CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://zenodo.org/records/13627827

https://www.iajps.com/volumes/volume11-september-2024/02-issue-09-september-24/

Available online at: http://www.iajps.com Research Article

PREPARATION AND EVALUATION OF ITRACONAZOLE MUCOADHESIVE MICROSPHERES

Abdur Rahman[1], Dharmendra Singh Rajput[1], Naveen Gupta[1]

[1]Madhyanchal professional University, Bhopal, M.P.

Abstract:

Microspheres are ideal targeting drug delivery system with high safety profile. The objective of the present study is to reduce dosing frequency and improve patient compliance by designing and systematically evaluating mucoadhesive microspheres. Various methods have been used to solve the issue associated to barriers, such as exploring alternate methods of delivering substances. Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesive micro-spheres exhibit a prolonged residence time at the site of application or absorption and facilitate an intimate contact with the underlying absorption surface and thus contribute to improved and/or better therapeutic performance of drugs. Mucoadhesive microspheres containing itraconazole were able to enhance the bioavailability of the medicine at the oral buccal site for the treatment of oral candidiasis. The IMM5 formulation, which consists of mucoadhesive microspheres containing itraconazole, is considered the most effective formulation. It is composed of a blend of naturally occurring polysaccharides, namely Drug: HPMC: Xanthan gum in a ratio of 1:1:1. This formulation releases over 98.13% of the drug in a controlled and sustained manner for up to 12 hours in the gastric environment.

Corresponding author:

Abdur Rahman,

Madhyanchal professional University,
Bhopal, M.P.

QR code

Please cite this article in press Abdur Rahman et al., ***Preparation And Evaluation Of Itraconazole Mucoadhesive Microspheres****., Indo Am. J. P. Sci, 2024; 11 (09).*

INTRODUCTION:

The bio adhesive delivery systems use for medication administration has become more important in recent years. The close interaction between the mucoadhesive polymer and the mucosal surface might lead to a longer duration of drug retention, hence enhancing the medication's availability and prolonging the contact between the drug and the mucosa. When the mucoadhesive dosage form is given as a tablet or capsule, it may or may not stick to the mucosal surface because of the weight of the dosage form and the strong movement of the gastrointestinal system, leading to significant variability. Nevertheless, mucoadhesive microspheres provide some benefits. These characteristics include a low mass and a reduced range of dosage fluctuations as a result of the significant quantity of microspheres delivered [1]. Nevertheless, the effectiveness of these innovative drug delivery systems is restricted by their brief duration of stay at the absorption site. Having a method to ensure close contact between the DDS and the absorbent membranes would be beneficial. The achievement may be accomplished by combining the properties of bioadhesion with microspheres and creating innovative delivery methods known as "bioadhesive microspheres". Bioadhesion may be defined as the process of attaching a synthetic or biological macromolecule to a biological tissue. An adhesive relationship may develop with either the epithelial cell layer, the continuous mucus layer, or a mix of both. The word "mucoadhesion" refers to the bonding between a mucous covering and an adhesive polymeric device, while "cytoadhesion" refers to the particular attachment of cells. The process of bioadhesion has been thoroughly examined [2-3]. The analysis of adhesion between mucin and mucoadhesive polymers often involves studying the attractive and repulsive forces at the molecular level. Bioadhesive microspheres include microparticles and microcapsules, ranging in diameter from 1 to 1000µm. These microspheres are composed either totally of a bioadhesive polymer or have an outside coating made of it, with the medicine contained in the core of the microcapsules. Microspheres have the potential to be used for targeted and controlled release drug delivery. However, when bioadhesive properties are added to microspheres, there are additional advantages. These include efficient absorption and enhanced bioavailability of drugs due to a high surface to volume ratio. The microspheres also have a closer contact with the mucus layer, allowing for specific targeting of drugs to the absorption site. This can be achieved by anchoring plant lectins, bacterial adhesins, antibodies, and other substances on the surface of the microspheres. Bioadhesive microspheres may be customized to stick to any mucosal tissue, such as those in the eye, nasal cavity, urinary tract, and gastrointestinal tract [4]. This allows for the potential of targeted and controlled release of medications, both locally and systemically. The usage of bioadhesive microspheres on the mucosal tissues of the ocular cavity, stomach, and colonic epithelium is used to deliver medications for localized effects. Candidiasis is a common and important cause of oral discomfort, pain, taste loss, and food aversion. Carrying Candida albicans and having a history of candidiasis are additional important variables that increase the likelihood of developing oral candidiasis [5]. Several research groups have developed and reported various mucoadhesive dosage forms, including discs, microspheres, and tablets. Mucoadhesive drug delivery devices are used to augment medication absorption in a targeted way. Mucoadhesion refers to the contact between the surface of mucin and a polymer, which may be either synthetic or natural. Mucoadhesion refers to the contact between the surface of mucin and a polymer, whether it be synthetic or natural. Mucoadhesion is often advocated as a method for obtaining targeted drug administration by including mucoadhesive hydrophilic polymers into pharmaceutical formulations, such as "microspheres," along with the active pharmaceutical ingredient (API) [6-7]. This includes brushing and flossing the teeth twice a day and ensuring sufficient moisture in the mouth. Itraconazole is a white or almost white substance that is not easily dissolved in water, only slightly soluble in alcohol, easily dissolved in dichloromethane, and only somewhat soluble in tetrahydrofuran. The proposed experimental study aims to create and assess mucoadhesive microspheres containing itraconazole for absorption at the oral buccal cavity. These microspheres will allow for drug absorption directly from the mouth cavity. The current study postulated that the medicine was administered via the buccal route, resulting in a rapid beginning of action and improved bioavailability. The buccal mucosa provides several benefits for the regulated and prolonged release of drugs. The mucosa is abundantly provided with both vascular and lymphatic drainage.

MATERIAL AND METHODS:

Preparation of mucoadhesive Microspheres: Solvent emulsification technique was used to

generate mucoadhesive microspheres. The dispersion of Hydroxy Propyl Methyl Cellulose (K15) in ethanol was created. Next, 1.0 gm of the medicine itraconazole and the necessary amount of xanthan gum powder were added to the previously prepared combination of polymeric solution. This mixture was left to stand for 24 hours. Next, the suspension was gradually mixed with 150 ml of light liquid paraffin that contained 2% Span 40. The mixing was done at a velocity of 300 rpm. Following a 30-minute emulsification process, the solvents were progressively evaporated using a water-circulating vacuum pump until the microspheres were created. The microspheres underwent a washing process using petroleum ether and were then dried under vacuum conditions at room temperature [8].

Table 1: Various combinations of IMM1 – IMM5 based mucoadhesive microspheres.

S. No.	Code	Ingredients	Drug : Polymer	Qty (mg)	Stabilizing agent (PVA) (% w/v)
1	IMM1	Drug : HPMC	01:01	150:150	1
2	IMM2	Drug : HPMC	01:02	100:200	1
3	IMM3	Drug : xanthan gum	01:01	150:150	1
4	IMM4	Drug : xanthan gum	01:02	100:200	1
5	IMM5	Drug : HPMC: xanthan gum	01:01:01	100:100:100	1

Characterization of mucoadhesive microspheres:

Shape and surface morphology: The surface properties were analyzed using scanning electron microscopy. The morphology, surface appearance, and inner structure of MS were thoroughly analyzed using Scanning Electron Microscope analysis (SEM Philips XL-30) on samples from various uncoated and coated batches. The analysis was conducted on both freshly prepared samples and at different time intervals during their storage. Before inspection, the samples were affixed to a brass stub using double-sided tape and coated with a layer of gold-palladium in the presence of argon gas to make them electrically conductive. This coating process was carried out using a gold sputter module in a high vacuum evaporator. The images were captured with an excitation voltage of 20 kV. The chosen magnifications were enough for seeing the detailed morphology of the materials being studied.

Particle Size and Size Distribution Determination: Particle size was evaluated using the optical microscope technique with a calibrated ocular lens. The study investigated the impact of process factors, such as drug concentration, polymer concentration, stirring rate, and stirring duration, on the particle size and size distribution.

Drug Encapsulation Efficiency: The efficiency of drug encapsulation was measured by measuring the amount of drug that remained after removing any drug that was attached to the surface. The medication attached to the surface was eliminated by adding a precise amount of microspheres to 10 ml of pH 6.8 phosphate buffer and shaking intermittently for 10 minutes. The suspension was subjected to centrifugation at a speed of 3000 revolutions per minute for a duration of 5 minutes, resulting in the separation of the liquid portion, known as the supernatant, which was set aside. The microspheres that had settled were treated again in the same way. The liquid that was separated from this centrifugation was combined with the initial liquid, and the concentration of the medication was measured using a UV spectrophotometer at a wavelength of 265 nm [9].

Swelling Degree: The microspheres were precisely weighed and then immersed in pH 6.8 phosphate buffer. They were allowed to swell till reaching a consistent weight. The degree of weight increase was determined using the equation

$$DS = (Wmf - Wmi) / Wmi,$$

where DS represents the degree of swelling, Wmi is the beginning weight of the microspheres, and Wmf is the final weight of the microspheres [10].

In-vitro mucoadhesion investigations: It was conducted using the Falling film method. The rat's intestinal mucosa was recently removed and placed on a tilted glass slide at a 45° angle. It was then

washed with phosphate buffer saline for 30 minutes at a flow rate of 30 ml per minute. A quantity of 100 mg of dehydrated microspheres was evenly distributed across the mucosal tissue and allowed to remain for a duration of 20 minutes to facilitate interaction. Throughout this duration, the whole system was positioned inside a humidity chamber that was set to a relative humidity (RH) of 90%. The system was rinsed for 5 minutes at a flow rate of 22 milliliters per minute at the conclusion of the session. Upon completion of this procedure, the dislodged particles were collected and measured in terms of weight. The percentage of mucoadhesion was determined using a mathematical procedure.

% Mucoadhesion =Wt of sample- Wt of detached particles / Wt of Sample X 100

In-vitro Drug Release: A drug release investigation was conducted utilizing a modified USP dissolving test equipment, with pH 6.8 phosphate buffer serving as the medium. Microspheres containing drug molecules were immersed in dissolving medium at a temperature of 37±0.1°C. Periodic samples were extracted and replaced with an equivalent volume of new dissolving medium. The drug content of the samples was evaluated by measuring absorbance at 265 nm using a UV spectrophotometer [11].

RESULTS AND DISCUSSION:

The current study focuses on the production of microspheres using solvent emulsification techniques. These microspheres were successfully created with the desired characteristics. Additionally, the study explores the potential of the buccal mucosa as a suitable location for controlled delivery of macromolecular therapeutic agents, including peptides, proteins, and polysaccharides. This is due to the buccal mucosa's accessibility and lower enzymatic activity when compared to the gastrointestinal tract. The drug entrapment effectiveness of the manufactured mucoadhesive microspheres was investigated to determine the percentage of drug that was successfully trapped. The results ranged from 81.71% to 85.77%. The degree of swelling of microspheres and the rate of swelling, as well as the percentage of mucoadhesion of mucoadhesive microspheres containing itraconazole, ranged from 42.5% to 53.9%. In-vitro dissolution studies serve as a means of ensuring the consistency and quality control of a product. These studies may also be used to evaluate the effectiveness of sustained release formulations. The drug release from the microspheres was assessed in a pH 6.8 phosphate buffer solution. The results showed that microspheres produced with a low drug to polymer ratio and high stirring speed in the simulated stomach fluid resulted in smaller microspheres. These smaller microspheres had a larger surface area, which led to a faster release of the medication. The first release of the medicine may occur from the substance that is not encapsulated. The deceleration of the second stage of the release process may be ascribed to the diffusion process of the enclosed medicine from the microspheres. The scanning electron microscopic examination revealed the non-uniformity on the surface of the HPMC polymer-based microspheres. The IMM5 formulation, which consists of mucoadhesive microspheres containing itraconazole, is considered the most effective formulation. It is composed of a blend of naturally occurring polysaccharides, namely Drug : HPMC : Xanthan gum (1:1:1). This formulation releases over 98.13% of the drug in a controlled and sustained manner for up to 12 hours in the gastric environment. The drug release tests conducted in simulated gastrointestinal fluids of pH 6.8 phosphate buffer were noted in Table 3. Buccal mucoadhesive microspheres ITHPCH5 is a superior formulation that consists of a naturally occurring polysaccharide polymeric mix, namely HPMC and Xanthan gum in a ratio of 1:1:1. This formulation is capable of releasing over 98.13% of the medicine in the stomach environment in a regulated and sustained way for up to 12 hours. Regression analysis was conducted and the R2 values indicated that the curves had a reasonably linear relationship. Additionally, the slope values were calculated based on the graph. All batches had a release exponent "n" value greater than 0.89, confirming the presence of Super-case II transport mechanism (Figure 2). Regression analysis was conducted, and the r2 values indicated that the curves had a reasonably linear relationship. Additionally, the slope values were calculated based on the graph. All batches had a release exponent "n" value greater than 0.89, confirming the presence of the Super-case II transport mechanism.

Table 2: Physical properties of mucoadhesive microsphere of itraconazole (IMM1 – IMM5)

S. No.	F. Code	dmean (µm)	Drug content	Encapsulation efficiency (%)	Swelling rate (%)	Percent Mucoadhesion
1	IMM1	361.45±0.540	428.1	85.62	42.5 ± 1.15	75.63 ± 0.018
2	IMM2	372.86±0.436	272.1	81.71	44.6 ± 1.18	77.64 ± 0.077
3	IMM3	371.15±0.495	431.2	86.24	47.7 ± 0.88	81.22 ± 0.123
4	IMM4	377.10±0.512	281.1	84.41	49.2 ± 1.38	84.64 ± 0.198
5	IMM5	382.12±0.436	427.8	85.56	53.9 ± 2.48	85.57 ± 0.208

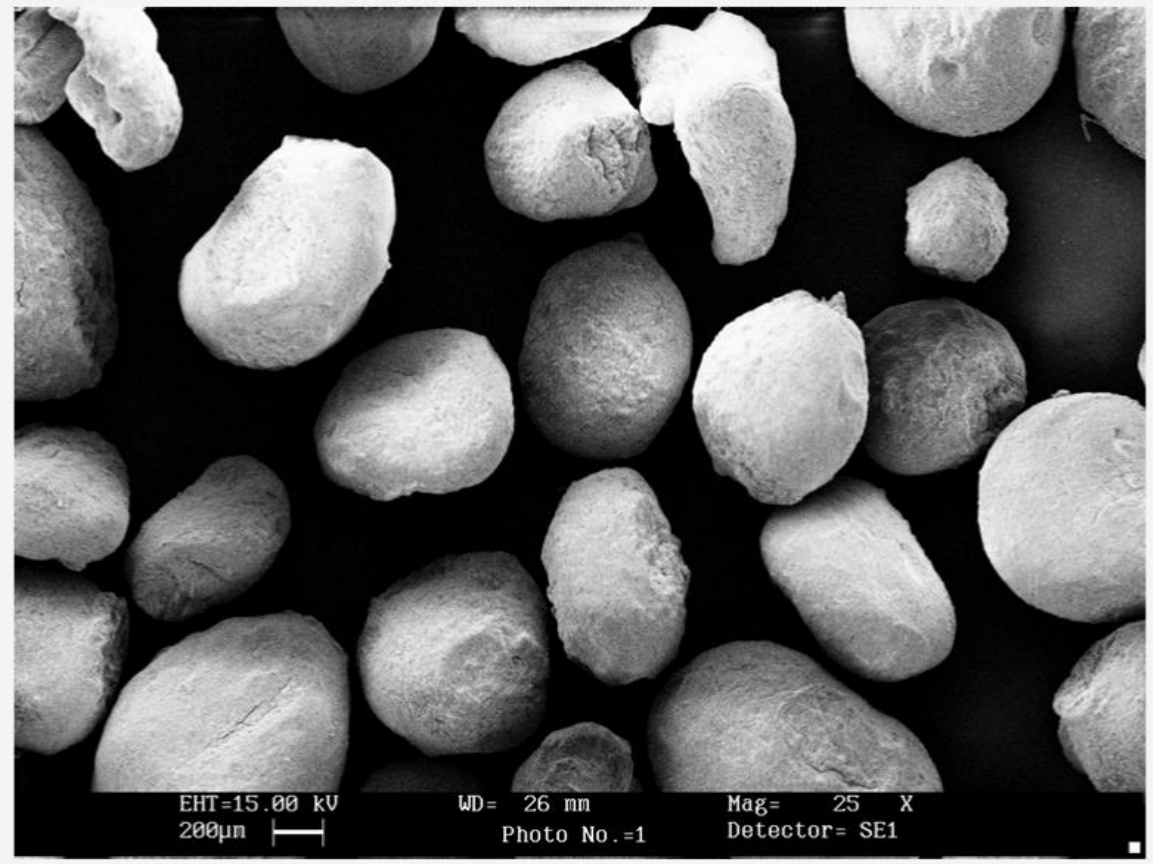

Figure 1: SEM analysis of mucoadhesive microsphere of itraconazole (IMM4)

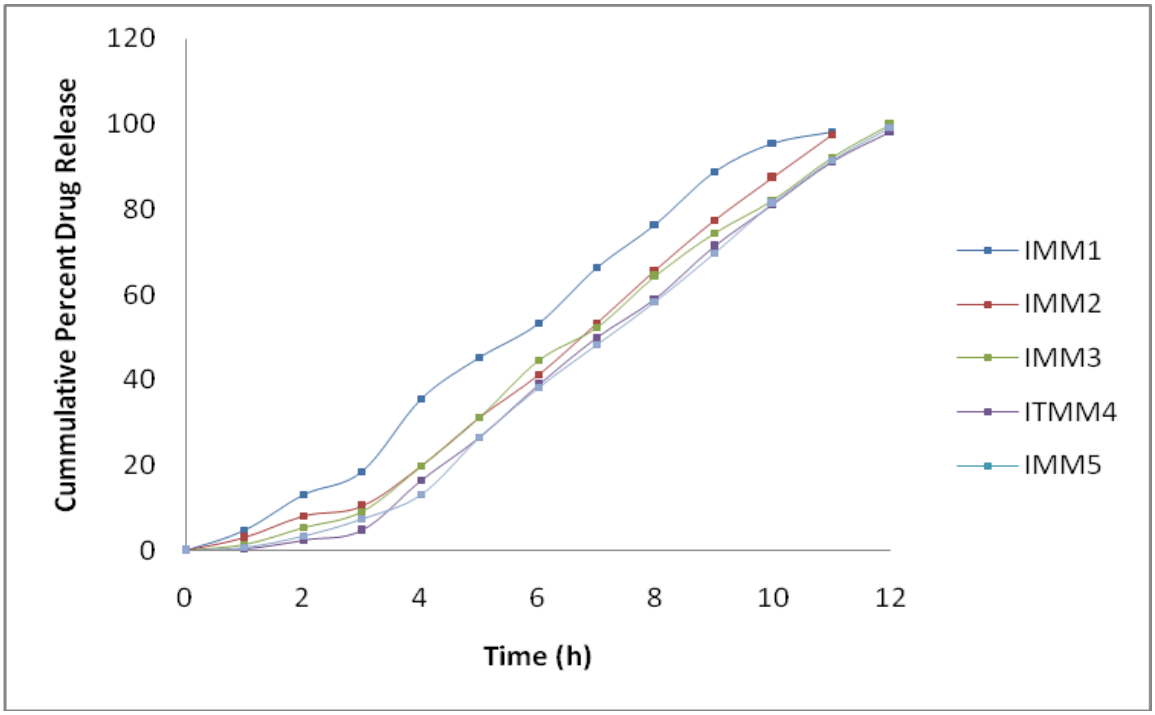

Figure 2: Zero-order kinetic dissolution data of mucoadhesive microsphere of itraconazole (IMM1 - IMM5)

SUMMARY AND CONCLUSION:

Mucoadhesive microspheres provide a distinct method of transportation due to their ability to stick to any mucosal tissue. The ionic orifice approach resulted in the formation of spherical and easily flowing microspheres. The release of rosiglitazone maleate was shown to be gradual and prolonged. The release was contingent upon the specific polymer used. The drug's release was extended when it was combined with mucoadhesive polymers.

Candidiasis is caused by candida albicans, a kind of fungus that may exist in two different forms and is usually found in the mouth of about 50% of healthy people without causing any harm. Buccal drug delivery offers a favorable option to oral drug administration, especially in addressing the limitations associated with the latter method of dosage. In addition, it is feasible to supply medication to patients who are unable to take it orally by this method. A appropriate buccal drug delivery system should be adaptable and have strong bioadhesive characteristics, allowing it to remain in the mouth cavity for the necessary amount of time. Furthermore, it is crucial for the medicine to be released in a regulated and foreseeable way in order to have the desired therapeutic effect.

REFERENCES:

1. Adikwu MU, Yoshikawa Y, Takada K. Bioadhesive delivery of Metformin using prosopsis gum with antidiabetic potential. Bio Pharm Bull. 2003; 26(5): 662-666.
2. Sachan NK and Bhattacharya A (2009) Modeling and characterization of drug release from glutinous rice starch based Hydrogel beads for controlled drug delivery. Int J Health Res. 2(1): 93-99.
3. Bonacucina G, Martelli S, Palmieri GF. Rheological, mucoadhesive and release properties of carbopol gels in hydrophilic cosolvents. Int J Pharm. 2004; 282: 115-130.
4. Chickering D E, Jacob J S, Desai T A, Harrison M, Harris W P, Morrell C N, Chaturvedi P, Mathiowitz E. 1997. Bioadhesive microspheres. An in vivo transit and bioavailability study of drug-loaded alginate and poly (fumaric-co-sebacic anhydride) microspheres. J Contr. Rel. 48(1), 35-46.
5. Carino PG, Jacob JS, Chen CJ, Santos CA, Hertzog BA, Mathiowitz E, Bioadhesive, bioerodible polymers for increased intestinal uptake In: Bioadhesive Drug Delivery Systems Fundamentals, Novel Approaches and Development ,98thed, New York: Marcel Dekker; 1999. p. 459-475.
6. Mathiowitz E, Langer R, Polyanhydride microspheres as drug carriers : Hot melt microencapsulation,Journal of Controledl Release, 1987,5,13-22.Patel KS, Patel MB. Preparation and evaluation of chitosan

microspheres containing nicorandil. Int J Pharm Investig. 2014 Jan;4(1):32-7.
7. Yadav Akash,Jain kumar Dinesh,Formulation and evaluation of mucoadhesive microspheres of propanolol hydrochloride for sustained drug delivery,Asian Journal of Pharmacy and Medical Sciences,2011,1(1) 1-8.
8. Allamneni Yaswanth Reddy B.V.V.V.K, Chary. P. Dayananda, N. Vankata Balakrishna Rao,Kumar Schaitanya,Kalekar Arun Kumar,performance evaluation of mucoadhesive microspheres containing an anti-diabetic drug: glipizide,International Journal of Pharmaceutical Sciences and Drug Research,2012,4(2),115 -122.
9. R. Saisree, Satyabrata Bhanja, Swarup Das, Bhavana. V, M. Sudhakar, B. B Panigrahi. Formulation and Evaluation of Mucoadhesive Microspheres of Valsartan. Research J. Pharm. and Tech 2019; 12(2):669-677.
10. Nagarjan S and Prakash K. Formulation and evaluation of mucoadhesive microspheres of pioglitazone Hydrochloride. J of Encapsulation and Adsorption Sci. 6; 2016:22-34.
11. Vikram KS and Nithin S. Formulation and evaluation of floating mucoadhesive microspheres of novel natural polysaccharide for delivery of ranitidine hydrochloride. Int J of Applied Pharmaceut. 9(3); 2017: 271-296.