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Research Article

FORMULATION AND CHARACTERIZATION OF GASTRORETENTIVE FLOATING MICROBALLOONS OF POORLY WATER-SOLUBLE DRUG DIACEREIN

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ABSTRACT

The drug can be released in a controlled manner using a gastro retentive dosage type. The main focus on the novel technological advances in the floating drug delivery method for gastric retention. The preparation of diacerein micro balloon is done by solvent diffusion method, using acrylic polymer like Eudragit S 100 and HPMC K4 M. The various evaluation of the prepared floating microsphere like its % yield, drug entrapment efficiency, particle size in-vitro dissolution, buoyancy, was studied. The floating microsphere was found to be spherical and range from 85 µm - 192 µm. Whereas the buoyancy in gastric mucosa between the range 30.5% -49.5%. The % yield and % entrapment efficiency were found under the range 61% - 82% and 45.1–84.1% respectively. The microsphere showed favorable in-vitro dissolution 76.8 to 94.45. The optimized formulation was found based on evaluation of floating micro-balloons, Formulation (M3E3) showed the best result as particle size 192 µm, DDE 84.1%, in vitro drug release 94.5%, and in vitro buoyancy 49.5%. all the formulations showed controlled release up to 24 hours.

Keywords: Micro-balloons, gastroretentive, buoyancy, absorption, floating drug delivery system, gastric residence time.

INTRODUCTION

Oral dosage form consisting of a tablet, capsule provides a calculated drug amount inside the circulation of the body system. where some of them don't discharge their medication at a constant rate for a delayed timeframe . The drug delivery in the Controlled-release framework releases its drug at a previously known rate either they are systemic or topical or locally for the calculated timeframe and optimize the corrective activity of drug because the drug release is in a controlled manner into the system with less dose & reduce frequency dose [1-2].

Micro-balloon is a gastro retentive drug delivery system that follows the category of non-effervescent technique [3]. Micro balloons are globular-shaped vacant particles in the absence of any core. These microspheres are, preferably having a size not more than 200 micrometers and having a property of free-flowing powder that is composed of protein or synthetic polymers [4].

Due to the central hollow space inside the microsphere, the micro balloons deal with the nearly all admiring buoyant system with a unique advantage of numerous unit systems and higher standard floating property. The preparation of micro balloons, involves some of these novel techniques include simple solvent evaporation method, solvent diffusion technique, phase separation coacervation technique, solvent evaporation-diffusion strategy, spray drying technique, spray congealing technique. The polymer's type, plasticizers, and solvent are the main component that affects the speed of drug at the desired rate and properties of buoy employed for the preparation. Several polymers like polylactic acid, cellulose acetate, etc were utilized in the formation of micro-balloon. By varying polymer concentration & the polymer plasticizer proportion, the arrival of the drug can be modulated [5-6].

By using some of the methods like the evaporation of solvent phase or solvent evaporation/diffusion method the hollow inner side core of micro-balloon, where the drug is loaded in their external outer shell could be created. the acrylic polymer mixture is solvate in ethanol/dichloromethane mixture and an unsettled arrangement of PVA that is previously thermally controlled at 30-degree calicoes mixed in the acrylic polymer solution. When enhancement of the temperature is done under the pressure condition by continuous stirring and previously prepared stable emulsion formed by evaporating the organic solvent from the emulsion [7-8].

When the inner cavity of the polymer present in the microsphere with the drug has been shaped at a point the phase that contains gas is accomplished in the droplets of the dispersed polymer by evaporating the dichloromethane. The micro balloon continuously floats over 12 hours period of time at the surface of an acidic dissolution [9-10].

MATERIALS AND METHODS

Diacerein was obtained as a gift sample from AMI Life Sciences Pvt. ltd (Gujarat). Eudragit S 100, HPMC K 100M, PVA were produced from Central Drug House Pvt Ltd. Ethanol, Dichloromethane, Methanol from Changshu Hongsheng Fine Chemicals Pvt ltd.

Characterization of diacerein by Spectral analysis

The standard diacerein was spectroscopically analyzed for confirmation of its structure. The instrumental spectral analysis such as:

UV spectroscopy: Maximum absorbance peak was obtained at 264 nm

FTIR Spectroscopy: : Characteristic peaks appeared at 1785.7,1403.9, 1276.6,1014.3 and 748.2 cm -1

DSC: characteristic peak onset at 247°C appeared at 254°C and ends at 255°C

Methods of preparation of hollow microsphere

The floating hollow microsphere of diacerein was prepared using the emulsion solvent diffusion method. The ratio of drug and polymer is used to prepare the micro balloon in 1:1 to 1:4. The mixture of drug and polymer is dissolved in a combination of dichloromethane and ethanol at the ratio of 5:8. The mixture was added dropwise in the solution of 0.75 % PVA and the resulting solution was stirred at 700 RPM for 1 hour at different temperatures. The resulting floating hollow microsphere was screened for particle size, filtered, washed, and dried at room temperature.

Characterization of floating microsphere

Micromeritic properties
Already prepared micro balloons were characterized for micromeritic properties like particle size, bulk density, tapped density, and flow property.

Determination of percentage yield
The percentage yield of the floating microsphere of diacerein can be calculated by the formula that contains total wt. of prepared microsphere and total wt of all non-volatile compounds.

% Yield = Total wt. of prepared micro balloons / Total wt. of all non-volatile compound

Determination drug entrapment efficiency
Weight accurately 10 mg of the already prepared micro-balloons of diacerein were crushed and the drug was extracted from the microsphere after 24 hours of shaking in 10 ml 0.1 N HCL (ph 1.2). The mixture was centrifuged at 2000 rpm for 30 minutes after 24 hours of shaking. After an appropriate dilution at 265 nm, the supernatant was analyzed with a UV spectrophotometer for drug content and the percent drug entrapment was measured.

% Drug Entrapment = Calculated drug concentration / Theoretical drug concentration

Size distribution and morphology of micro-balloons
The floating microsphere of diacerein was examined by the photomicroscope. A freshly prepared suspension of micro-balloons is evaluated for particle size under a photomicroscope. Around 100 particles of each formulation are selected and measure the particle size then the average value of particle size is noted.

Floating behavior
The floating behavior of diacerein micro balloons was determined by accurately measure 50 mg of prepared micro balloons and placed them in simulated gastric fluid (ph 1.2) in 100 ml and the whole mixture was stirred at 100 RPM. After 24 hours the floating and settled micro balloons were collected separately by the filtration process. The collected micro balloon was dried and weighed separately. Both the micro balloons were weighted and calculate the buoyancy by the following formula.

$$\text{buoyancy \%} = Wf / (Wf + Ws) \times 100$$

Where Wf = wt of floating microsphere, Ws = wt of settled microsphere

Invitro release rate studies
The release rate of diacerein micro balloons is determined by paddle-type dissolution apparatus. The calculated number of micro balloons that contain 50 mg of the drug spread over the gastric solution (ph. 1.2 900 ml) the temperature of the medium was maintained at the 37 degree which is equivalent to the human body at 100 RPM. The accurate sink condition was maintained for dissolution rate. After every 1 hour, the 5 ml sample suck out from the medium and check the absorbance at 264 nm after suitable dilution. Every time 5 ml fresh dissolution solution is added to the medium so that the initial volume of the dissolution medium can be maintained

Stabilities studies
Based on the result of in-vitro drug release, percentage buoyancy, and % drug release the best formulation was selected for the stability study. A borosilicate glass bottle is used to store the formulation for a different time. And the samples were assayed for % drug content at regular intervals.

OPTIMIZED PARAMETER

Optimization of Process Variables- for the preparation of micro-balloon various processes are optimized out of which some of the followings were selected.
Solvent ratio
Drug: polymer ratio
Emulsifier concentration
Temperature
Stirring rate

Effect of the drug: polymer ratio
For this study, the amount of drug was kept constant and the amount of polymer was varied which gives the different drug-polymer ratio. Based on the different ratios the size distribution and percentage yield were observed. While other parameters were kept constant.

Effect of solvent ratio
For this study, the organic solvent varied but all other variables were kept constant. Different combinations of solvents of ethanol and dichloromethane are used in different ratios.

Effect of emulsifier concentration
Polyvinyl alcohol (PVA) aqueous solution of different concentrations are used for the preparation of micro-balloon while other variables are kept constant

Different polymer ratio
Eudragit S 100 and HPMC K4M two different polymers were used in the different ratios as shown in table 2.

RESULTS

Particle size: The diacerein floating microsphere of formulations' average particle size from M1E1 to M5E5 was found under the range 72.3 to 95.5 as shown in the table. The results show that the size of the microsphere of M3E3 shows the best result among all which contain an equal amount of polymer as shown in Table 3 and the hollow structure was shown in fig 3.

% Yield: The percentage yield of diacerein floating micro-balloons was varied based on different polymer concentrations. the percentage yield of floating micro-balloons was observed under the range of 59 to 75 %. The percentage yield of different ratios is shown in table 3.

% Drug Entrapment: The % drug entrapment of different ratios of the polymer was observed under the range of 45.1 to 84%. The data of % drug entrapped has shown in table 3.

Micromeritic Property

***The bulk density*:** The bulk density of the diacerein micro-balloons was found to be under the range of,0.105 to 0.144. the results are shown in Table 4.

***Tapped density*:** The tapped density of the diacerein micro-balloons was found to be under the range of 0.117 to 0.143. . the results are shown in Table 4.

***Hausner's ratio*:** The Hausner's ratio of the diacerein floating microsphere was found under the range 1.14 to 1.35. . the results are shown in Table 4.

***The angle of repose*:** The angle of repose of the diacerein microballoons was found to be under the range17.1 of 21.9 respectively. . the results are shown in Table 4.

***In-vitro floating test*:** The buoyancy in vitro test of diacerein micro balloons was done to find out the ability to float in a gastric environment. The floating range of the microsphere is shown in the table. It also shows that as the size of the microsphere is increases the capability of floating will also increase. The results are shown in Table 3

In-vitro drug release: The drug release of the different formulations is shown in the figure. after 24 hours the formulation M1E1 showed a 90 % release of the drug. The other formulation M2E2, M3E3, M4E4, M5E5 showed the 88, 94, 81, 76 % drug release respectively. In all the formulations M3E3 showed the best drug release for 24 hours. The results are shown in Table 6 and graphically shown in fig 4.

Table 1: different process variables and selected parameter

Process Variables	Selected Parameter
Solvent ratio	5:8 ml
Drug: polymer	1:3 mg
Emulsifier concentration	0.75%
Temperature	30ºC
Stirring speed	700 RPM

Table 2: Eudragit S100 and HPMC K4M are used in different proportions

Formulation code	Eudragit S100, HPMC K4M
M1E1	1:0
M2E2	0:1
M3E3	1:1
M4E4	1:2
M5E5	2:1

Table 3: Evaluation of prepared microballoons

Formulation Code	Mean particle size (µm)	% Yield	% Drug Entrapment	% buoyancy 24(hours)
M1E1	112	73.3	59.4	45.2
M2E2	85	61.2	61.2	30.5
M3E3	192	82.1	84.1	49.5
M4E4	125	74.6	45.1	36.6
M5E5	105	68.2	55.3	40.6

Table 4: Physical evaluation of prepared microballoons

Formulation Code	Bulk density	Tapped density	Hausner's ratio	Angle of repose
M1E1	0.105	0.142	1.35	17.1
M2E2	0.112	0.138	1.23	21.4
M3E3	0.103	0.117	1.14	19.6
M4E4	0.144	0.190	1.36	20.6
M5E5	0.129	0.143	1.31	21.9

Table 5: In-vitro drug release studies by dissolution test apparatus

Dissolution media	0.1 N HCL (1.2)
The volume of dissolution medium	900 ml
Volume pipette	5 ml
Volume replaced	5ml of respective receptor medium
Set rpm	100 rpm
Temperature	37±2oC
λmax	264 nm

Table 6: Cumulative % drug releases of prepared microballoons in 0.1 N HCL pH 1.2

Time	M1E1	M2E2	M3E3	M4E4	M5E5
0	**0**	**0**	**0**	**0**	**0**
30 min	2.3	2.4	2.85	1.06	1.67
1 hour	5.5	3.6	5.71	3.9	5.82
2 hour	12.42	11.1	14.21	9.7	12.77
3 hour	22.45	21.6	27.57	20.7	22.89
4 hour	36.74	36.5	43.02	33.5	33.97
5 hour	54.28	56.5	61.8	50.9	51.57
24 hour	88.05	90.3	94.45	76.8	81.66

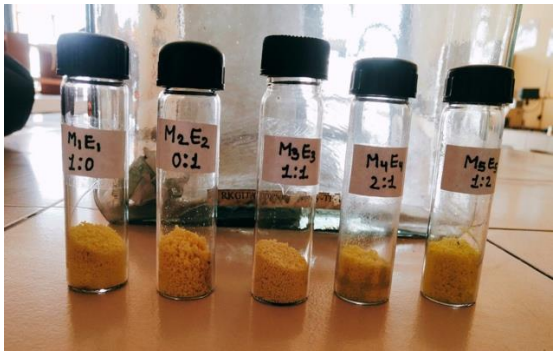


Fig.1: Prepared micro-balloon with different polymer ratio

Fig.2: Optimized formulation

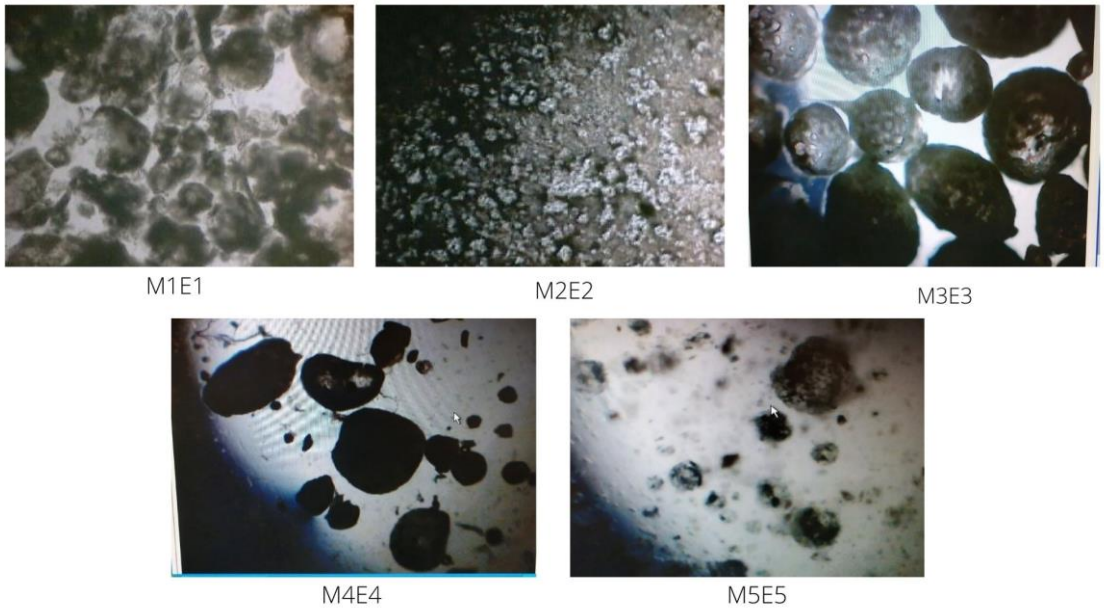
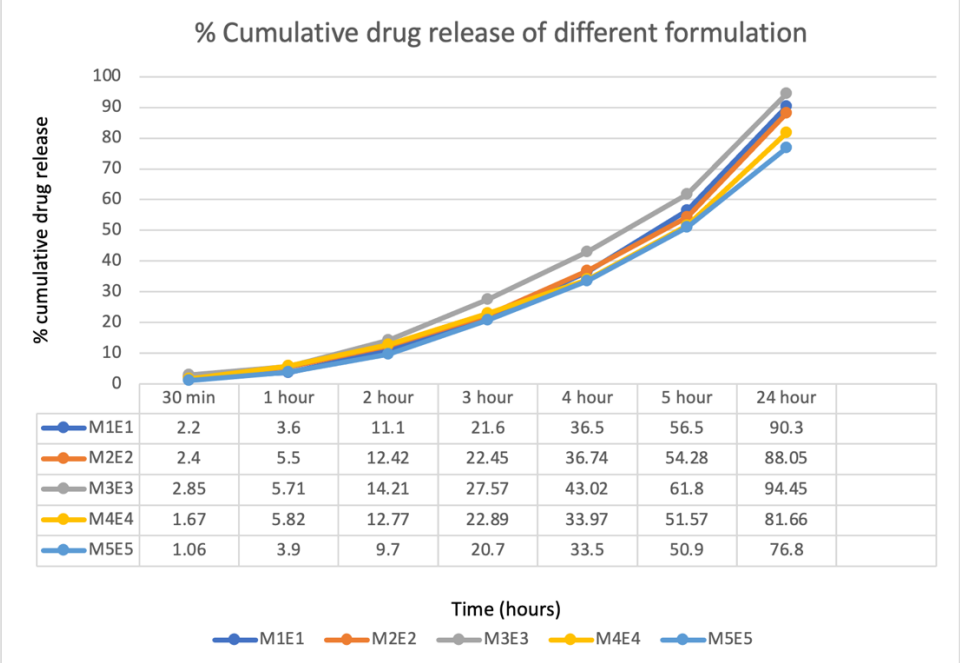


Fig.3: Photo microscopic image of prepared microballoons



	30 min	1 hour	2 hour	3 hour	4 hour	5 hour	24 hour
M1E1	2.2	3.6	11.1	21.6	36.5	56.5	90.3
M2E2	2.4	5.5	12.42	22.45	36.74	54.28	88.05
M3E3	2.85	5.71	14.21	27.57	43.02	61.8	94.45
M4E4	1.67	5.82	12.77	22.89	33.97	51.57	81.66
M5E5	1.06	3.9	9.7	20.7	33.5	50.9	76.8

Fig.4: % Drug release of different formulation

DISCUSSION

Five formulations (M1E1, M2E2, M3E3, M4E4, and M5E5) were prepared with solvent diffusion evaporation method by using two polymers (Eudragit S100 and HPMC K4M) in a different ratio. Ethanol and dichloromethane were used as a solvent system for this preparation and they were also used in different proportions. The surface of the microballoons was found to be smooth at surface, spherical in shape, and light yellow in colour. The drug content of prepared microballoons was analyzed by UV spectrophotometer in the range of 200 to 400 nm and the maximum absorbance was obtained at 264 nm.

All formulations were subjected to physiochemical evaluation i.e. particle size, entrapment efficiency, % yield, and drug release profile.

The % yields of all the formulations (M1E1 to M5E5) were found to be in the range of 61% - 82%. The formulation M3E3 and M2E2 were found to have maximum and minimum % yield respectively.

The particle sizes of all the formulations (M1E1 to M5E5) were found to be in the range of 85 µm - 192 µm. The formulation M3E3 and M2E2 were found to have minimum and maximum particle sizes respectively.

The entrapment efficiency of all the formulations (M1E1 to M5E5) was found to be in the range of 45.1–84.1%. The formulations M3E3 and M4E4 were found to have maximum and minimum drug entrapment efficiency respectively.

The drug release profile of all the formulations (M1E1 to M5E5) was found to be in the range of 90.3, 88.05, 94.45, 81.66, 76.8 respectively. The formulation M3E3 shows the maximum in-vitro drug release.

The % buoyancy of microspheres of all the formulations (M1E1 to M5E5) was found to be in the range of 30.5% -49.5%. The formulation M3E3 and M2E2 show the maximum and minimum buoyancy of micro-balloons respectively.

CONCLUSION

The goals and floating microballoons of diacerein have been successfully formulated and characterized, according to the findings of the study. Diacerein micro balloons were made by solvent diffusion evaporation using eudragit S100 and HPMC K4M as polymers, ethanol, and dichloromethane as solvent systems, and PVA as an emulsifier, according to the study's findings. Prepared formulation M3E3 has been considered as the optimized formulation because it has shown the acceptable % yield, % DEE, % Drug release, % buoyancy. For the better and longer therapeutic effect, the microballoons could be filled in a hard gelatin capsule.

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