

# Formulation and Evaluation of Doxycycline Microspheres Using Guar Gum as the Release Retardant

Suraj Kumar Yadav<sup>\*1</sup>, Bhupendra Tiwari<sup>1</sup>, Gopesh Gunjan<sup>1</sup>, V P Gupta<sup>1</sup>  
*Globus College of Pharmacy, Bhopal*

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## ABSTRACT

The objective of the present investigation was to formulate microballoons loaded with doxycycline in the polymeric shell for attaining sustained release and hence improved bioavailability. Microballoons loaded with doxycycline loaded in their polymer shell were prepared by simple solvent evaporation method using either ethyl cellulose alone or a blend of varying ratio of ethylcellulose with Eudragit S100 and a fixed amount of guar gum was used as the release retardant. The percent yield of the microballoons ranged from 76.64 to 82.58% with highest yield obtained in F3. The particle size was measured using optical microscopy and the particles were observed to be spherical in shape. The particle size ranged from  $32.96 \pm 18.33 \mu\text{m}$  (F3) to  $60.06 \pm 14.95 \mu\text{m}$  (F1). The angle of repose ranged from  $24.68$  to  $25.98^\circ$  (a value less than  $35^\circ$  suggest good flow of powder). The Carr's index and Hausner's ratio were in between 13.44 to 17.09 and 1.16 to 1.21 respectively. It was found that all the formulations exhibited buoyancy in the range of 61.11 to 73.60% over a period of 8h. This suggests that the formulations were able to float for sufficient time and would be able to control the release of doxycycline for longer duration. Formulation F3 exhibited the highest buoyancy percentage of all the formulations. The in vitro drug release study depicted that the highest amount of drug was released from F1 (68.96%) while the lowest was released from F5 (51.21%) at the end of 8 hours of study.

**Keywords:** Doxycycline, microballoons, gastroretention, controlled release, guar gum

## I. INTRODUCTION

Oral route of drug administration is the most advantageous and widely utilized method of drug administration but it produces specific drug concentration in systemic circulation but they are not able to release the drug at a constant rate for a longer duration of time. This leads to the optimization of the therapeutic effect of the drug thereby reducing its dose and frequency of administration in turn improving the patient

compliance<sup>1</sup>. Gastro retentive drug delivery is based on design and development of systems that might be able to retain the dosage form in the stomach for longer time periods. These systems are particularly beneficial in improving the bioavailability of drugs that possess low solubility in the high pH environment (like intestine)<sup>2</sup>. Therefore, extended-release DDS which possess gastric retention properties are thought to be significantly useful<sup>3-7</sup>.

Doxycycline (DOX) is a broad-spectrum antibiotic synthetically derived from oxytetracycline<sup>8</sup>. Doxycycline is virtually completely absorbed after oral administration with a bioavailability of ranging from 73-95%. It is rapidly metabolized but has an elimination half life of 18-22 h. The objective of this work was the development and investigation of floating microspheres (microballoons) of Doxycycline to modulate its pharmacokinetic profile. Treatment of disease requires maintenance of uniform concentration of drug in blood for a long period of time. Floating microspheres were envisaged as the most promising drug delivery system owing to their slow dissolution in gastric fluid thereby rendering the capability to prolong the release of drug at the site of absorption. The particular goals of the study are preparation of microballoons of Doxycycline using guar gum as the release retardant.

## II. MATERIAL AND METHODS

### Preformulation Studies<sup>9,10</sup>

Preformulation studies are an aid to have the required information of the drug to make it sure that the drug is pure as well as to determine the utility of drug in the type of dosage form that is being developed. The organoleptic features, solubility, melting and calibration curve were studied.

### Calibration curve of DOX

The maximum absorption of doxycycline hydrochloride was observed at 276 nm using purified water pH 6.8 as the solvent. The calibration curve was obtained using different concentrations of the drug at the above wave

length. The stock solution was freshly prepared by dissolving 10 mg of doxycycline hydrochloride in 1 ml of water in a 10 ml volumetric flask and then made up the solution upto the mark using purified water for obtaining the solution of strength 1000 µg/mL (stock I). 1 ml of this solution is diluted to 10 ml with purified water to obtain a solution of strength 100 µg/mL (stock II). From this solution with draw 1, 2, 3, 4 & 5 ml of solution in to the 10 ml volumetric flask and volume made up to 10 ml by using purified water to get the solutions of 10, 20, 30, 40 & 50µg/ml.

### Formulation of Microballoons<sup>12</sup>

Emulsion solvent diffusion method has been used for formulating the microballoons using ethyl cellulose and Eudragit S100 as the polymer for forming the shell of the particles and guar gum

as the release retardant (Table 1). A blend of dichloromethane and ethanol in the ratio 1:1 (solvent blend) was used as the solvent to impart floating characteristic to the particles. The drug and the polymers were accurately weighed using a calibrated electronic weighing balance and dissolved in 20 mL of the solvent blend. In a separate beaker, 100 mL aqueous solution comprising of 0.75% w/v polyvinyl alcohol and 0.2 % w/v Tween 80 was prepared at and stirred continuously at 40°C using mechanical stirrer. The stirring speed was maintained at 200 rpm. To this solution was added dropwise under stirring the solvent blend containing the drug and polymers. The microballoons formed were collected, washed with distilled water, dried in hot air oven and stored in desiccator for evaluation studies.

**Table 1 Composition of microballoons**

Ingredients	F1	F2	F3	F4	F5
DOX(mg)	50	50	50	50	50
EC (mg)	250	237.5	225	200	150
Eudragit S100 (mg)	0	12.5	25.0	50.0	100.0
Guar Gum (mg)	25	25	25	25	25

### Evaluation of Microballoons

#### Percentage Yield

The yield of each batch of microballoon was calculated by measuring the dry weight of the microballoons and calculating the yield percent considering the weight of polymers and drug used for preparing the formulation.

$$\% \text{ yield} = \frac{\text{weight of dry microballoons} \times 100}{(\text{Weight of drug} + \text{polymers})}$$

#### Determination of particle size

The size of the microballoons was determined using optical microscope using a calibrated stage and ocular micrometer. The microballoons were dispersed in small amount of water a drop was placed on a glass slide. The drop was covered with a cover slip and observed under the microscope. The number of graduations covered by each particle was counted and the particle size was calculated using the calibration data of the ocular micrometer.

#### Entrapment Efficiency

An accurately weighed 10 mg of microballoons were crushed and to it was added 10 mL of ethanol. The contents were vortexed for 2

min to extract out the drug and dissolve it. The solution was filtered and the filtrate was diluted using phosphate buffer. The absorbance of the diluted filtrate was recorded using UV spectrophotometer against phosphate buffer as the solvent blank. The concentration of DOX was calculated from the absorbance using the calibration curve equation. The entrapment efficiency was calculated by the formula:

$$\% \text{ Entrapment efficiency} = \frac{\text{Drug content calculated} \times 100}{\text{Theoretical Drug Content}}$$

#### Determination of floating capacity (buoyancy)

Microballoons (20 mg) were transferred to a 100 mL Simulated Gastric Fluid (SGF), pH 1.2 consisting of 0.02% Tween 20 (for preventing aggregation of microballoons) maintained at 37°C. The mixture was stirred on a magnetic stirrer. After 8 h, the settled microballoons and the floating microballoons were separately collected and dried at 40°C and weighed. The buoyancy was calculated by the following equation:

$$\% \text{ Buoyancy} = \frac{\text{Weight of floating microballoons} \times 100}{(\text{Weight of floating} + \text{settled microballoons})}$$

**Micromeritic features**

**Angle of Repose**

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose ( $\theta$ ) was then calculated by measuring the height and radius (r) of the heap of powder formed.

**Bulk and Tapped Density**

A weighed quantity of blend (1 g) was taken into a graduated cylinder (50 mL) and measuring the volume of this weight. The bulk density ( $\rho$  bulk) was calculated. The above cylinder containing the powder blend was tapped until no further volume change occurs. The tapped density ( $\rho$  tap) was calculated.

**Hausner’s ratio and Carr’s Index**

Hausner’s ratio is the ratio of tapped density to bulk density and is calculated. The Compressibility index is also known as Carr’s Index and is calculated using the values of bulk and tapped density using formula.

**In vitro drug release**

The amount of drug released at various time intervals for various batches of microballoons was determined using paddle type dissolution apparatus. The dissolution medium comprised of 900 mL of simulated gastric fluid, pH 1.2 supplemented with 0.02% Tween 20 maintained at  $37 \pm 0.5^\circ\text{C}$  and stirred at 100 rpm. A weighed amount of microballoons equivalent to 50 mg of

DOX was transferred to the dissolution flask and at predetermined time intervals, 1 mL of sample were withdrawn from the dissolution medium, replenishing with fresh medium after each withdrawal up to 8<sup>th</sup> hour. Samples were appropriately diluted and analyzed by UV spectrophotometer at 310.4 nm. The concentration of DOX after each withdrawal was determined using the equation of the calibration curve.

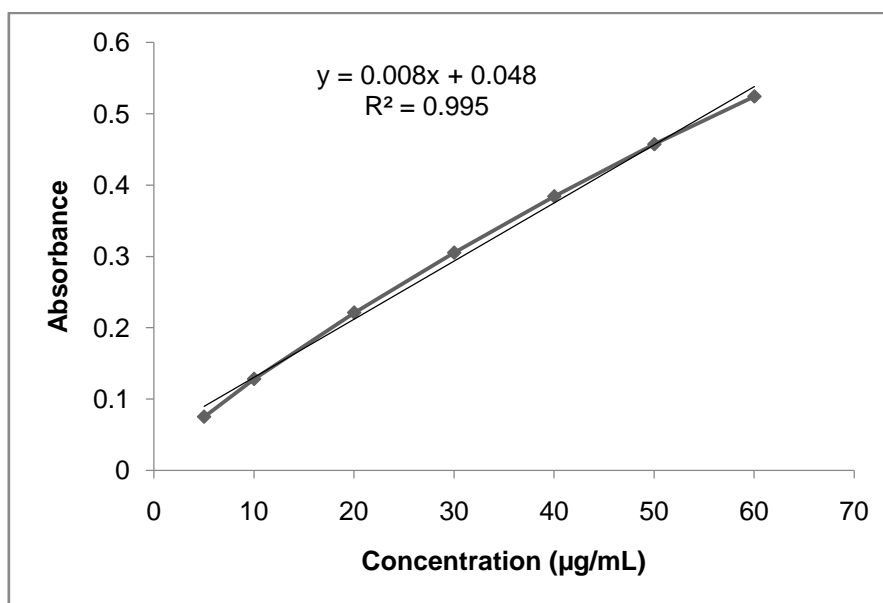
**III. RESULTS AND DISCUSSION**

Preformulation studies were carried out for DOX for determination of its physical and chemical properties and also to confirm the specifications of the sample (Table 2).

**Table 2 Prefromulation study results**

Test	Observation
Color	White
Odor	Odorless
Taste	Bitter
Solubility	Soluble in water and DMF
Melting Range	203-204°C

The absorption maximum of DOX was obtained to be 276.0 nm and its calibration curve was prepared in water at the above wavelength using UV spectrophotometer. Calibration curve of DOX was determined by plotting absorbance (nm) versus concentration ( $\mu\text{g/ml}$ ) at 276.0 nm (Figure 1).



**Figure 1 Calibration curve of DOX**

**Micro-balloon evaluation**

Gastro-retentive floating microspheres are low density systems that possess adequate buoyancy to let them float over the contents of the gastric medium and linger in stomach for enhanced period. As the system floats over gastric contents, the loaded drug releases slowly resulting in reduced fluctuations in plasma drug concentration. Microballoons loaded with DOX loaded in their polymer shell were prepared by simple solvent evaporation method using either ethyl cellulose alone or a blend of varying ratios of ethylcellulose

and Eudragit S100 using fixed amount of guar gum for slowing down the release.

**Percentage yield**

The percentage yield of the microballoons was calculated in relation to weight of drug and polymers used for formulation. It was witnessed from the results that the yield was dependent on the binding properties of the polymer which could be inferred as the highest yield was obtained when 9:1 ratio of ethylcellulose to Eudragit S100 was used as the in the formulation (Table 3).

**Table 3 Percent yield of the microballoon formulations**

Formulation	Yield	
	mg	%
F1	249.1	76.64
F2	253.7	78.06
F3	268.4	82.58
F4	257.3	79.16
F5	252.5	77.69

The highest yield was obtained in F3 for preparing the shell of the microballoons whereas the lowest yield was obtained when only ethyl cellulose was used. The hydrophobicity of ethyl cellulose decreases the binding capability and hence the formulation of particles is reduced. The particle size was measured using optical microscopy and the particles were observed to be spherical in shape. It was found that F3 had the

lowest particle size suggesting a potential effect of the binding capability of the blend in comparison to the other blends or ethyl cellulose alone (Table 4). The entrapment of DOX was also found to be maximum in F3 though all the formulations exhibited almost similar entrapment of DOX. The higher amount in F3 suggests formation of a strong polymeric shell of the microballoons.

**Table 6.6 Particle size and entrapment efficiency of microballoons**

Formulation	Particle Size (µm)	Entrapment Efficiency (%)
F1	60.06 ± 14.95	56.54
F2	41.75 ± 18.57	61.22
F3	32.96 ± 18.33	73.75
F4	40.28 ± 14.15	68.61
F5	41.02 ± 19.94	63.87

The flow properties of all the microballoon formulations were studied and it was found that all the formulations were able to exhibit optimum flow properties. The angle of repose

ranged from 24.68 to 25.98° (a value less than 35° suggest good flow of powder). The Carr’s index and Hausner’s ratio were in between 13.44 to 17.09 and 1.16 to 1.21 respectively (Table 5).

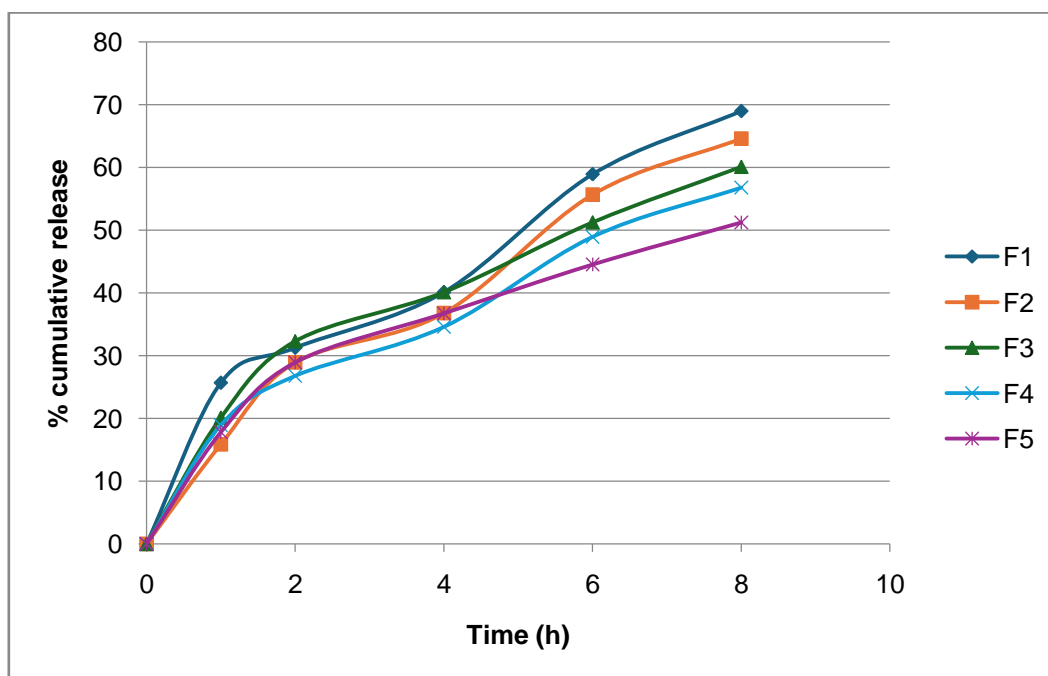
**Table 5 Micromeritic features of microballoons**

Formulation code	Angle of Repose (°)	Bulk density (g/cm <sup>3</sup> )	Tapped density (g/cm <sup>3</sup> )	Carr's Index	Hausner's Ratio	Buoyancy (%)
F1	24.68	0.381	0.452	15.71	1.19	61.11
F2	25.17	0.461	0.533	13.51	1.16	69.69
F3	25.64	0.438	0.506	13.44	1.16	73.60
F4	25.98	0.562	0.665	15.49	1.18	64.46
F5	26.33	0.621	0.749	17.09	1.21	60.10

The buoyancy was calculated using the reported formula from the weight of floating as well as settled microballoons over 8 h of study (Table 5). It was found that all the formulations exhibited buoyancy in the range of 61.11 to 73.60% over a period of 8h. This suggests that the formulations were able to float for sufficient time and would be able to control the release of DOX for longer duration. Formulation F3 exhibited the highest buoyancy percentage of all the formulations.

**In-vitro release of DOX from microballoons**

The amount of drug that released from the microballoons was determined using paddle type dissolution apparatus. The in vitro drug release study depicted that the highest amount of drug was released from F1 (68.96%) while the lowest was released from F5 (51.21%) at the end of 8 hours of study. An initial burst release was witnessed in each formulation suggesting loosely trapped drug on the surface of the polymeric particles. Guar gum was able to slow down the release of DOX from the microballoons (Figure 2).



**Figure 2 In vitro release of DOX from microballoons**

**IV. CONCLUSION**

The primary objective of the present investigation was formulating microballoons loaded with doxycycline, for sustained release and improved bioavailability. The best formulation was

achieved using ethyl cellulose with Eudragit S100 (9:1) as the polymeric shell and guar gum as the release retardant. The floating ability in the formulations was imparted by the evaporation of the organic solvent blend (ethanol-

dichloromethane) used in the formulation. The formulation is expected to overcome the problems of poor bioavailability, poor distribution and high metabolism associated with oral administration of amiodarone. The formulation F3 released the highest amount of drug and presented highest entrapment efficiency as well as the lowest particle size. Thus it could be concluded that F3 was the best formulation with optimum properties required for improving the oral bioavailability of doxycycline.

The results obtained from the study would be subjected to optimization using various quality-by-design (QbD) approaches. This would be helpful in designing a delivery system doxycycline that might present excellent bioavailability overcoming its own metabolism issue. Such formulation would be helpful in managing the conditions of angina pain along with acute attacks and emergencies without precipitation of severe side effects of the drug.

#### REFERENCES

- [1]. Kumar R and Philip A. Gastro retentive dosage forms for prolonging gastric residence time. *Int J Pharm Med.* 2007; 21(2): 157-171
- [2]. Srivastava A, Shukla R, Sharma K, Jain H, Meshram DB. *J Drug Del Ther.* 2019; 9(4-s): 625-630
- [3]. Tripathi P, Ubaidulla U, Khan RK, Vishwavibhuti. Floating drug delivery system. *Int J Res Dev Pharm Life Sci.* 2012; 1(1): 1-10.
- [4]. Yildirim Y, Ince I, Gumustas B, Vardar O, Yakar N, Mujakovic H, Ozdemir G, Emingil G. Development of doxycycline and atorvastatin loaded chitosan nanoparticles for local delivery in periodontal disease. *Journal of Drug Delivery Science and Technology.* 2023; 82: 104322. Doi: 10.1016/j.jddst.2023.104322
- [5]. Lee CY, Su C-T, Tsai T, Hsieh C-M, Hung K-Y, Huang J-W, Chen C-T. Formulation development of doxycycline loaded lipid nanocarriers using microfluidics by QbD Approach. *Journal of Pharmaceutical Sciences.* 2023; 112(3): 740-750
- [6]. Savadi P, Lotfipour F, McMillan NAJ, Hashemzadeh M, Hallaj-Nezhadi S. Passive and pH-gradient loading of doxycycline into nanoliposomes using modified freeze-drying of a monophasic solution method for enhanced antibacterial activity. *Chemical Papers.* 2022; 76: 3097-3108
- [7]. Soriano-Souza C, Valiense H, Mavropoulos E, Martinez-Zelaya V, Costa AM, Alves AT, Longuinho M, Resende R, Mourão C, Granjeiro J, Rocha-Leao MH, Rossi A, Calasans-Maia M. Doxycycline containing hydroxyapatite ceramic microspheres as a bone-targeting drug delivery system. *Journal of Biomedical Material Research B: Applied Biomaterials.* 2020; 108(4): 1351-1362  
<https://go.drugbank.com/drugs/DB00254>
- [8]. Khare R, Tripathi D, Lal M, Kondalkar A. Formulation and evaluation of transdermal patches of etodolac for topical application. *Journal of Pharmacology and Biomedicine.* 2023; 7(2): 589-297
- [9]. Mishra A, Kondalkar AK, Lal M, Tripathi D, Singh N. Formulation and characterization of chrysin loaded niosomal vesicular delivery system. *Journal of Pharmacology and Biomedicine.* 2023; 7(4): 642-650
- [10]. Yadav A, Jain DK. Gastroretentive microballoons of metformin: Formulation development and characterization. *Journal of Advanced Pharmaceutical Technology and Research.* 2011; 2(1): 51-55
- [11].