CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.7299482

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

FORMULATION AND EVALUATION OF AMIODARONE MICROBALLOONS USING XANTHAN GUM AS RELEASE RETARDANT

Yagvendra Singh, Rajkumar Dhangar, Rishikesh Sharma
Bhabha Pharmacy Research Institute, Bhopal (M.P.)

Article Received: October 2022 **Accepted:** October 2022 **Published: October** 2022

Abstract:
*The current research was aimed to formulate, evaluate and optimize gastro retentive formulations (*microballoons*) of amiodarone using a combination of natural and synthetic polymers such as guar gum, Ethyl Cellulose, Xanthan Gum and HPMC. Floating microballoons containing Amiodarone with a central hollow cavity were prepared by the solvent evaporation technique using Amiodarone, HPMC, EC and Xanthan Gum. The prepared microballoons were evaluated for Percentage yield, Drug entrapment, Percentage buoyancies, floating lag time, Mean particle size, Zeta potential, In vitro drug release and Stability study. The results of the present study demonstrated that xanthan gum could be a successful hydrophilic polymer for the formulation of sustained release Floating microballoons. In vitro dissolution studies indicated a sustained release pattern throughout the 12 h study period, which was compatible with theoretical release profile. Hence xanthan gum based microballoons seem to have a desirable sustained pattern of drug release, in order to reduce the dosing frequency.*

Key words: Micro balloons, *Ethyl Cellulose, Xanthan Gum and HPMC, Floating*

Corresponding author:
Yagvendra Singh,
yagvendrasingh0706@gmail.com

QR code

Please cite this article in Yagvendra Singh *et al*, ***Formulation And Evaluation Of Amiodarone* Microballoons Using Xanthan Gum As Release Retardant**., *Indo Am. J. P. Sci, 2022; 09(10).*

INTRODUCTION:

Conventional oral dosage forms such as tablets, capsules provide a specific drug concentration in systemic circulation which do not release at the constant rate for prolonged period of time. Controlled release drug delivery system (CRDDS) provides drug release at a pre controlled, predictable rate either systematically or locally for intended duration of time and optimizes the therapeutic effect of a drug by controlling its release into the body with lower and less frequent dosing.

Controlled-release drug delivery system is capable of achieving the benefits like maintenance of therapeutic amount of drug concentration in blood with controlled release rate for an extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing the fluctuations of drug concentration and frequency of dosing; it optimized therapy and better patient compliances.
Dosage forms that can be retained in stomach for longer periods of time are called gastroretentive drug delivery systems (GRDDS). GRDDS are suitable and beneficial for such drugs by improving their absolute bioavailability, therapeutics efficiency, increase gastric residence time (GRT), possible reduction of the dose, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment.

Oral drug delivery systems have dominated other drug delivery systems for human administration due to their various advantages including ease of administration, flexibility in formulation, cost-effectiveness, easy storage and transport, and high patient compliance. However, oral drug delivery systems face challenges such as low bioavailability due to the heterogeneity of the gastrointestinal system, pH of the commensal flora, gastric retention time of the dosage form, surface area, and enzymatic activity. [1]

Oral drug delivery system is the most preferable route of drug delivery due to the ease of administration, patient compliance, non-evasive in nature and flexibility formulation. With several drugs, absorption may be as little as 30% or less of orally administered dose. To compensate for this effect, a very large dose is often administered so that absorption of therapeutically required quantity of drug can occur. This technique may prove costly with expensive drugs; and the absorbed drug may also have undesirable side effect within the gastrointestinal tract. In addition, poorly absorb drug often display large inter and intra variability in bioavailability. This problem may overcome by modified release drug delivery system with prolonged residence time in the stomach. [2]

Gastro retentive drug delivery system (GRDDS) is thus beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by possible reduction of dose. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastro intestinal tract for local and systemic effect. Gastro retentive dosage form can remain in the gastric region for a longer period and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades several gastro retentive drug delivery approaches been designed and developed, including high density (sinking) system that is retained in themucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendable or swellable system which limits emptying of the dosage forms through the pyloric sphincter of the stomach, super porous hydrogel system, magnetic system etc. [3-5]

Amiodarone hydrochloride is an anti-anginal and antiarrhythmic drug used to increase the duration of ventricular and atrial muscle action by inhibiting Sodium-Potassium activated myocardial adenosine tri-phosphatase. There is a resulting decrease in heart rate and in vascular resistance. It is a benzofuran derivative related to the now obsolete vasodilator khellin. The most striking structural features of the drug are its high iodine content and its resemblance to the thyroid hormone thyroxine (Florey, 2001). Amiodarone Hydrochloride is a highly lipophilic (log p (octanol/water) 7.9) (www.drugbank.com) poorly water soluble drug with absolute bioavailability of 20-55%.The drug exhibits physicochemical properties highly suitable for diffusion across lipophilic absorbing membranes, but its low aqueous solubility can act as the rate limiting step for absorption.

To overcome this problem several attempts have been made to develop oral dosage forms having prolonged retention time in the stomach to extend the duration of drug delivery. Several gastrointestinal targeting dosage forms, including intragastric floating, high density, bioadhesive, swelling and magnetic systems have been developed.

Microballoons are in a strict sense, spherical empty particles without core having internal hollow structure with air inside. Microballoons incorporating a drug dispersed or dissolved throughout particle

matrix have the potential for controlled release of drugs. Certain types of drugs can benefit from using gastroretentive devices.

The current research was aimed to formulate, evaluate and optimize gastro retentive formulations (micro balloons) of amiodarone using a combination of natural and synthetic polymers such as guar gum, Ethyl Cellulose, Xanthan Gum and HPMC.

MATERIAL AND METHODS:

Formulation of Amiodarone loaded microballoons

Floating microballoons containing Amiodarone with a central hollow cavity were prepared by the solvent evaporation technique [6-7]. Weighed quantities of acebrophylline, HPMC, EC and Xanthan Gum were dissolved in a mixture of ethanol and DEM (1:1 solvent ratio) at room temperature. The polymer solution was poured into 250 mL distilled water containing 0.01% Tween 80 and the resulting solution was stirred with a propeller-type agitator at 300 rpm and 40°C for 1 hr to allow the volatile solvent to evaporate. The finely developed microballoons were then filtered, washed with distilled water, and dried in vacuum. The different ratios of polymers were used to prepare the microballoons. The various formulations are tabulated (Table 1).

Table 1: Formulations of the floating microballoons prepared

S. No.	Formulation Code	Amiodarone (mg)	HPMC (mg)	EC (mg)	Xanthan Gum (mg)
1.	F1	75	100	25	-
2.	F2	75	100	50	-
3.	F3	75	100	75	-
4.	F4	75	150	25	10
5.	F5	75	150	50	20
6.	F6	75	150	75	30

Evaluation of microballoons

Percentage Yield

The prepared microballoons with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microballoons[8].

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} x\ 100$$

Drug Entrapment

The various formulations of the Floating microballoons were subjected for drug content. 10 mg of Floating microballoons from all batches were accurately weighed and crushed [9]. The powder of microballoons were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method.

Floating behavior

Ten milligrams of the floating microballoons were placed in 0.1 N HCl (100 mL). The mixture was stirred at 100 rpm in a magnetic stirrer [10]. After 10 h, the layer of buoyant microsphere was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. Both the fractions of microballoons were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} x\ 100$$

Measurement of mean particle size

The mean size of the microballoons was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microballoons suspended in 5 ml of distilled water was used for the measurement [11].

Determination of zeta potential

The zeta potential of the drug-loaded microballoons was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate [12].

Shape and surface characterization of microballoons by scanning electron microscopy (SEM)

From the formulated batches of microballoons, formulations (F5) which showed an appropriate balance between the percentage releases were examined for surface morphology and shape using scanning electron microscope Jeol Japan 6000[13]. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

***In-vitro* release studies**

The *in vitro* drug release rate from Floating microballoons was carried out using the USP type I (Electro Lab.) dissolution assembly. A weighed amount of floating microballoons equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH=1.2) maintained at 37 ± 0.5°C and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 240nm to determine the concentration of drug present in the dissolution medium.

RESULTS AND DISCUSSION:

Floating microballoons containing Amiodarone with a central hollow cavity were prepared by the solvent evaporation technique using Amiodarone, HPMC, EC and Xanthan Gum. The prepared microballoons were evaluated for Percentage yield, Drug entrapment, Percentage buoyancies, floating lag time, Mean particle size, Zeta potential, *In vitro* drug release and Stability study.

The percentage buoyancies of formulations F1–F3 at the end of 10 h were found to be 63.32±0.25%, 68.85±0.32% and 65.45±0.14%, and for the formulations F4-F6 at the end of 10 h were 72.23±0.65%, 78.85±0.27%, and 70.12±0.54%. The result indicates that with an increase in the concentration of polymers, HPMC, EC and Xanthan gum slight decrease the floating time (table 8.3). Formulations F5 of prepared microballoons were found to be the best compare to other formulation. The Floating Lag Time (Sec.) lag time of formulation F5 was also found less (50±4), compare to other formulation.

The maximum percentage yield, drug entrapment, percentage buoyancy and less floating lag time was found to be formulation F5 in floating microballoons. The optimized formulation of batche subjected to further studies.

The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, in order to determine the mechanism of drug release. When the regression coefficient values were compared, it was observed that an 'r' value of microballoons was maximum Zero order release i.e 0.994 hence indicating drug releases from formulations was found to follow Zero order release kinetics for floating microballoons.

Table 2: Percentage yield for different formulation

S. No.	Formulation	Percentage Yield
1.	F1	68.85±0.85
2.	F2	66.96±0.23
3.	F3	67.78±0.65
4.	F4	71.12±0.74
5.	F5	76.65±0.96
6.	F6	70.25±0.35

Table 3: Drug entrapment for different formulations

S. No.	Formulation	Drug entrapment (% w/w) of prepared microballoons
1.	F1	65.85±0.25
2.	F2	63.32±0.32
3.	F3	66.65±0.15
4.	F4	70.25±0.42
5.	F5	75.85±0.36
6.	F6	69.74±0.52

Table 4: Percentage Buoyancy and floating lag time of floating microballoons

Formulation	Floating Lag Time (Sec.)	Percentage Buoyancy
F1	72±4	63.32±0.25
F2	67±6	68.85±0.32
F3	65±5	65.45±0.14
F4	68±2	72.23±0.65
F5	50±4	78.85±0.27
F6	68±2	70.12±0.54

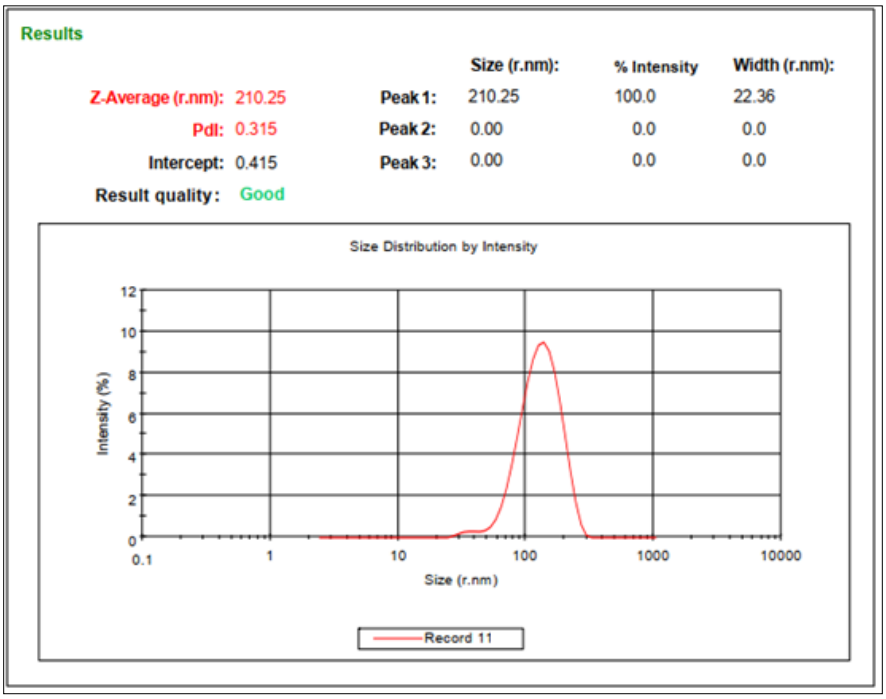

Figure 1: Particle size data of optimized microballoons formulation F5

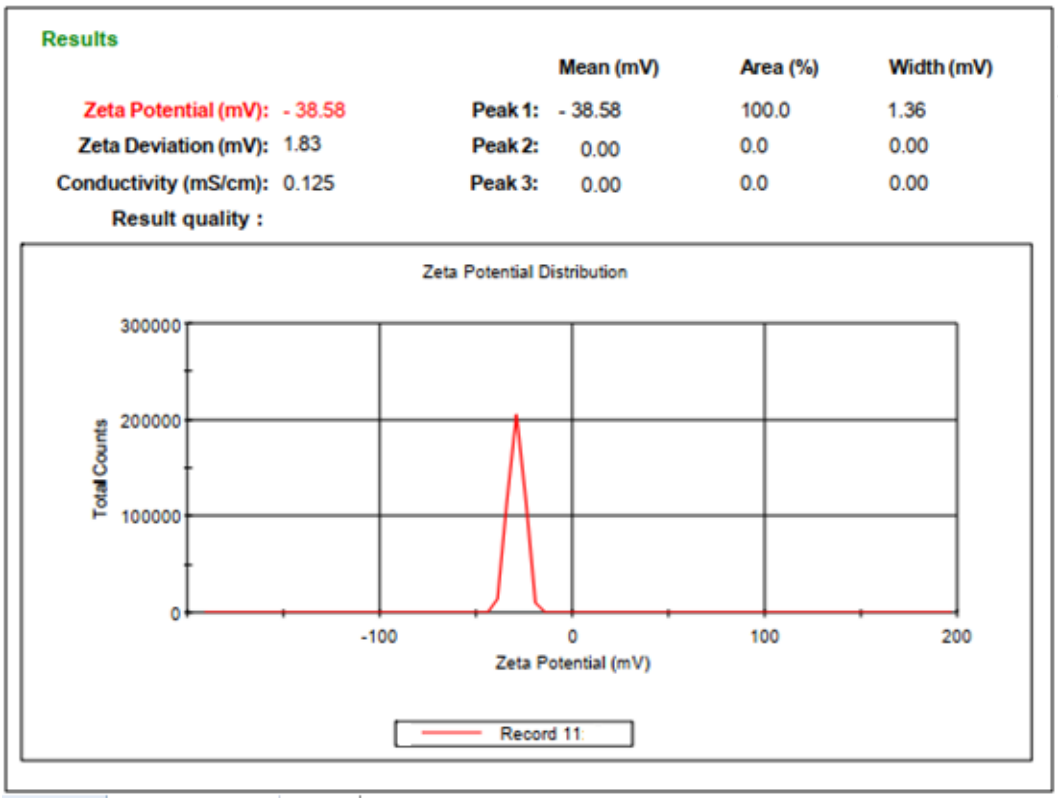

Figure 2: Zeta potential data of floating microballoons F5

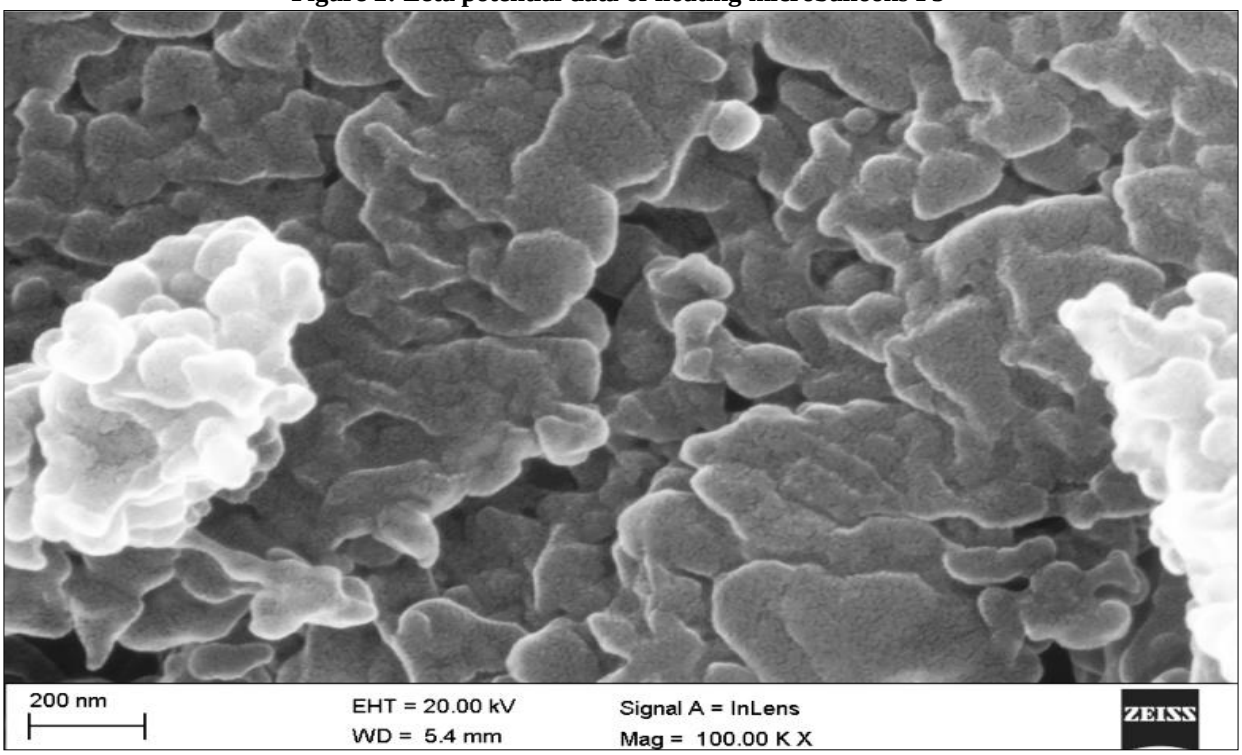

Figure 3: Graph of scanning electron microscopy (SEM) of optimized formulation F5

Table 7: Release Study data of formulation F1-F6

Time (Hrs)	% of Drug Release						
	F1	F2	F3	F4	F5	F6	Marketed Formulation
0.5	38.85	35.85	30.23	28.85	20.23	16.65	35.65
1	53.32	48.85	36.65	39.98	28.89	23.32	63.32
2	65.85	63.32	63.36	58.85	33.32	30.65	91.14
4	79.98	74.45	68.98	69.45	49.95	35.74	99.74
6	98.85	92.23	73.32	76.65	58.85	43.32	-
8	99.05	97.74	86.65	86.65	73.32	58.89	-
10	99.45	99.12	98.87	98.85	89.98	63.32	-
12	99.65	99.45	99.74	99.12	99.74	85.65	-

Table 8: Comparative study of regression coefficient for selection of optimized Formulation F5

Release Kinetics	Zero order	First order	Higuchi	Korsmeyer peppas
R^2	0.994	0.704	0.974	0.443

CONCLUSION:

In conclusion, the results of the present study demonstrated that xanthan gum could be a successful hydrophilic polymer for the formulation of sustained release Floating microballoons. In vitro dissolution studies indicated a sustained release pattern throughout the 12 h study period, which was compatible with theoretical release profile. Hence xanthan gum based microballoons seem to have a desirable sustained pattern of drug release, in order to reduce the dosing frequency.

REFERENCES:

1. Lopes C.M., Bettencourt C., Rossi A., Buttini F., Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. Int. J. Pharm. 2016;510:144–158.
2. Timmermans J, Moes AJ. How Well Floating Dosage Form Float?. Int J Pharm 1990; 62:207-16
3. Streubel A, Siepmann J. Bodmeier R. Multiple unit Gastroretentive drug delivery: A new preparation method for low density microparticles. J Microcapsule 2003;20:329- 47.
4. Goole J, Vanderbist F, Aruighi K. Development and Evaluation of new multipleunit Levodopa sustainedrelease floating dosage forms. Int J Pharm 2007:334:35-41.
5. Sharma S, Pawar A. Low density multiparticulate system for pulasatile release of Meloxicam. Int J.Pharm 2006:313:150-58.
6. Yadav A, Kumar D, Gastroretentive microballoons of Metformin: Formulation Development and Characterization, J Adv Pharm Technol Res, 2011; 2(1): 51-55.
7. Senthil P, Senthil C, Abdul AH, Microballoons - from formulation to pharmaceutical design and applications, World Journal of Pharmacy and Pharmaceutical Sciences, 2016; 5(5): 341-352.
8. Azza AH, Marwa H, Gastro retentive Nizatidine Loading Microballoons for Treatment of Peptic Ulcer, International Journal of Pharmacy and Pharmaceutical Sciences, 2015; 7(10): 315-333.
9. Kumar DJ, Formulation and Evaluation of Gastro retentive floating microballoons of Anti diabetic drugs, Asian Journal of Pharmacy and Life Science, 2011; 1(2): 402-408.
10. Swami G, Saraf SA, Preparation and Evaluation of sustained release micro balloons of propranolol, Daru Journal of Pharmaceutical Sciences, 2011; 19(3): 502-507.
11. Joshi VK, Jaimini M, Microballons drug delivery system: A review, Asian Journal of

Pharmaceutical Research and Development, 2013; 1(1): 7 –17.
12. Saneshan GV, Kanth K, Preparation and in vitro evaluation of microballoon drug delivery system of Telmisartan, Int. J. Pharm. Sci. and Drug Res, 2013; 5(4): 141-145.
13. Chaurasia H, Chaurasia D, Singh S, Formulation and In-Vitro Evaluation of Floating Microballoons of Indomethacin, Acta Poloniae Pharmaceutical Drug Research, 2010; 67(3): 291 – 298.