti-ulcer, anti-bacterial, anti-viral, and anti-cancer properties. Thus, in order to treat peptic ulcers, the current work manufactures and evaluates mucoadhesiveBoswellic acid microspheres.

2. Material and methods

Materials

As a standard or reference substance, a pure medicine sample of boswellic acid was acquired from Sigma Aldrich, Mubmai, India. The sole authorised suppliers of boswelliaserrata resin were found at AzadpurMandi, KharBauri, Delhi, India. In our laboratory, boswellic acid was extracted using an extraction technique that had previously been established and verified. The remaining chemicals and reagents were all analytical grade and came from reliable suppliers. Among these substances and reagents are ammonium hydroxide, liquid paraffin, silica gel, hydrochloric acid, glutaraldehyde, carbopol, acetone, and bovine serum albumin (BSA).

Formulation of microspheres

Method of Chemical stabilization

Boswellic acid mucoadhesive microspheres were created using a single-phase emulsification technique. Glutaraldehyde served as a chemical cross-linker, and the polymers employed were bovine serum albumin and carbopol 934P. Water was used to dissolve the medication and polymers in the prescribed amounts. A beaker of liquid paraffin was poured with the mixture, and at 15 degrees Celsius, shear (100 rpm) was applied to form the main emulsion.Drop by drop, glutaraldehyde was applied to the polymer to facilitate surface cross-linking. Centrifugation was used after six hours to separate the microspheres. Microspheres were finally vacuum-dried after three acetone washes. MC1, MC2, MC3, and MC4 are the names of the four microsphere formulations that were created in this manner, with drug polymer ratios of 1:1, 1:2, 1:3, and 1: 4.

Heat stabilization method

In the heat stabilisation procedure, the Boswellic acid-loaded microspheres were finally rigidified and stabilised by applying heat, or a rise in temperature. The polymers that were employed were Carbopol 934P and bovine serum albumin. The protein at the surface became denaturized when heat was applied. The main emulsion was prepared by dissolving a certain amount of medicine and polymers in water. This mixture was then added to a beaker that was filled with liquid paraffin and heated to 15 degrees Celsius. Next, shear (100 rpm) was used.Consequently, rigidization at the surface results from the application of heat and a linear temperature increase up to 70°C. After that, the microspheres were separated using a 6-hour centrifugation process. After three rounds of acetone washing, the microspheres were vacuum-dried. In a similar manner, four formulations of microspheres with drug polymer ratios of1:1,1:2,1:3, and 1: 4 were created and given the names MH1, MH2, MH3, and MH4.

Microspheres Characterization

Particle size study, Assessment of Uniformity Index and Elongation ratio

The particle size of the microspheres was measured using a stage micrometer scale. Dry microspheres (5 mg) were suspended in distilled water and ultrasonicated for 5s. A drop of suspension was placed on a clean glass slide and microspheres were counted under stage ocular micrometer. A minimum of 200 microspheres was counted per batch. The microspheres' mean diameter (µm) ± standard deviation represented the average size of every batch (SD). By calculating the elongation ratio (ER), or the microspheres' quotient of length and width, the form of the microspheres was ascertained. The ideal spherical, spherical, and non-spherical shapes are represented by ER = 1.1 < ER < 1.15, and ER > 1.15, respectively (Das and Ng 2010).

The following formula was used to get the Uniformity Index (UI):

$$UI = \frac{D_W}{D_N}$$

where the following formulas are used to obtain Dw and Dn, which stand for weight average diameter and number average diameter, respectively:

Uniformity Index (UI):

UI = Σ(N_i * D_i^4) / Σ(N_i * D_i^3)

Mean Diameter (Dn):

Dn = Σ(N_i * D_i) / Σ(N_i)

Where:

N_i is the number of particles with diameter D_i.

The Uniformity Index, or UI, has values over 1.2 indicating a wide particle size distribution and values below 1.2 indicating a monodisperse distribution.

Scanning Electron Microscopy (SEM): ***Morphological Examination***

The morphology of microspheres was examined by scanning electron microscopy (SEM, JSM-5310LV scanning microscope Tokyo, Japan). The microspheres were mounted on metal stubs using double-sided tape and coated with a 150 Å layer of gold under vacuum. Stubs were visualized under scanning electron microscope (Hardenia et al. 2011).

Encapsulation Efficiency and Drug Loading

Using a UV spectrophotometer, samples from each batch of microspheres were dissolved in a phosphate buffer solution (pH 7.4) to ascertain the true drug concentration (Shimadzu UV, 1601). The ratio of real to theoretical drug content was used to compute encapsulation efficiency, which was then reported as a percentage (Yadav and Jain 2011).

Percentage Yield

The number of microspheres collected in proportion to the microsphere's theoretical content was used to compute the production yield. The % yield was calculated using the following formula: (Yadav and Jain 2011)

$$\text{Yield (\%)} = \frac{Quantity\ of\ microspheres\ acquired}{Theoretical\ content} \times 100$$

Swelling Index

The swelling of microspheres was conducted in phosphate buffer pH 6.8. The sizes of dried microsphere and those after incubation in phosphate buffer (pH 6.8) for 0.3, 1.0, 3.0 and 5.0 h were measured by using microscopic method. The percentage of swelling at different time interval was determined by the difference between diameter of microspheres at time t (Dt) and initial time (t = 0 [D0]) as calculated from the following equation(Shivanand et al. 2010).

$$\textbf{Swelling Index} = \frac{We - W_O}{W_O}$$

Where Wo denotes the dry microspheres' initial weight and We denotes the bigger, swollen microspheres' weight in the medium at equilibrium.

Mucoadhesion study

Using an in-vitro adhesion testing technique called the "wash off method," the mucoadhesive capability of the microspheres was assessed. A 1x1 cm piece of goat stomach mucosa was secured with thread to a glass slide. The tissue samples was wet washed and then coated with about 100 microspheres. The prepared slide was then placed in one of the grooves of a USP pill dissolving test device. The tissue specimen was regularly moved up and down in the disintegrating equipment's beaker, which held the gastric juice, as the disintegrating test device was run (pH 1.2). The amount of microspheres that were remained attached to the tissue was counted after 30 minutes, an hour, and then every hour for the next four hours (Hardenia et al. 2011).

$$Percent\ mucoadhesion = \frac{weight\ of\ adhered\ microspheres}{weight\ of\ applied\ microspheres} \times 100$$

Drug release study In vitro

Utilizing 900ml of 0.1N HCL medium as a dissolving media, the drug release investigation was conducted at 37 ± 0.5ºC and 100 RPM using a USP paddle type equipment. Five millilitres of the aliquot were taken out every twelve hours at prearranged intervals. Every time, 5 millilitres of brand-new buffer were added to the medium. At a wavelength of 250 nm, the absorbance was measured using UV spectrophotometry, and the formulations' percent cumulative release was computed (Shivanand et al. 2010).

3. Results and Discussion

Preparation of microspheres, Encapsulation efficiency, and Drug loading of microspheres

Microspheres containing boswellic acid were developed with a high drug encapsulation effectiveness. The range of encapsulation efficiency was 95% to 98%. (Table 2). High drug encapsulation efficiency was a common characteristic of chemical stabilisation techniques. Table 2 shows that the manufacturing yield for both the chemical stabilisation and the heat stabilisation techniques varied from 95 to 99 percent. It is clear from the high encapsulation efficiency and adequate manufacturing yield that the chemical stabilisation process is a straightforward and effective way to create microspheres loaded with boswellic acid.

Microspheres Characterization

Scanning Electron Microscopy (SEM)&Analysis of Particle size

Table 1 reports the particle sizes for each microsphere formulation coded (MC1 to MC4 & MH1 to MH4). The microsphere compositions' particle sizes varied from 3.96±0.12 to8.32±0.11 mm. It was discovered that every microsphere ranged from being spherical to non-spherical, with not a single one being perfectly spherical. Figure 1 displays SEM photomicrographs of the MC1–MC4 coded microsphere formulations. The microspheres' surface was crumpled and their form was asymmetrical. It appeared as though they were hollow microspheres that disintegrated in the process of preparation. Figure 2 displays the micrographs associated with formulations MH1 and MH4.These microspheres had a smooth surface and a spherical form. The findings demonstrated that the drug/polymer ratio had a significant impact on the spray-dried microspheres'

morphological properties. More spherical microspheres with smoother surfaces were produced as the polymer ratio rose.

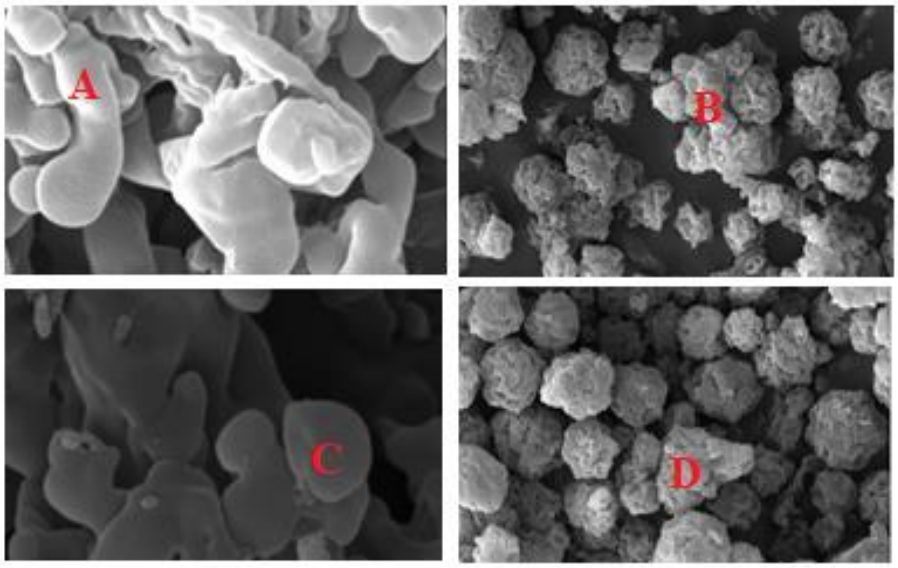

Figure 1. SEM Photomicrograph of microsphere formulation A = MC1, B = MC2, C = MC3 and D = MC4

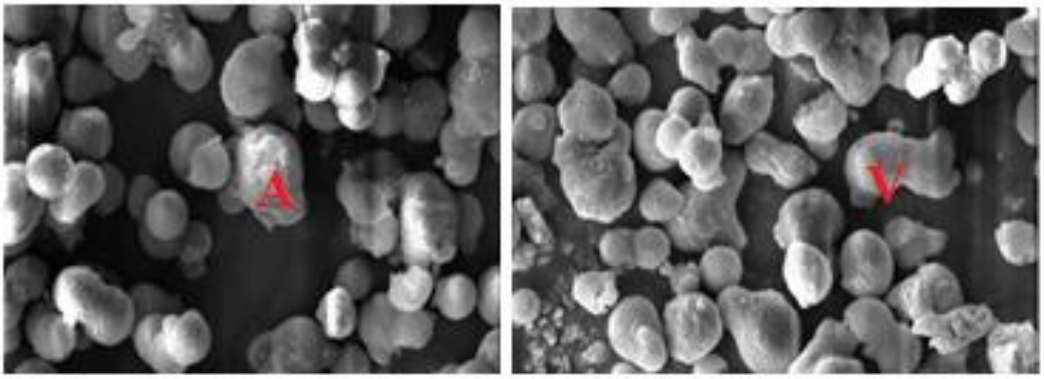

Figure 2. SEM Photomicrograph of microsphere formulation MH1, MH2, MH3 and MH4

Table 1. Particle sizes, Elongation ratio, Uniformity index and microspheres shape

Formulation	Particle size (µm) ± SD	UI	ER	Shape
MC1	7.43±0.14	1.230	1.32±0.12	Non spherical
MC2	6.48±0.16	1.0897	1.17±0.12	Spherical
MC3	5.47±0.16	1.2086	1.27±0.18	Non spherical
MC4	7.30±0.18	0.91	1.21±0.17	Spherical
MH1	3.96±0.12	1.787	1.30±0.09	Non spherical
MH2	7.13±0.18	1.014	1.18±0.08	Spherical
MH3	4.98±0.14	0.98	1.20±0.11	Spherical
MH4	8.32±0.11	0.9824	1.15±0.08	Spherical

Where UI= Uniformity index and ER= Elongation ratio

Swelling Index and Percentage yield

Table 1 displays the swelling index and percentage yield of the microspheres. The findings unequivocally demonstrate that each formulation has an adequate percentage yield and swelling property. For formulations MC1 and MC2, the largest percentage yield and swelling, respectively, are observed.

In vitro drug release &Mucoadhesioon

Table 2 provides the percentages of mucoadhesion as demonstrated by microspheres. The outcomes demonstrated that the microspheres could sufficiently attach to the stomach mucosa and had good mucoadhesive qualities. The outcomes also demonstrated that the chemically stabilized microspheres had superior mucoadhesive qualities compared to the heat-stabilized microspheres. Given that the MC2 formulation yielded the greatest percentage (98.12±1.23), it was deemed to possess good mucoadhesive properties.
Figure 3 and Table 3 display the in vitro release characteristics of the Boswellic acid microsphere formulations. Not every formulation released the same percentage of the medication. The formulations with codes MC1 (drug/polymer ratio:1:1) and MC4 (drug/polymer ratio:1:4) had the greatest and lowest release profiles, respectively. This outcome demonstrates how the drug's release rate is influenced by the drug/polymer ratio. Drug release rates decline as the amount of polymer rises.

Table 2. Percentage yield, Encapsulation efficiency, Loading capacity, Swelling index and % Mucoadhesion

Formulation	Percentage yield	EE	LC	Swelling index	Percentage Mucoadhesion after 600 min
MC1	97.44±0.95	97.45	51.23	0.97±0.03	63.66±1.41
MC2	98.12±1.23	98.32	51.46	0.24±0.01	75.48±1.71
MC3	95.13±0.89	95.23	34.45	0.96±0.02	69.33±1.31
MC4	95.45±1.15	95.45	35.87	0.18±0.02	55.42±1.23
MH1	96.46±1.08	96.51	53.43	0.97±0.01	66.17±2.45
MH2	96.75±1.23	96.69	50.65	0.22±0.01	53.45±1.22
MH3	94.65±1.13	94.72	27.75	0.96±0.02	59.32±1.16
MH4	94.75±1.07	94.81	33.76	0.18±0.02	48.32±1.02

Where EE= Encapsulation efficiency, LC= Loading capacity

Table 3.*In vitro* drug release at pH 1.2

Formulation	MC1	MC2	MC3	MC4	MH1	MH2	MH3	MH4
1hr	17.64±0.98	15.87±0.91	14.86±0.94	14.5±0.78	15.85±0.98	14.34±	13.21±0.98	9.89±0.87
2hr	29.25±1.01	27.65±0.99	26.52±1.03	24.75±1.12	26.53±1.08	24.98±1.01	23.97±0.99	19.7±0.99
3hr	33.98±1.11	31.97±1.01	30.2±1.21	29.86±1.01	31.2±1.03	30.98±1.01	29.65±1.03	27.76±1.05
4hr	36.98±1.21	36.5±1.01	35.97±1.01	34.65±1.21	34.2±1.21	33.98±1.16	31.87±1.21	29.97±1.21
5hr	46.4±1.34	44.97±1.16	39.38±1.21	37.98±1.21	44.02±1.16	39.45±1.21	37.48±1.01	36.67±1.34
6hr	54.97±1.16	53.95±1.21	51.85±1.16	47.63±1.01	49.74±1.21	49.01±1.16	47.98±1.21	39.98±1.21
7hr	59.96±1.21	59.3±1.16	58.85±1.21	57.66±1.21	55.97±1.16	54.85±1.21	53.4±1.34	49.96±1.14
8hr	64.54±1.34	64.1±1.34	63.98±1.16	61.2±1.16	61.92±1.21	59.29±1.34	58.96±1.21	58.56±1.21
9hr	69.98±1.16	67.98±1.21	67.1±1.21	66.54±1.21	67.4±1.21	65.65±1.21	63.98±1.16	59.32±1.34
10hr	77.65±1.21	76.64±1.16	73.45±1.34	72.78±1.34	75.87±1.34	73.98±1.34	71.89±1.21	69.2±1.21
11hr	86.01±1.16	84.02±1.34	82.57±1.21	82.11±1.21	84.2±1.21	81.2±1.21	79.92±1.34	78.86±1.34
12hr	97.01±1.21	95.01±1.21	93.1±1.16	91.11±1.34	90.21±1.34	89.75±1.16	89.12±1.21	88.21±1.21

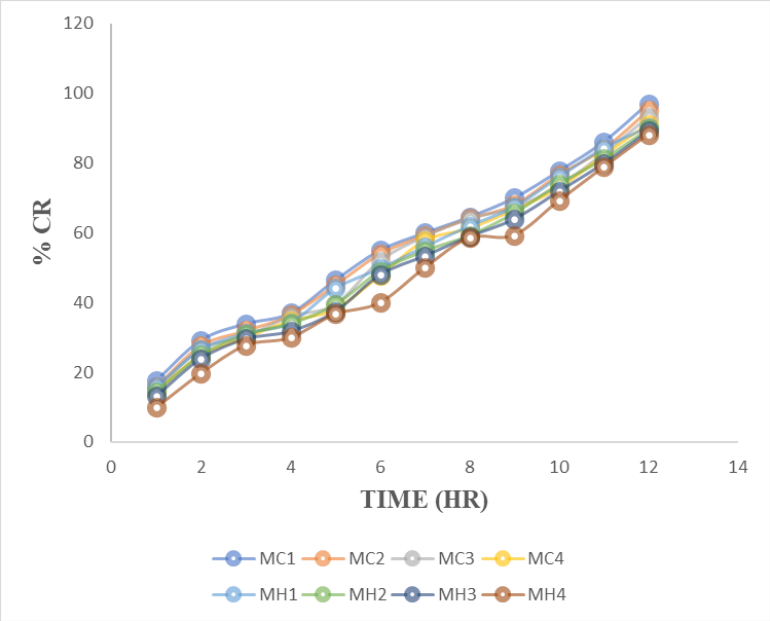

Figure 3.*In vitro* drug release at pH 1.2

4. Conclusion

A fast and easy method of developing Boswellic acid-loaded microspheres is chemical stabilization. They were manufactured with a high drug encapsulation efficiency, a significant manufacturing yield, and batch-to-batch reproducibility. Every microsphere had an appropriate size and strong mucoadhesive qualities for delivery. According to the tests, the best microspheres for in vitro drug release and mucoadhesive qualities were those made using chemical stabilisation and having a drug:polymer ratio of 1:2 (MC2). Since the drug-to-polymer ratio of 1:2 in the microspheres had the greatest mucoadhesive and drug-release properties, it was thought to be the ideal formulation.

Declaration of Interest

There is no conflict of interest, according to the authors.

5. References

1. Brenner GM and Stevens C. (2009) Pharmacology: Elsevier Health Sciences.
2. Chun M-K, Cho C-S, and Choi H-K. (2005) Mucoadhesive microspheres prepared by interpolymer complexation and solvent diffusion method.International Journal of Pharmaceutics. 288(2): 295-303. doi:http://dx.doi.org/10.1016/j.ijpharm.2004.10.016
3. Chun M-K, Sah H, and Choi H-K. (2005) Preparation of mucoadhesive microspheres containing antimicrobial agents for eradication of h. Pylori.International Journal of Pharmaceutics. 297(1–2): 172-179. doi:http://dx.doi.org/10.1016/j.ijpharm.2005.03.011
4. Das S and Ng K-Y. (2010) Colon-specific delivery of resveratrol: Optimization of multi-particulate calcium-pectinate carrier.International Journal of Pharmaceutics. 385: 20-28.
5. Goodman LLS, Brunton LL, Gilman A, Chabner B, and Knollmann BC. (2011) Goodman and gilman's the pharmacological basis of therapeutics: McGraw-Hill Medical.
6. Hall JE. (2010) Guyton and hall textbook of medical physiology: Enhanced e-book: Elsevier Health Sciences.
7. Hardenia SS, Jain A, Patel R, and Kaushal A. (2011) Formulation and evaluation of mucoadhesive microspheres of ciprofloxacin.Journal of Advanced Pharmacy Education & Research. 1(4): 214-224.
8. Jain N, Gulat N, Kumar D, and Nagaich U. (2012) Microspheres: Mucoadhesion based controlled drug delivery system.RGUHS J Pharm Sci. 2(3): 28-40.
9. Khan M, Ansari VA, Kushwaha P, Kumar A, and Akhtar J. (2015) Mucoadhesive microspheres for controlled delivery of drugs.Asian J Pharm Clin Res. 8(4): 17-20.
10. Khare CP. (2007) Indian medicinal plants: An illustrated dictionary: Springer.

11. Mohan M, Sujitha H, Rao VU, Ashok M, and Kumar AB. (2014) A brief review on mucoadhesive microspheres.IJRRPAS. 4(1): 975-986.
12. Mukherjee M, Bhaskaran N, Srinath R, Shivaprasad HN, Allan JJ, Shekhar D, and Agarwal A. (2010) Anti-ulcer and antioxidant activity of gutgard[tm].Indian Journal of Experimental Biology. 48: 269-274.
13. N CR and Chopra IC. (2006) Indigenous drugs of india: Academic Publishers.
14. Patil SB and Sawant KK. (2008) Mucoadhesive microspheres: A promising tool in drug delivery.Current drug delivery. 5(4): 312-318.
15. Shadab MD, Singh GK, Ahuja A, Khar RK, Baboota S, Sahni JK, and Ali J. (2012) Mucoadhesive microspheres as a controlled drug delivery system for gastroretention.Systematic Reviews in Pharmacy. 3(1).
16. Shivanand P. (2010) Mucoadhesive microspheres.International journal of pharma and bio sciences. 1: 2.
17. Shivanand P, Viral D, Manish G, Muzaffar F, and Venkateswaramurthy N. (2010) Formulation and evaluation of mucoadhesive microspheres of amoxicillin trihydrate by using eudragit rs 100.nternational Journal of ChemTech Research. 2(1): 466-470.
18. Shukla RK and Tiwari A. (2012) Carbohydrate polymers: Applications and recent advances in delivering drugs to the colon.Carbohydrate Polymers. 88(2): 399-416. doi:http://dx.doi.org/10.1016/j.carbpol.2011.12.021
19. Sinha VR, Singla AK, Wadhawan S, Kaushik R, Kumria R, Bansal K, and Dhawan S. (2004) Chitosan microspheres as a potential carrier for drugs.International Journal of Pharmaceutics. 274(1–2): 1-33. doi:http://dx.doi.org/10.1016/j.ijpharm.2003.12.026
20. Sivadas N, O'rourke D, Tobin A, Buckley V, Ramtoola Z, Kelly JG, Hickey AJ, and Cryan S-A. (2008) A comparative study of a range of polymeric microspheres as potential carriers for the inhalation of proteins.International Journal of Pharmaceutics. 358(1–2): 159-167. doi:http://dx.doi.org/10.1016/j.ijpharm.2008.03.024
21. Soane RJ, Frier M, Perkins AC, Jones NS, Davis SS, and Illum L. (1999) Evaluation of the clearance characteristics of bioadhesive systems in humans.International Journal of Pharmaceutics. 178(1): 55-65. doi:http://dx.doi.org/10.1016/S0378-5173(98)00367-6
22. Sun L, Zhou S, Wang W, Li X, Wang J, and Weng J. (2009) Preparation and characterization of porous biodegradable microspheres used for controlled protein delivery.Colloids and Surfaces A: Physicochemical and Engineering Aspects. 345(1–3): 173-181. doi:http://dx.doi.org/10.1016/j.colsurfa.2009.04.053
23. Tai FWD and Mcalindon ME. (2021) Non-steroidal anti-inflammatory drugs and the gastrointestinal tract.Clin Med (Lond). 21(2): 131-134. doi:10.7861/clinmed.2021-0039
24. Tripathi KD. (2008) Essentials of medical pharmacology: Jaypee Brothers Medical Publishers.
25. Yadav A and Jain DK. (2011) Formulation and evaluation of mucoadhesive microspheres of propranolol hydrochloride for sustained drug delivery.Asian Journal of Pharmacy and Medical Science. 1(1): 1-8.