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FORMULATION AND CHARACTERIZATION OF GASTRORETENTIVE MICROBALLOONS OF AMIODARONE HYDROCHLORIDE

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ABSTRACT

Cardiac arrhythmic disorders which is present 1.5% to 5% of the population overall can lead to lethal cardiovascular diseases. Anti-arrhythmic medication amiodarone, a benzofuran derivative, is frequently employed in a number of contexts. But as it has very short half-life there is need to design a novel drug delivery system. Thus, this study aims at formulating & evaluating microballons of Amiodarone. The formualtion & evaluation of microballon was performed according to standard protocol. In total 6 formulations of microballons were made and evaluated for various parameters. Results showed that the percentage yield was found to be varied from 65.52±0.15 for F1 to 74.45±0.15% for F5. The highest drug was found to be entrapped in F5 formulation which is 75.65±0.17%. The floating time was found to be ranged from 52 seconds to 69 seconds while the percentage Buoyancy spananed from 63.32 to 79.98%. The results of measurement of mean particle size of optimized formulation F5 of floating microballoons was found to be 220.36 nm. The zeta potential value obtained for the optimized Formulation F5 of floating microballoons was -37.12 mV. After examining drug release data from F1 to F6 formualtions the highest % of Drug Release was with the F5 formulation which is 99.74 in 12 hours. The R^2 value obtained for Zero order was 0.994 thus it is clear that the floating microballoons of Amiodarone follows zero order release kinetics. Results of stability studies indicated no significant difference in the drug content between initial and formulations stored at 40±2°c & 75±5% RH for 3 months. So, it can be concluded that microballoons may prove to be a useful method of delivering Amiodarone because they increase bioavailability in contrast to traditional dose forms.

Keywords: Microballoons, Amiodaron, Gastroretentive, Novel drug delivery system, Cardiac arrhythmic disorders.

INTRODUCTION

Cardiac arrhythmic disorders are classified as either bradycardia or tachycardia depending on the ventricular response, which must be less than 60 beats per minute for bradyarrhythmias and more than 100 beats per minute for tachyarrhythmias. All patients who experience syncope should be evaluated for arrhythmias, especially when cardiac illness is present. Arrhythmias are a major cause of syncope.

Bradycardia or tachycardia, two ventricular rate extremes, can seriously reduce cardiac output and cause syncope. Outside of this range, the cerebral blood flow may be reduced. Profound sinus bradycardia, high-grade atrioventricular (AV) block, supraventricular tachycardia (SVTs), ventricular tachycardia, pacemaker malfunction, pacemaker induced arrhythmias, and pacemaker syndrome are the most frequent arrhythmias causing syncope or presyncope [1-3].

Anti-arrhythmic medication amiodarone, a benzofuran derivative, is frequently employed in a number of contexts. It is most well-known for its approved usage in life-threatening ventricular arrhythmias, but it is widely used off-label for atrial fibrillation in outpatient and inpatient settings. The prescribing advice for amiodarone states that it should only be used for the conditions for which it has been approved; nonetheless, one source claims that the plasma half-life of amiodarone after a single dose ranges from 3.2 to 79.7 hours. PRH was thought to be a viable candidate for floating controlled release formulations due to its short half-life, frequent dosage, and stomach adverse effects at high concentration [4-5].

A family of gastroretentive medication delivery systems called floating drug delivery systems are increasingly being used to treat cardiovascular disorders. Cardiovascular diseases are those conditions that affect how the heart works and operates. Drugs' stomach residence times can be greatly extended by gastroretentive systems since they can stay in the gastric region for several hours. For medications that are less soluble in a high pH environment, prolonged stomach retention increases bioavailability, lowers drug waste, and enhances solubility [6-7].

Innovative drug delivery methods called micro-balloons are designed to float over the contents of the stomach for an extended period of time. In order to avoid changes in stomach emptying and to release the medicine for extended periods of time, floating micro-balloons have the benefit of being buoyant and evenly dispersed over the gastric fluid. Microballoons are low-density systems with enough buoyancy to float above gastric fluid and stay in the stomach for a considerable amount of time. As the device floats over the gastric fluid, the drug is given gradually and at a controlled rate, increasing gastric retention and reducing changes in plasma drug concentration. The gel solidifies and the polymers hydrate to create a colloidal gel barrier that slows the rate of fluid penetration into the device as stomach fluid comes into contact with the microballoons. The microspheres are buoyant because of the air trapped by the inflated polymer, which reduces their density below that of stomach fluid. However, optimum buoyancy requires a minimum amount of gastric content [8-9].

The micro-balloons are often free-flowing powders made of proteins or artificial polymers, and they should preferably be less than 200 micrometers. Promising possibilities for the development of a gastro-

retentive drug delivery system for possible therapeutic use include floating micro-balloons [10]. Thus, this study aims at formulating & evaluating microballons of Amiodarone to treat Cardiac arrhythmic disorders.

MATERIALS & METHODS

Procurement of drug

Amiodarone was obtained as gift sample from Micro labs, Baddi, India.

Chemicals and reagents

HPMC, Xanthan Gum, Guar Gum Ethanol, methanol, distilled water were obtained from S.D. Fine chemicals Mumbai.

Formulation of Amiodarone loaded microballoons

Floating microballoons containing Amiodarone with a central hollow cavity were prepared by the solvent evaporation technique [11]. Weighed quantities of acebrophylline, HPMC, Guar Gum 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: Formulations of the floating microballoons prepared

S. No.	Formulation Code	Amiodarone (mg)	HPMC (mg)	Xanthan Gum (mg)	Guar 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. The % yield was calculated by dividing weight of actual product by total weight of drug & polymer multiplied by 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 [60]. 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 [12]. 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.

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 [13].

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

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.

Stability studies for optimized formulation

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a re-test period for the drug substance or a shelf life for drug product and recommended storage conditions. In general, a drug substance should be evaluated under storage condition (with appropriate tolerances) that test its thermal stability and if applicable, its sensitivity to moisture. Three types of storage conditions are used i.e. long term, Accelerated and where appropriate, Intermediate.

RESULTS & DISCUSSION

In total 6 formulations of microballons were made and evaluated for various parameters. The percentage yield was found to be varied from 65.52±0.15 for F1 to 74.45±0.15% for F5. The highest drug was found to be entrapped in F5 formulation which is 75.65±0.17%. The floating time was found to be ranged from 52 seconds to 69 seconds while the percentage Buoyancy spananed from 63.32 to 79.98%. The results of measurement of mean particle size of optimized formulation F5 of floating microballoons was found to be 220.36 nm. Since stirring speed and emulsifier concentration affect drug entrapment, buoyancy, and particle size, an increase in polymer concentration may have caused a shift in the equilibrium between these factors. This was demonstrated by a decrease in drug entrapment and percentage buoyancy.

The number, ratio, and kind of solvents employed in formulation all affect how buoyant a microparticulate system . Microballoons constantly floated over the dissolve for more than 12 hours in the current investigation. The presence of pores formed by the quick evaporation of dichloromethane

may have contributed to the buoyancy of microballoons by trapping air in the pores and causing them to float.

The zeta potential of the drug-loaded microballoons was determined using a zeta sizer (Malvern Instruments) by measuring their electrophoretic mobility in a micro electrophoresis flow cell. These measurements were conducted in triplicate, using water as the solvent, at a temperature of 25°C. The zeta potential value obtained for the optimized Formulation F5 of floating microballoons was -37.12 mV. After examining drug release data from F1 to F6 formualtions the highest % of Drug Release was with the F5 formulation which is 99.74 in 12 hours. From microballoons, a consistent drug release (Figure 2) was seen, which might be related to diffusion and erosion mechanisms. This further revealed that the formulation had "no burst effect" because the drug was released gradually.

The R^2 value obtained for Zero order & First order was 0.994 & 0.709 respectively while for Higuchi and Korsmeyer peppas model the R^2 value was noted as 0.974 and 0.977 respectively. From the regression coefficient data obtained it is clear that the floating microballoons of Amiodarone follows zero order release kinetics.

Additionally the stability studies of formulation was carried out it was 3 months accelerated stability study at 40±2°C and 75±5% RH optimized formulations. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference observed in the drug content between initial and formulations stored at 40±2°c & 75±5% RH for 3 months.

The created microballoons will continue to float on the surface of the stomach fluid and release Amiodarone over time. According to in vitro research, microballoons may prove to be a useful method of delivering Amiodarone because they increase bioavailability in contrast to traditional dose forms.

Table 2: Percentage yield for different formulation

S. No.	Formulation	Percentage Yield*
1.	F1	65.52±0.15
2.	F2	67.74±0.25
3.	F3	66.36±0.14
4.	F4	69.98±0.22
5.	F5	74.45±0.15
6.	F6	68.85±0.28

Table 3: Drug entrapment for different formulations

S. No.	Formulation	Drug entrapment (% w/w) of prepared microballoons
1.	F1	66.45±0.15
2.	F2	67.85±0.25
3.	F3	65.45±0.32
4.	F4	70.12±0.18
5.	F5	75.65±0.17
6.	F6	68.85±0.22

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

Formulation	Floating Lag Time (Sec.)	Percentage Buoyancy
F1	68	71.12
F2	67	65.58
F3	65	69.98
F4	52	79.98
F5	63	65.45
F6	69	63.32

Table 5: 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 6: Release Kinetics of optimized formulation of microballoons F5

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative% Drug Release	Log Cumulative % Drug Released	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	20.23	1.306	79.77	1.902
1	1	0	28.89	1.461	71.11	1.852
2	1.414	0.301	33.32	1.523	66.68	1.824
4	2	0.602	49.95	1.699	50.05	1.699
6	2.449	0.778	58.85	1.770	41.15	1.614
8	2.828	0.903	73.32	1.865	26.68	1.426
10	3.162	1	89.98	1.954	10.02	1.001
12	3.464	1.079	99.74	1.999	0.26	-0.585

Table 7: Comparative study of regression coefficient for selection of optimized Formulation F5

Release Kinetics	Zero order	First order	Higuchi	Korsmeyer peppas
R^2	0.994	0.709	0.974	0.977

CONCLUSION

Drug absorption in the digestive system is a very variable process, prolonging dosage forms' stomach retention and lengthening the time of drug absorption. A promising method for gastric retention is the hollow microballoons, gastroretentive controlled release delivery device. When it is formulated on a large scale, biocompatible and affordable polymers like Xanthan Gum and Guar Gum can be used in conjunction with HPMC to create an effective floating microparticulate system. Therefore, the Amiodarone floating microballoons that have been created show promise as multiple-unit delivery devices that can administer drugs safely and effectively over an extended period of time in patient suffering from Cardiac arrhythmic disorders.

REFERENCES

1. Mohapatra D, Mishra S and Dash AK. A review article on "Concept of the five 'A's in the treatment of Cardiac Arrhythmia". Research Journal of Pharmacology and Pharmacodynamics. 2020;12(3):133-6.
2. Schwartz PJ, Ackerman MJ, Antzelevitch C, Bezzina CR, Borggrefe M, Cuneo BF and Wilde AA. Inherited cardiac arrhythmias. Nature Reviews Disease Primers. 2020;6(1):58.
3. Ettinger PO, Wu CF, De La Cruz Jr C, Weisse AB, Ahmed SS and Regan TJ. Arrhythmias and the "Holiday Heart": alcohol associated cardiac rhythm disorders. American heart journal. 1978;95(5):555-62.
4. Holt DW, Tucker GT, Jackson PR and Storey GC. Amiodarone pharmacokinetics. American heart journal. 1983;106(4):840-7.
5. Siddoway LA. Amiodarone: guidelines for use and monitoring. American family physician. 2003;68(11):2189-97.
6. Lopes CM, Bettencourt C, Rossi A, Buttini F and Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. International journal of pharmaceutics. 2016;510(1):144-58.
7. Mandal UK, Chatterjee B and Senjoti FG. Gastro-retentive drug delivery systems and their in vivo success: A recent update. asian journal of pharmaceutical sciences. 2016;11(5):575-84.
8. Negi R, Goswami L and Kothiyal P. Microballoons: A better approach for gastro retention. Indian Journal of Pharmaceutical and Biological Research. 2014;2(2):100.
9. Yadav A and Jain DK. Gastroretentive microballoons of metformin: Formulation development and characterization. Journal of advanced pharmaceutical technology & research. 2011;2(1):51.
10. Kumar R, Kamboj S, Chandra A, Gautam PK and Sharma VK. Microballoons: An advance avenue for gastroretentive drug delivery system-A review. Pharmaceutical and Biosciences Journal. 2016:29-40.
11. Bhardwaj P, Chaurasia H, Chaurasia D, Prajapati SK and Singh S. Formulation and in-vitro evaluation of floating microballoons of indomethacin. Acta Pol. Pharm. 2010;67(3):291-8.
12. Chandra SM, Dharan SS and Aji kumar A. Formulation and evaluation of gastroretentive floating microballoons containing selected anti-ulcer drug. Journal of Pharmaceutical Sciences and Research. 2021;13(1):49-63.
13. Vidyadhara S, Sasidhar RL, Balakrishna T, Balaji B and Amrutha R. Formulation and evaluation of controlled release floating Microballoons of stavudine. Scientia Pharmaceutica. 2015;83(4):671-82.