JOURNAL OF PHARMA INSIGHTS AND RESEARCH

RESEARCH ARTICLE

Preparation and Evaluation of Gastroretentive Microballoons of Dexlansoprazole Containing Natural and Synthetic Polymers

Vijaykumar Darshanam *[1], Madhusudhan Merugu [2]

[1]*HOD & Professor, Department of Pharmaceutics, Swami Vivekananda Institute of Pharmaceutical Sciences, Vangapally, Telangana, India*
[2]*HOD & Professor, Department of Pharmaceutical Analysis, Swami Vivekananda Institute of Pharmaceutical Sciences, Vangapally, Telangana, India*

Publication history: Received on 8thJanuary; Revised on 26th January; Accepted on 30thJanuary

Article DOI: 10.5281/zenodo.10615495

Abstract: In oral drug delivery, multi-particulate systems hold greater significance than single-unit dosage forms. Among various multi-particulate drug delivery systems, floating microballoons stand out as an effective method to enhance gastric retention. These microballoons contribute to more reproducible drug absorption, mitigate the risk of local irritation, and enhance the bioavailability of the drug. This research focuses on Dexlansoprazole (DSP), a BCS class-II drug and proton pump inhibitor utilized in treating gastroesophageal reflux disease (GERD) and ulcer colitis. Dexlansoprazole acts by reducing stomach acid quantity and was formulated into non-effervescent floating microballoons using both natural and synthetic polymers. Sodium alginate and chitosan served as natural polymers, while ethyl cellulose and HPMC acted as synthetic polymers, with Span 80 employed as the surfactant. Pre-formulation studies encompassed solubility, partition coefficient, and micromeritics for the pure Dexlansoprazole drug. Additionally, drug-excipient compatibility studies were conducted using FTIR. Various formulations of floating microballoons were prepared via the solvent evaporation method. In-vitro drug release and kinetic studies were performed on all Dexlansoprazole microballoons, with results systematically analyzed. Formulation F7 exhibited favorable release characteristics up to 10 hours, leading to its identification as the optimized formulation. The Peppas n values for all formulations exceeded 0.5, indicating a non-Fickian diffusion mechanism for the drug release in all formulated Dexlansoprazole microballoons.

Keywords: Chitosan; Dexlansoprazole; Microballoons; Gastroretentive; Gastric emptying; HPMC; Sodium alginate.

1. Introduction

The oral route of drug administration has attracted significant attention due to its inherent advantages in dosage form design when compared to alternative administration routes. Gastroretentive systems, specifically designed to prolong the residence of drugs in the gastric region, offer potential benefits such as increased drug bioavailability and solubility, minimized drug wastage, and targeted drug delivery to specific anatomical regions, including the stomach and proximal small intestines. This extended retention is achieved by synchronization with the inter-digestive myoelectric cycle or migrating myoelectric complex (MMC), which consists of four distinct phases. In terms of anatomy, the stomach is divided into three key regions: the fundus, body, and antrum (pylorus). The proximal segment, comprising the fundus and body, functions as a reservoir for undigested material, while the antrum is responsible for coordinating mixing motions and acting as a pump for gastric emptying. This strategic retention becomes particularly advantageous for drugs that exhibit lower solubility in a high pH environment, effectively addressing challenges associated with their bioavailability and solubility in the gastrointestinal environment. [1]

Dexlansoprazole, an H/K ATPase enzyme inhibitor, plays a crucial role in healing erosive esophagitis (EE), maintaining and healing EE, relieving heartburn, and treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD). By inhibiting the enzyme involved in hydrochloric acid secretion, Dexlansoprazole modulates gastric acidity. Despite its short half-life of 1 to 2 hours, it remains effective in managing GERD symptoms. This study aims to formulate and evaluate Dexlansoprazole floating microballoons using different polymers, namely HPMC, EC, chitosan, and sodium alginate, in varying ratios and concentrations. [2,3] The investigation seeks to optimize a gastroretentive system that enhances the therapeutic profile of Dexlansoprazole, offering extended gastric residence time and improved drug delivery characteristics.

* Corresponding author: Vijaykumar Darshanam

2. Experimental methods

2.1. Materials

Dexlansoprazole was provided as a generous gift from Aurobindo Pharma in Hyderabad, India. Sodium alginate, Chitosan, HPMC, and EC were obtained from S.D. Fine Chem. Ltd. Ethanol, Dichloromethane, Light liquid paraffin, Tween 80, and Petroleum ether were sourced from Finar Chemicals Ltd.

2.2. Preparation of floating hollow microballoons

The microspheres were produced using the solvent evaporation method. Ethyl cellulose and hydroxypropyl methyl cellulose were dissolved in a mixture of ethanol and dichloromethane at a ratio of (1:1). The drug was introduced into the polymer solution and stirred for 10 minutes at 200 rpm. The resulting mixture was slowly poured into distilled water (dispersion medium) containing 0.01% Tween 80 under continuous stirring. Stirring was maintained at 200 rpm, and the temperature was kept at 30°C. The stirring process continued for 1 hour to allow the complete evaporation of dichloromethane and ethanol. Following the evaporation of these solvents, the formed microspheres were filtered using filter paper, washed 3 to 4 times with distilled water, and left to dry at room temperature for 24 hours. [4,5] Subsequently, the dried microspheres were stored in a desiccator. The prepared floating microballoons are shown in Figure 1.

Table 1 Formulation development of Dexlansoprazole floating microballoons.

Formulation code	Drug mg	SA	EC	CS	HPMC	DCM: Ethanol	Dispersion medium (ml)
F1	60	100	--	--	--	1:1	200
F2	60	200	--	--	--	1:1	200
F3	60	--	100	--	--	1:1	200
F4	60	--	200	--	--	1:1	200
F5	60	--	--	100	--	1:1	200
F6	60	--	--	200	--	1:1	200
F7	60	--	--	--	100	1:1	200
F8	60	--	--	--	200	1:1	200

SA- Sodium alginate, EC-Ethyl cellulose, CS-Chitosan and HPMC-Hydroxy propyl methyl cellulose

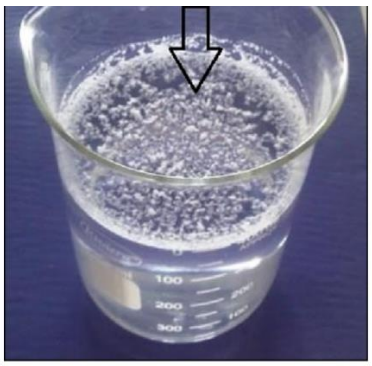

Figure 1. Floating microballoons

2.3. Analytical methods

Determination of the absorption maximum (λmax) for Dexlansoprazole involved obtaining a spectrum of working standards through scanning from 200 to 400 nm against the reagent blank to establish the absorption maxima. The identified λmax was 282 nm, and subsequent investigations were conducted at this wavelength. [6,7] For the preparation of the standard stock solution, 100 mg of Dexlansoprazole was dissolved in 0.1 N HCl in a 100 ml volumetric flask, and the solution was made up to the mark using 0.1 N HCl, resulting in a solution with a strength of 1000 µg/ml (1 mg/1 ml) (stock I). A 10 ml aliquot of stock I solution was diluted to 100 ml with 0.1 N HCl to obtain a solution with a strength of 100 µg/ml (stock II). From this secondary stock solution, separate volumes of 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, and 2.0 ml were taken and made up to 10 ml with 0.1 N HCl, resulting in concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 µg/ml, respectively

2.4. Evaluation of prepared floating microballoons

The flow characteristics of each batch were assessed by measuring parameters such as the angle of repose, loose bulk density, tapped bulk density, compressibility index, and Hausner's ratio. Surface morphology of the microballoons was determined using Scanning Electron Microscopy (SEM) techniques. To calculate the percentage yield of floating microballoons, the actual weight of the product was divided by the total amount of all non-volatile components used in the preparation of floating microballoons [8,9]

3. Results and Discussion

3.1. Analytical Methods

The standard calibration curve showed linearity in the concentration range of 2 to 20 µg/mL with r^2 value of 0.997 indicating good fit. This method is later used for estimation of drug during evaluation of prepared microballoons. The calibration curve is shown in Figure 2.

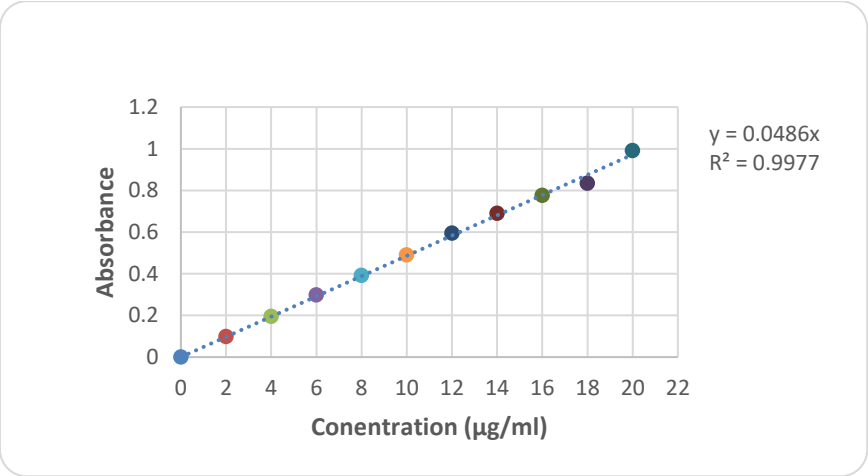

Figure 2. Standard calibration curve Dexlansoprazole in 0.1 N HCl

3.2. Evaluation of flow properties

All formulations of floating microspheres, denoted as F1 to F8, underwent assessment for different micrometric parameters, including bulk density, tapped density, Hausner's ratio, angle of repose, and % compressibility index, as presented in the table. The Hausner's ratio ranged from 1.14 to 1.18, indicating favorable flow properties. Similarly, the angle of repose and % compressibility index fell within a range that signifies good flow properties. [10] The results are shown in Table 2.

Table 2 Results of evaluation of flow properties of microballoons.

Formulation code	Bulk density (g/cm³)#	Tapped density (g/cm³) #	Hausner's ratio#	Angle of repose# (⁰)	Carr's index # (%)
F1	0.012±0.01	0.016±0.01	1,14	31.92±2.33	14.28
F2	0.015±0.02	0.018±0.02	1.18	32.35±1.34	12.01
F3	0.022±0.01	0.025±0.02	1.13	35.64±1.91	18.75
F4	0.018±0.03	0.020±0.01	1.17	29.09±1.46	17.64
F5	0.016±0.01	0.019±0.02	1.18	30.86±1.56	18.75
F6	0.020±0.02	0.023±0.01	1.15	30.69±2.12	15.11
F7	0.017±0.02	0.017±0.02	1.16	31.89±1.45	13.33
F8	0.018±0.01	0.021±0.01	1.14	34.62±1.23	16.65

Mean ± SD (n = 3 observations)

3.3. Characterization of prepared microballoons

Table 3 presents various parameters for different formulations (F1 to F8) of floating hollow microspheres. The percentage yield, indicating the efficiency of the manufacturing process, ranges from 67.50% (F1) to 98.58% (F8). Particle size, measured in

micrometers, varies across formulations, with F8 having the largest particles at 278.1 μm. The drug content percentage reflects the amount of Dexlansoprazole present in each formulation, showing an increase from 65.07% (F1) to 84.65% (F8). The swelling index, denoting the extent of swelling upon contact with a liquid medium, demonstrates variation among formulations, with F7 and F8 exhibiting the highest swelling indices at 34.78% and 46.89%, respectively. The SEM micrograph of the prepared microballoons is shown in Figure 3 indicating a smooth and uniform surface appearance of microballoons. [11, 12]

Table 3 Results of characterization of prepared microballoons.

Formulation Code	Percentage yield (%)#	Particle size (μm) #	% Drug content#	% Swelling index#
F1	67.50±1.20	258.1±2.21	65.07±3.21	25.27±1.22
F2	83.66±1.72	260.3±3.39	67.12±1.65	29.43±2.45
F3	91.75±1.26	262.1±4.17	70.07±2.54	15.69±1.45
F4	96.00±2.84	269.3±3.17	72.03±3.21	20.76±2.12
F5	89.67±0.89	259.7±4.26	69.72±1.36	18.32±1.28
F6	97.52±1.56	274.4±3.07	73.45±2.43	22.24±2.01
F7	91.84±2.56	266.7±2.59	80.17±3.23	34.78±1.49
F8	98.58±2.23	278.1±3.18	84.65±4.85	46.89±2.23

Mean ± SD (n = 3 observations)

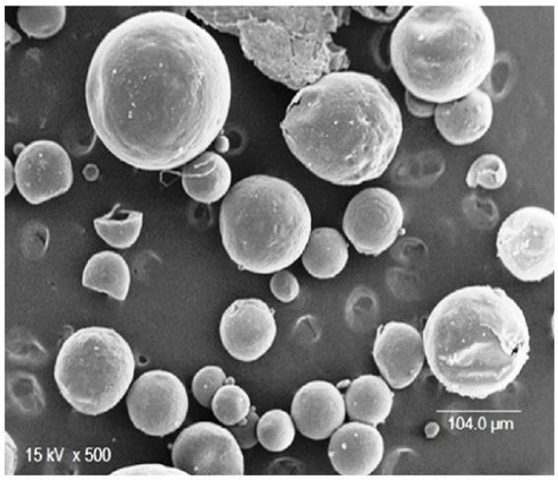

Figure 3. SEM of Floating Hallow Microspheres of Dexlansoprazole

3.4. *In vitro* drug release studies

The in vitro drug dissolution study was conducted in 0.1 N HCl over a period of 10 hours, measuring the percentage cumulative drug release at different time points for various formulations (F1 to F8) of floating hollow microspheres. In the first hour, the drug release ranged from 4.48% (F6) to 5.02% (F8). Over the subsequent hours, the drug release gradually increased, with F7 and F8 exhibiting the highest cumulative release of around 67.28% and 82.21%, respectively, at the 10th hour. Formulations F1 to F5 demonstrated similar release patterns, indicating a controlled and sustained drug release from the floating microspheres. These results suggest that the formulations with different polymer compositions and concentrations affect the drug release profile, highlighting the potential for tailoring drug delivery kinetics based on specific formulation parameters. [13,14] The results are shown in Figure 4.

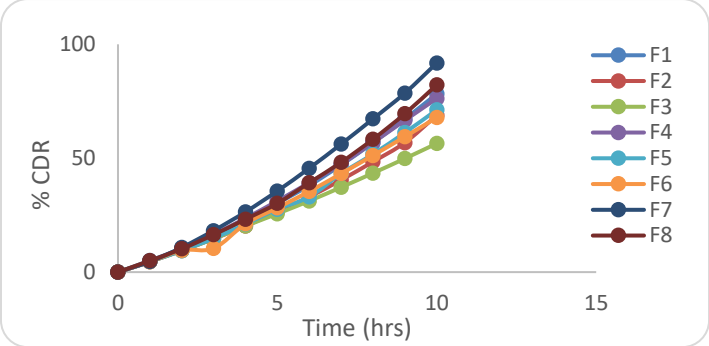

Figure 4. *In vitro* drug release from all formulations

4. Conclusion

The successful preparation of floating hollow microspheres containing Dexlansoprazole was achieved through the utilization of both natural and synthetic polymers. Chitosan and sodium alginate served as natural polymers, while ethyl cellulose and HPMC were employed as synthetic polymers, employing the solvent evaporation method. These microspheres, designed to float in the stomach, facilitate a controlled release mechanism for Dexlansoprazole, thereby extending its therapeutic effect over an extended period. The formulation, particularly F7, was identified as the optimized one, demonstrating controlled drug release up to 10 hours, reaching a release rate of 90.79±0.89%. This controlled release contributes to increased gastric residence time, improved bioavailability, and a reduction in the frequency of drug dosing. Beyond enhancing drug bioavailability, the floating hollow microspheres also play a significant role in promoting patient compliance with the treatment regimen.

References

[1] Prasad AR, Ratna JV. Development and validation of a simple UV-Spectrophotometric method for the determination of ciprofloxacin HCl present in taste masked drug resin complex. Int J Appl Pharm 2018; 10:37-41.

[2] Chandra MS, Dharan SS, Athira A. Formulation and evaluation of gastro retentive floating microballoons containing selected anti-ulcer drug. J Pharm Sci Res 2021; 13:49-63.

[3] Chouhan M, Chundawat AVS, Chauhan CS. Development and characterization of floating microspheres of esomeprazole magnesium trihydrate by solvent evaporation method. Int J Pharm Sci Res 2017; 8:689-97.

[4] Bangale GS, Shinde GV, Rajesh KS. Development and evaluation of microballoons based extended-release drug delivery system for hypertension therapy. Global J Pham Pharm Sci 2019; 7:1- 11.

[5] Mannaa S, Lakshmia US, Racharlaa M, Sinhab P, Kanthala LK, Kumara SP. Bioadhesive HPMC gel containing gelatin nanoparticles for intravaginal delivery of tenofovir. Journal of Applied Pharmaceutical Science. 2016 Aug 30;6(8):022-9.

[6] Purohit KK, Garud N. Formulation and evaluation of floating microspheres of losartan potassium using sodium alginate and HPMC by solvent evaporation method. J Drug Delivery There 2019; 9:60-6.

[7] Ramalingam N, Mohamed JA, Sunusha P, Palanivelu M, Surendiran NS, Ganesan B. Preparation and characterization of floating microspheres of ciprofloxacin hydrochloride. World J Pharm Sci 2017; 6:1394-408.

[8] Thummala UK, Vallabhareddy PS, Sarella PN. Enhancing Oral Absorption of Orlistat through Gastroretentive Mucoadhesive Pellets: Formulation and Evaluation. Journal of Clinical and Pharmaceutical Research. 2023 Apr 30:9-17.

[9] Ramu S, Suresh P, Rao DS, Ramakrishna G. Formulation and evaluation of floating microspheres of rosiglitazone. Int J Pharm Chem Biol Sci 2015; 5:907-18.

[10] Sarella PN, Thammana PK. Potential applications of Folate-conjugated Chitosan Nanoparticles for Targeted delivery of Anticancer drugs. Research Journal of Pharmaceutical Dosage Forms and Technology. 2023 Oct 1;15(4):281-8.

[11] Khan, Rizwana, S.K. Prajapati, R. Irchhiaya and Gyanendra Singh. 2010."Formulationand Evaluation of Mucoadhesive Microspheres of Flurbiprofen. Pharmacology online 3(4): 659–70

[12] Kudupudi V, Kakarparthy RS, Sarella PN, Kolapalli VR. Formulation Development and Characterization of Vancomycin Hydrochloride Colon-Targeted Tablets Using In-Situ Polyelectrolyte Complexation Technique. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN). 2023 May 31;16(3):6533-45.

[13] Jalodiya S, Gupta MK, Jain NK. Formulation, development and evaluation of floating microspheres of acyclovir. J Drug Delivery There 2019; 9:967-73.

[14] Negi R, Goswami L, Kothiyal P. Microballoons: A better approach for gastro retention. Indian Journal of Pharmaceutical and Biological Research. 2014 Apr 1;2(2):100.

Author's short biography

Dr. Vijaykumar Darshanam

Dr. Vijaykumar Darshanam is a Professor and Head of the Department of Pharmaceutics at Swami Vivekananda Institute of Pharmaceutical Sciences, located in Vangapally, Yadagirigutta, Yadadri-Bhongir, Telangana, India. With a decade of experience in both teaching and research within the field of pharmacy, he has provided guidance to over 30 students in their undergraduate and postgraduate dissertation work. He possesses numerous patents and has contributed scientific publications to both national and international journals. Additionally, he holds qualifications in the Graduate Pharmacy Aptitude Test (G-PAT) and is a lifelong member of the Association of Pharmaceutical Teachers of India (APTI)

Dr. Madhusudhan Merugu

Dr. Madhusudhan Merugu holds the position of Professor and Head of the Department of Pharmaceutical Analysis at Swami Vivekananda Institute of Pharmaceutical Sciences in Vangapally, Yadagirigutta, Yadadri-Bhongir, Telangana, India. With a focus on fostering dedicated and accomplished students within the Faculty of Pharmacy, he brings a wealth of experience to the field. He boasts a decade of expertise in both teaching and research in the realm of pharmacy. Throughout his career, he has provided support and guidance to over 20 students in their undergraduate and postgraduate dissertation works. His contributions extend to numerous patents and scientific publications in both national and international journals. Heis also a committed lifelong member of the Association of Pharmaceutical Teachers of India (APTI).