IJAIPS
International Journal of Advance Innovations in Pharmacy and Sciences

INTERNATIONAL JOURNAL OF ADVANCE INNOVATIONS IN PHARMACY AND SCIENCES

Volume 1
Issue 1
March-April 2025
www.ijaips.com

Research Article

Formulation and Evaluation of Gastro-retentive floating microballoons of Acetohydroxamic

Ravi Prakash, Surendra Pratap Singh*, Jitendra Malik
Faculty of Pharmacy, PK University Shivpuri (M.P.) 473665

ABSTRACT
Develop a drug delivery system which can provide therapeutically effective plasma drug concentration for a longer period there by reducing the dosing frequency and minimizing fluctuation in plasma drug concentration at steady state by delivering the drug in a controlled and reproducible manner. Increased gastric retention time of dosage form improves bioavailability, reduces drug waste and improves solubility of drugs which are less soluble. These dosage forms also deliver drugs locally to stomach and proximal small intestine. Microballoons(Hollow microsphere) are gastro retentive drug-delivery systems with non effervescent approach. Microballoons are empty particles of spherical shape without core. These microspheres are usually free flowing powders consisting of proteins or synthetic polymers, ideally with a size less than 200 micrometer. In the development of floating microballoons of Acetohydroxamic acid, Drug-Excipient compatibility study was conducted using DSC& FTIR and found that the drug was compatible with all the excipients used in the study. The solubility of drug was also determined in different media like 0.1 N HCl, 6.8 pH buffer, 7.4 pH buffer and distilled water. The results showed that the drug was very freely soluble indistilled water and the solubility was increased with increase in pH. The floating microballoons were prepared by solvent evaporation method using Eudragit RS 100, Eudragit S 100, HPMC K4M and Ethylcellulose as polymers. Prepared microballoons were evaluated for the following *in vitro* evaluation tests such as *micromeritic properties*, tapped density, particle size measurement, percentage yield, entrapment efficiency, *In vitro* buoyancy, drug content, results of all the tests were within the pharmacopoeial specifications and the microballoons remained buoyant for more than 12 hrs in 0.1NHCl. Based on the evaluation of floating and dissolution behaviour, formulation **(AHF5)** which showed complete release with in 12hours and superior entrapment efficiency and stability was selected as optimized formulation.

KEYWORDS: Gastroretentive systems, Microballoons, solvent vaporation bioavailability

INTRODUCTION

The oral route of drug delivery is typically considered the preferred and most patient-convenient means of administration [1]. This is the most common route of administration of drugs because of the several advantages such as ease of administration, least aseptic constraints and the ease of the manufacture of the dosage form. Another great advantage that oral route offers for formulation design is it has variable and versatile physiological conditions at different parts starting from mouth [2,3]. These enabling developing formulations that can be selectively release the medicament for optimal absorption and therapeutic advantage.

Controlled release dosage forms (CRDF) have been developed for over three decades [4]. They have increasingly gained popularity over other dosage forms in treating disease. Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability [5]. But an ideal drug delivery system is one which provides the drug only when and where it is needed and in the minimum dose level required to elicit the desired therapeutic effects [6].

Microballoons (Hollow microsphere) are gastro retentive drug-delivery systems with non-

***Corresponding Author:**
Surendra Pratap Singh
Faculty of Pharmacy, PK University Shivpuri (M.P.) 473665
Email:spspharma2001@gmail.com
Article Received: 10 March 2025
Article Revised and accepted: 30 April 2025
This article can be accessed online on www.ijaips.com

effervescent approach[7]. Microballoons are empty particles of spherical shape without core. These microspheres are usually free flowing powders consisting of proteins or synthetic polymers, ideally with a size less than 200 micrometer[8].

Microballoons are one of the most favourable floating systems with the unique advantages of multiple unit systems with good floating properties, because of central hollow space inside the microsphere. The slow drug release at desired rate and better buoyant properties mainly depends on the type of polymer, the solvents employed for the preparation and plasticizer. Polymers like hydroxy propyl methyl cellulose, Eudragit S, cellulose acetate and polylactic acid are used in these systems and the release rate depends on polymer concentration and the polymer -plasticizer ratio. Different methods used in their preparation are emulsion-solvent diffusion method, phase separation coacervation technique [9], polymerization technique, single emulsion technique, double emulsion technique simple, solvent evaporation method, hot melt encapsulation technique, spray drying and spray congealing technique.

MATERIALANDMETHOD

API Acetohydroxamic acid and all excipients like EudragitRS100, HPMCK4M, Ethyl cellulose, Ethanol, Dichloromethane all are used as analytical grade.

Preliminary studies for screening of polymers:

Preliminary trials of polymers were performed and the excipients which are suitable for the preparation of floating microballoons were selected based on percentage yield[10], buoyancy and entrapment efficiency. Based on preliminary trials different polymers such as eudragit RS 100, eudragit S 100, ethyl cellulose and HPMC K4M in different ratios alone or in combinations were selected to formulate floating Microballoons[11].

Determination of absorption maxima:

A solution of containing the concentration 10 µg/ mL was prepared in 0.1N HCl, water, 7.4 pH & phosphate buffer 6.8pH respectively, UV spectrum was taken using double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.

Preparation of calibration curve:

10 mg of drug was accurately weighed and dissolved in 10 mL of 0.1N HCl, water, 7.4 pH buffer, and 6.8 pH buffer in 10 mL volumetric flask, to make (1000 µg/mL) standard stock solution (1). Then 1 mL from stock solution (1)was taken in another 10 mL volumetric flask to make(100µg/mL)standard stock solution(2),then again 1 mL of stock solution (2) was taken in another 10 mL volumetric flask and prepared stock solution(3) then final concentrations were prepared 1 µg/mL,2 µg/mL,3 µg/mL,4 µg/mL,5 µg/mL with 0.1N HCl, 0.6 µg/mL,1.2 µg/mL,1.8 µg/mL, 2.4 µg/mL, 3 µg/mL with water, 0.2 µg/mL,0.4 µg/mL,0.6 µg/mL,0.8 µg/mL,1 µg/mL,1.2 µg/mL with 6.8 pH buffer and 2 µg/mL, 4 µg/mL, 6 µg/mL, 8 µg/mL, 10 µg/mL with 7.4 pH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 294nm, 294nm, 286nm and 286nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis[12].

Solubility studies:

The equilibrium solubility of Acetohydroxamic Acid was measured in 0.1M hydrochloric acid (pH of 1.2), phosphate buffer of pH 6.8, distilled water and phosphate buffer of pH 7.4 respectively in order to determine its solubility. Excess amount of the drug were added to 50 mL-stoppered conical flasks (n=3). The flasks were shaken mechanically at 37°C±0.5°C for 24 hrs, in a horizontal shaker (HS 501 Digital, IKA-Labortechnik, and Staufen, Germany). After 2 days of equilibrium, aliquots were withdrawn and filtered (0.22 µm pore syringe filter). Then, the filtered samples were diluted with an appropriate amount of dissolution medium and assayed by UV-spectrophotometer at 299nm for Acetohydroxamic acid[13].

Determination of acid stability studies of a drug in 0.1N HCl:

Stock solution of Acetohydroxamic acid was prepared in 0.1N HCl in order to determineits acid stability. At predetermined time points 0,1, 2, 4, 6, 8, 10, 12 and 24hrs, the samples were analyzed by using UV-Visible spectrophotometer at 299nm for Acetohydroxamic acid to see whether there is any change in the absorbance and concentration in the prepared stock solutions[14].

Drug-excipients compatibility study:

Differential scanning calorimetry

The physicochemical compatibilities of the drug and the excipients were tested by differential scanning calorimetric (DSC) analysis. DSC thermograms of the drug alone and optimized formulation were derived from DSC (DSC 4000, Perkin-Elmer, New York, NY).The instrument was calibrated with an indium standard. The samples (2-4 mg) were heated (20- 300°C) at a constant scanning speed (10°C/min) in sealed aluminum pans, using nitrogen purged gas[15].

FTIR spectroscopy:

Compatibility studies were carried out to know the possible interactions between Acetohydroxamic acid and excipients used in the formulation[16]. Drug-polymer compatibility studies were carried out using FTIR spectrophotometer (Shimadzu) by KBr pellet technique. IR spectrum of pure drug and optimized formulation were seen in between 4000-400 cm-1.

Table 1: Formulation composition of Acetohydroxamic acid floating microballoons

S.No.	Materials	AHF1	AHF2	AHF3	AHF4	AHF5	AHF6	AHF7	AHF8	AHF9	AHF10	AHF11	AHF12	AHF13	AHF14	AHF15
1	Drug(mg)	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
2	EudragitRS100	250	250	250	500	500	500	250	250	500	500	NA	NA	NA	NA	NA
3	EudragitS100	250	500	750	250	500	750	750	750	500	500	NA	NA	NA	NA	NA
4	HPMCK4M	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	250	250	250	500	500
5	Ethyl cellulose	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	250	500	750	250	500
6	Ethanol	15	15	15	15	15	15	20	10	20	10	15	15	15	15	15
7	Dichloro methane	15	15	15	15	15	15	10	20	10	20	15	15	15	15	15
Ratio of Drug to Polymer		1:1:1	1:1:2	1:1:3	1:2:1	1:2:2	1:2:3	1:1:3	1:1:3	1:2:2	1:2:2	1:1:1	1:1:2	1:1:3	1:2:1	1:2:2
Ratio of Solvent		1:1	1:1	1:1	1:1	1:1	1:1	2:1	1:2	2:1	1:2	1:1	1:1	1:1	1:1	1:1

Formulation of Acetohydroxamic acid floating microballoons:

The floating microballoons were formulated by solvent evaporation method[17]. The polymer is dissolved in an organic solvent and the drug is dissolved or dispersed in the formed polymer solution[18]. The solution containing the drug is then introduced into an aqueous phase containing suitable additive (polymer/ surfactants) to form oil in water emulsion. Once the stable emulsion has formed, the organic solvent is evaporated either by continuous stirring or by increasing the temperature under pressure. Stirring was continued for 6 hunder 3 blade propeller at 500 rpm, 40°C until the smell disappears. The solvent removal leads to the precipitation of polymer at the oil/water interface of droplets, which forms cavity thus makes the microballoons hollow to impart the floating properties[19]. Those are collected and washed with excess amount of distilled water to remove any remnants. Collected microballoons were dried at room temperature.

Floating microballoons of Acetohydroxamic Acid were successfully formulated by solvent evaporation technique. All the possible experimental trials were successfully carried out and were further evaluated[20].

***In-vitro* evaluation methods Micromeritic properties**

Microballoons are evaluated for following micromeritic properties like bulk density, tapped density, particle shape and size, Hausner‟s ratio and flow properties by angle of repose and Carr‟s index.

Bulk density:

Bulk density is defined as mass of the powder divided by its bulk volume and is expressed in gm/cm^3. The bulk density of a powder depends on particle shape, particle size distribution and the particles tendency to adhere together. Bulk density is very important in the size of containers needed for handling, shipping and storage of raw material and blend[21].10gm powder blend was sieved and introduced into a dry 20 mL cylinder, without compacting. The powder was carefully levelled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated from:

Bulk density = M / Vo

Tapped density:

Where, Vo=apparent volume of sample M=mass of sample

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tapped density= M / V Where, M = Weight of sample

V=Tapped volume of powder

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose which is defined as the maximum angle achievable between the powder pile surface and the horizontal plane. If more powder is added to the pile, its lides down the sides of the pile until the mutual friction of the particles producing a surface angle is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was fixed with its tip at a given height(h),over a graph paper that is place dona

flat horizontal surface[22]. The blend was carefully pored through the funnel until the apex of the conical pile just touches the funnel. The radius (r) of the conical pile base was measured.
The angle of repose was calculated from:
Tan θ = h / r
Where, Tanθ=Angle of repose,
r=Radius of the cone base, h=Cone height

Determination of powder compressibility:
The Compressibility Index (Carr‟s Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is a measure of the relative importance of inter particulate interactions. In a free- flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value[23]. For poorer flowing materials, there are frequently greater inter particle interactions and a greater difference between the bulk and tapped densities will be observed.

Particle size measurement
Particle size of prepared microballoons was estimated by an optical microscope and the mean particle size was calculated with the help of a calibrated ocular micrometer by measuring 100 particles.

Scanning electron microscope(SEM)
The surface morphology and surface characteristics of best formulation were carried out by Scanning Electron Microscope (SEM). Microballoons were scanned and examined under Electron Microscope connected with fine coat, Ion sputter. The sample was loaded on copper sample holder and sputter coated with carbon followed by gold[24].,

Drug content:
Drug content of each formulation equivalent to unit dose (250mg) was determined spectrophotometrically. Each formulation was taken and finely powdered in glass mortor and dissolved in 0.1 N HCl for 6 hours and absorbance was noted at 299 nm.

Percentage yield
The prepared microballoons were weighed accurately. Weighed quantity of microballoons was divided by the total amount of all the excipients and drug used in the preparation of the microballoons which give the total percentage yield of floating microballoons[25]. It was calculated by using following formula,
Percentage yield = Actual yield of product/Total weight of excipients and drug

Entrapment efficiency

The amount of entrapped drug in the microballoons was calculated based on the total drug content and the un entrapped drug of the floating microballoons. The un entrapped drug was determined by taking one dose equivalent of floating microballoons and washed with 0.1N HCl to remove the free drug on the surface. The drug content in microballoons was estimated by dispersing 50 mg of microballoons in 10 mL of 0.1 N HCl and the microballoons are agitated with a magnetic stirrer for 12 h to extract the drug by dissolving the polymer. Both the solutions of unentrapped drug and total drug were filtered through a whatman filter paper and the drug concentration was determined spectrophotometrically at 299 nm by making desired dilution with 0.1N HCl [26,27]. Percentage entrapment efficiency was calculated as follows
% Entrapment efficiency = (Total drug content – unentrapped drug)*100/Total drug content

***In-vitro* Buoyancy:**
Microballoons were spread over the 900 mL of 0.1 NHCl placed in USP dissolution apparatus type II. With the help of paddle rotating at 50 rpm the medium was agitated for 12 h. The floating microballoons and the settled microballoons were collected separately and dried. Then they are weighed[28]. From the ratio of the mass of the microballoons that are floating and the total mass of the microballoons buoyancy percentage was calculated.
%Buoyancy=Qf*100/(Qf+Qs)
Where Qf= floating microballoons weight Qs = settled microballoons weight.

***In vitro* release study:**
The *in-vitro* drug release was carried out by using USP basket type dissolution apparatus containing 900 mL of 0.1N HCl (pH 1.2) as a dissolution medium at 37 ± 0.5ºCat50 rpm. At predetermined time intervals such as 0, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12hrs 5 mL of sample was withdrawn and the samples were filtered through whatmann filter paper, diluted suitably and analyzed spectrophotometrically with UV-Visible spectrophotometer at λmax299 nm. After withdrawal of the test sample, equal amount of fresh dissolution medium was added immediately to maintain 900 mL of dissolution media. The dissolution studies were performed and the average percentage drug release was calculated [29,30].

Drug release kinetic studies:
The mechanism of drug release was determined by fitting the release data to the following kinetic models like zero-order kinetics, first-order kinetics, Higuchi, Korsmeyer-Peppas models and calculate the R2 values of the drug release profiles corresponding to each model using PCP Disso v3 software[31,32].

Zero order release rate kinetics:
To study the zero–order release kinetics the release rate data are fitted to the following equation.
F=Ko t
Where, F ‟is the drug release at time„ t‟, and Ko‟ is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics:
The release rate data was fitted to the following equation Log (100-F) = kt
A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model:
To study the higuchi release kinetics, the release rate data was fitted to the following equation.
F=kt1/2
Where, k‟ is the higuchi constant.
In higuchi model, a plot of percentage drug release versus square root of time is linear.

Korsmeyer and Peppas release model:
The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent „n‟ indicates the mechanism of drug release calculated through the slope of the straight Line.
Mt/M∞=Ktn
Where, Mt/M∞ is fraction of drug released at time „t‟, „n‟ represents diffusional exponent and K is a constant, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n=1; and for super case II transport, n>1. In this model, a plot of log (Mt/ M∞) versus log (time) is linear.

Stability studies [33]:
Stability studies were conducted according to international conference on harmonization (ICH) guidelines. Optimized Microballoons**(AHF5)** were enclosed in polyethylene covers and placed in dessicator containing saturated sodium chloride solution (75% RH). The dessicator was stored at 40°C for 3 months. After every month, microballoons were evaluated for physical appearance, drug content and percentage of drug release for 12 hr .Finally microballoons were tested for any statistical difference using the student paired t –test , the differences were considered to be significant at $p < 0.05$.

RESULTSANDDISCUSSION

Calibration curve of Acetohydroxamicacid in various solvents

Calibrationcurvein0.1NHCl

Table 2: Calibration curve of Acetohydroxamic acid in 0.1N HCl (n=3)

Concentration (µg/mL)	Absorbance
0	0.000
1	0.218
2	0.394
3	0.568
4	0.718
5	0.916

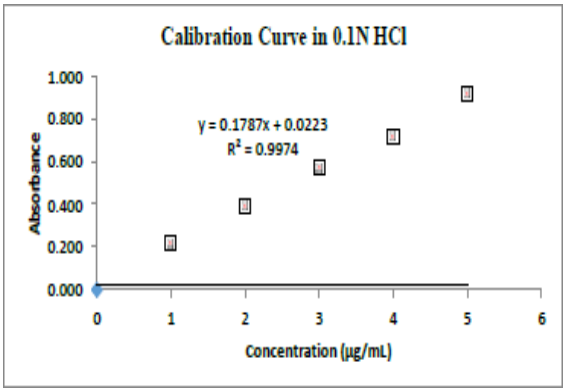

Figure 1: Calibration curve of Acetohydroxamic acid in 0.1N HCl (n=3)

Solubility studies
Table 3: Solubility studies of Acetohydroxamic acid

Solvent	Solubility(mg/mL)				
	1	2	3	Average	SD
Double distilled water	1022	1023	1020	1021.7	1.5
0.1NHCl	330	353	345	342.7	1.6
pH6.8Phosphate buffer	650	675	682	669.0	1.8
pH7.4Phosphate buffer	1123	1124	1138	1128.3	1.3

In vitro evaluation of Acetohydroxamic acid floating microballoons

Table 4: Physicochemical properties of Acetohydroxamic acid microballoons

Formulation	Bulk Density*	Tapped Density*	Compressibility Index*	Mean Particle Size (µm)**	Angle of Repose*
AHF1	0.72± 0.11	0.65± 0.02	9.72± 1.21	135.35±2.35	15.2±1.2
AHF2	0.74± 0.21	0.64± 0.04	13.51± 1.25	145.35±3.36	16.1±1.4
AHF3	0.76± 0.13	0.67± 0.05	11.84± 2.21	157.45±5.21	17.2±1.5
AHF4	0.8± 0.12	0.69± 0.06	13.75± 1.24	146.38±1.36	15.4±1.4
AHF5	0.76± 0.22	0.65± 0.02	14.47± 1.34	128.29±3.56	15.6±2.1
AHF6	0.76± 0.12	0.64± 0.04	15.79± 1.21	129.45±5.36	19.8±3.4
AHF7	0.79± 0.02	0.65± 0.02	17.72± 2.35	148.35±3.67	15.7±3.5
AHF8	0.72± 0.03	0.68± 0.05	5.56± 1.25	153.26±5.67	15.5±2.5
AHF9	0.71± 0.04	0.67± 0.01	5.63± 1.20	138.37±2.48	15.3±2.3
AHF10	0.76± 0.04	0.68± 0.02	10.53± 2.12	135.31±2.46	15.7±1.2
AHF11	0.75± 0.05	0.69± 0.04	8.00± 1.26	125.37±2.45	15.6±1.1
AHF12	0.74± 0.12	0.66± 0.02	10.81± 2.21	129.39±2.46	16.2±1.3
AHF13	0.76± 0.02	0.67± 0.01	11.84± 2.15	164.35±2.55	16.8±1.2
AHF14	0.77± 0.03	0.69± 0.02	10.39± 1.26	172.35±3.56	15.9±2.3
AHF15	0.81± 0.05	0.67± 0.05	17.28± 3.21	129.35±3.26	15.9±2.2

*All values represent Mean±SD: n=3**All values represent t Mean±SD: n=100

Table 5: *In vitro* evaluation parameters of prepared Acetohydroxamic acid microballoons

Formulation Code	% Yield (n=6)	%EE (n=6)	%Buoyancy (n=6)	Drug Content (n=6)
AHF1	85.2 ±1.2	82.5±2.2	75.8±1.1	98.8±2.1
AHF2	84.6±2.3	92.1±1.2	82.5±1.8	98.9±1.3
AHF3	83.7±1.8	93.4±0.72	83.1±2.3	97.8±3.6
AHF4	75.9±1.6	91.5±0.98	86.5±2.7	100.2±0.9
AHF5	79.7±2.7	89.6±1.6	85.5±2.1	100.3±0.7
AHF6	82.1±0.9	92.7±1.2	85.6±2.8	99.8±0.6
AHF7	82.5±0.7	93.7±2.8	85.4±3.1	99.6±1.2
AHF8	83.4±1.2	86.5±2.6	82.4±0.9	100.2±2.1
AHF9	82.4±0.8	94.5±1.7	78.3±0.6	101.2±1.8
AHF10	75.4±3.1	92.6±3.1	79.5±0.8	100.5±1.3
AHF11	69.8±2.2	68.9±1.2	65.4±1.8	99.8±3.1
AHF12	65.4±3.1	64.5±1.8	64.5±1.2	99.7±1.9
AHF13	64.2±0.9	62.4±2.9	63.2±1.9	99.7±2.7
AHF14	63.2±1.2	61.2±2.7	62.4±3.1	98.9±2.8
AHF15	61.4±0.8	60.2±3.1	61.5±0.9	97.8±2.3

Scanning Electron Microscopy of optimized Acetohydroxamicacid floating microballoons

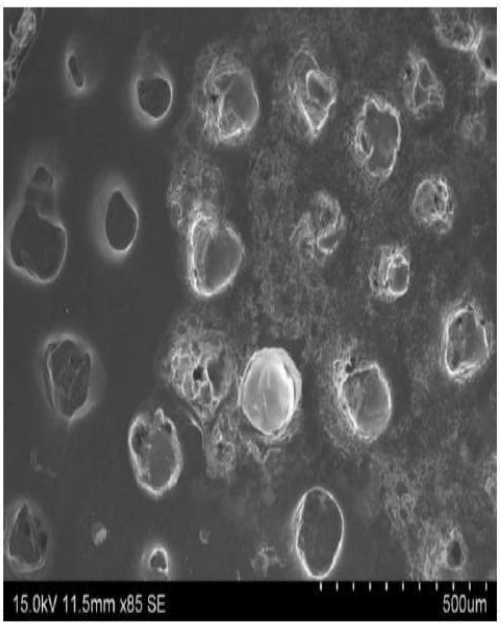

Figure 2: Scanning electron micrographs of optimized floating microballoons of Acetohydroxamic acid

Table 6: Percentage drug released at a of Acetohydroxamicacid Microballoons

Time (Hr)	% Drug Release														
	AH F1	AH F2	AH F3	AH F4	AH F5	AH F6	AH F7	AH F8	AH F9	AH F10	AH F11	AH F12	AH F13	AH F14	AH F15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	25.6±1.1	20.2±3.3	15.8±3.4	20.5±2.6	4.6±5.2	4.2±2.3	15.7±2.8	15.8±3.7	4.8±2.4	5.2±2.8	5.6±2.8	4.5±2.7	3.5±3.2	5.8±2.4	4.9±3.4
1	42.9±5.2	35.6±4.4	25.9±4.2	35.9±3.8	8.5±3.6	7.5±3.9	24.6±3.5	25.6±3.9	8.8±1.2	10.2±2.7	9.5±6.4	8.5±2.7	5.5±1.6	10.2±2.4	9.2±2.1
2	62.5±4.2	52.1±0.5	45.9±3.7	55.5±3.8	17.5±6.3	12.5±3.9	42.5±6.4	45.5±3.9	18.2±2.3	20.2±2.5	15.5±5.8	12.5±3.7	10.2±2.4	15.5±3.7	13.2±2.8
3	85.9±4.3	64.8±5.6	59.7±6.4	65.6±4.5	25.6±3.8	20.2±4.6	58.7±5.6	60.2±3.8	26.5±2.3	26.7±3.7	20.5±5.7	15.5±3.9	12.5±2.9	22.2±3.8	16.5±2.7
4	99.6±3.5	75.2±7.5	67.9±3.9	75.9±5.6	34.5±3.9	30.2±2.8	65.6±5.6	66.4±4.6	35.6±2.8	36.5±0.8	26.9±3.7	20.2±2.8	15.9±2.7	26.5±3.8	21.2±1.2
6	100.2±2.6	85.9±5.6	75.9±4.3	87.9±6.3	52.6±6.9	45.5±1.5	72.5±5.8	73.5±5.9	53.6±3.7	56.3±4.6	39.5±5.7	35.4±3.7	25.6±3.7	41.2±2.9	36.5±2.7
8		100.2±3.8	87.6±7.2	99.5±3.9	65.8±7.2	55.6±4.5	85.6±6.7	86.5±2.9	66.5±3.8	65.6±6.7	45.5±2.7	40.2±2.9	35.6±2.9	46.5±3.7	41.2±4.3
10			100.2±3.9	100.2±6.7	82.6±6.7	65.4±5.7	99.5±6.9	100.2±2.7	83.6±3.8	86.8±4.9	67.5±2.8	55.5±3.7	45.6±3.7	68.5±2.6	56.8±4.7
12					100.1±3.8	72.5±5.6	100.1±5.8		100.1±2.7	100.3±5.7	72.5±2.6	65.2±2.9	56.5±3.7	73.5±2.4	66.5±4.8

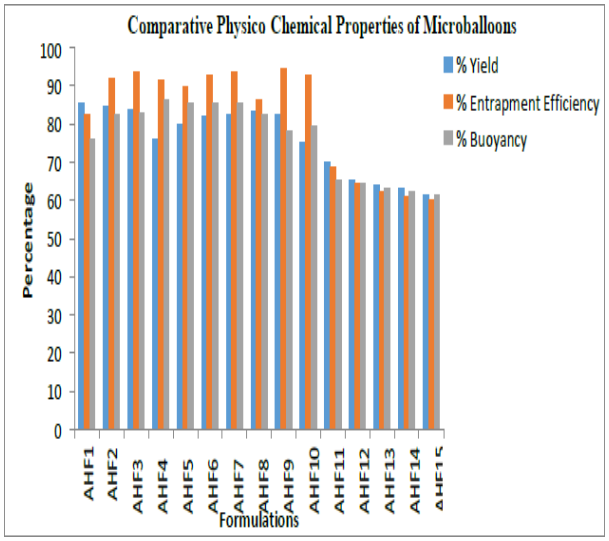

Figure 3: Comparative physico chemical properties of Acetohydroxamic acid microballoons

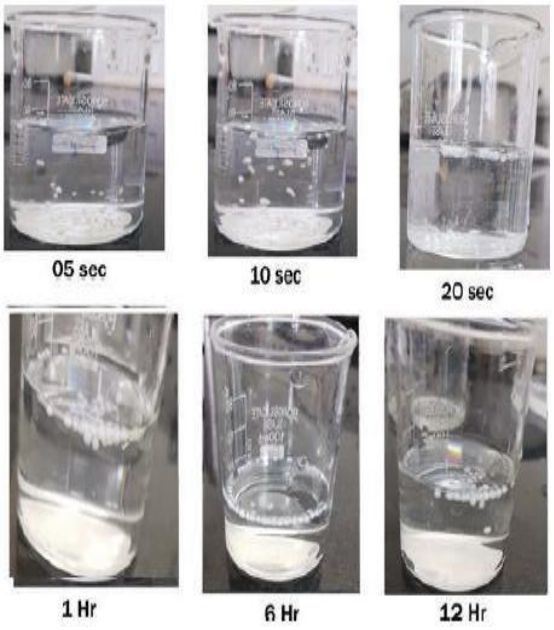

Figure 4: *In-vitro* buoyancy of Acetohydroxamic Acid floating microballoons in 0.1N HCl

Release Kinetics of Floating Microballoons

Table 7: Release kinetic parameters of Acetohydroxamic acid Microballoons

Formulation	Release Kinetics Parameters				
	Zero Order	First Order	Higuchi Model	Korse-Meyer Peppas	Hixson-Crowell
AHF1	0.791	0.994	0.92	0.909	0.983
AHF2	0.902	0.996	0.981	0.979	0.994
AHF3	0.935	0.995	0.991	0.987	0.992
AHF4	0.895	0.997	0.978	0.977	0.994
AHF5	0.999	0.98	0.964	0.999	0.989
AHF6	0.993	0.996	0.927	0.995	0.997
AHF7	0.944	0.993	0.991	0.989	0.992
AHF8	0.938	0.993	0.991	0.987	0.99
AHF9	0.999	0.981	0.967	0.999	0.99
AHF10	0.998	0.98	0.968	0.998	0.989
AHF11	0.994	0.986	0.964	0.993	0.99
AHF12	0.996	0.987	0.958	0.995	0.991
AHF13	0.997	0.998	0.949	0.998	0.991
AHF14	0.994	0.986	0.965	0.993	0.99
AHF15	0.902	0.996	0.981	0.979	0.994

Stability studies:

Table 8: Stability data Acetohydroxamic acid optimized Microballoons formulation (AHF5)

Optimize Formulation AHF5	Bulk Density	Tapped Density	Compressibility Index	Angle	Mean Particle Size(µm)	% Buoyancy	Drug Content
1st Month	0.74±0.12	0.61±0.04	14.31±1.32	15.2± 2.4	128.25±3.46	85.5±0.12	100.3±0.2
2nd Month	0.72±0.11	0.59±0.01	14.25±1.29	15.01±2.2	128.19±3.41	85.1±0.18	100.1±0.82
3rd Month	0.72±0.04	0.55±0.02	14.27±1.09	15.07±1.9	128.79±3.39	85.13±1.2	100.1±0.23

Table 9: Percentage drug release of Acetohydroxamic acid optimized Microballoons formulation (AHF5) during stability studies.

AHF5	1st Month	2nd Month	3rd Month
0	0	0	0
0.5	4.3±5.1	4.1±4.1	3.9±4.6
1	8.1±2.1	7.6±1.9	7.2±2.2
2	17.1±5.1	16.5±4.9	16.1±4.7
3	24.5±3.6	24.1±3.1	23.3±2.8
4	33.4±2.8	32.1±2.4	31.5±2.1
6	51.3±6.1	50.9±5.9	49.1±5.5
8	65.1±7.1	64.2±6.9	63.5±6.3
10	81.3±6.7	80.3±6.3	81.2±6.1
12	100.0±2.8	100.0±1.5	100.0±0.8

DISCUSSION

Acetohydroxamic acid exhibited a pH dependent solubility phenomenon in different buffers. Solubility of Acetohydroxamic acid indifferent buffer solutions of pH 1.2, 6.8, 7.4and water was 342.7,669,1128.3and1021.7mg/mL respectively The results showed that the drug was very freely soluble in distilled water. Solubility was found to be comparatively lesser in 0.1N HCl and the solubility was increased with increase in pH.

Drug–excipients compatibility studies

Differential scanning calorimetry was conducted to assess the interaction among drug and different components used in the formulation DSC thermogram of pure drug. Endothermic peak was observed at 78.3°C indicates the drug melting point for pure drug (88-90^{o}C). DSC studies of optimized formulation of Acetohydroxamic acid shows endothermic peak at 77.1^{o}C. As the shift in the endothermic peak was very less it indicates that the drug and polymers used were compatible with one another.

The drug-excipient compatibility study was done by Fourier transform infrared (FT-IR) spectroscopy study. The prominent peaks of Acetohydroxamic acid pure drug were shown at 3400-3000cm-^{1}(dueto–O-H), 1401.645cm^{-1}(due to C=O),1370.83cm^{-1} (due to –C-H) and1124 cm-^{1}(dueto-C-N). These prominent peaks of drug were also observed in the IR spectrum of optimized formulation. Which indicates that the drug was not interacted with the polymers used in the study which confirms the stability of the drug.

Particle size measurement

The particle size was measured using caliberated optical microscope and the average particle size of floating microballoons was found to be in the range of120-180µm.

Percentage yield

The floating microballoons were prepared and percentage yield was calculated for all the Formulations. The percentage yield was in the range of 60-90 % for all the formulations. It was found to be less than 70% yield with ethyl cellulose and for optimized formulation the yield was around 80 %.

Entrapment efficiency

The entrapment efficiency of floating microballoons of Acetohydroxamic Acid was calculated. The entrapment efficiency was in the range of 60-90 % for all the formulations and was found to be 89.6%for optimized formulation. The entrapment efficiency was low with formulations prepared with ethyl cellulose and HPMC K4M. There was no effect of solvent ratio was observed in the percentage entrapment efficiency.

The percentage buoyancy was calculated for all the formulations and it was found that all the formulations were able to float on the dissolution medium (0.1N HCl) over a period of 12h. Even after 12h of agitation of the dissolution medium, the microballoons continued to float without any apparent gelation. The high buoyancy of the microballoons is mainly due to the presence of pores and cavities which were formed during solvent evaporation. The percentage buoyancy was slightly less with formulations prepared with ethylcellulose and HPMC K4M and decreased as the concentration of the polymers increased. This is because of high viscosity of the polymer solution which in turn is the reason for the less formation of pores and cavities in microballoons during solvent evaporation. The percentage buoyancy was in the range of 60- 90 % for all the formulations and was found to be 85.5% for optimized formulation.

Drug content of all the prepared formulations was found to be within the acceptable range of 90.0-110.0%.

Scanning electron microscope was used to study the surface morphology of the microballoons. The surface morphology of optimized formulation (AHF5) was shown in the From the SEM micrographsit is apparent that the acetohydroxamic

acid loaded microballoons were predominately spherical in appearance. The surface was observed to be smooth, dense and less porous, where as the internal core was highly porous and irregular with numerous depressions that are expression of evaporation of water, ethanol and dichloromethane. The less porous outer surface and highly porous internal surface supported controlled release of drug from the microballoons and good buoyancy.

Dissolution studies of all the formulations were carried out using USP basket type dissolution apparatus. The dissolution profiles were compared among different formulations. The cumulative percentage drug release was decreased with increase in the polymer concentration. Based on the results of *in vitro* drug release studies it was found thatAHF5 has shown sustained drug release for 12h with zero order drug release.
Data of the *in vitro* release of optimized formulation (AHF5) was fit into kinetic models to explain the release kinetics of Acetohydroxamic acid from microballoons. The kinetic models used were zero order, first order, Higuchi and Korsmeyer-peppas models. The *in vitro* drug release kinetics based on the regression values reveals that the optimized formulation (AHF5) releases the drug in zero order manners.

The stability studies were conducted only on optimized formulation (AHF5). The stability study was conducted for 3 months and the results were analyzed. No significant change was observed in particle size, flow properties, drug content, percentage buoyancy and percentage drug release of microballoons. Microballoons were found to be stable at storage conditions for three months.

CONCLUSION

Floating microballoons were successfully developed and evaluated for the selected drugs Acetohydroxamic acid, gastric retention. All the optimized formulations showed improved bioavailability compared to the marketed formulations due to controlled floating technology.

Reference

1. Gattani, YS, Kawtikwar PS, Sakarkar DM. Formulation and evaluation of gastroretentive multiparticulate drug delivery system of aceclofenac. Int. J. Chem. Tech. Res. 2009; 1:1-10.
2. Girish Kumar Tripathi, Satyawan Singh, Gopal Nath Evaluation of pH trigger oil entrapped buoyant beads of acetohydroxamic acid for eradication of Helicobacter pylori Int.J. PharmTech Res.2011,3(3)
3. Girish Kumar Tripathi, Satyawan Singh, Kiran Kushoha, Archana Singh. U.V. Spectroscopy technique for analysis to Acetohydroxamic acid for gastric p H sensitive formulation. Scholars Research Library 2014, 6 (1):214-218
4. Gopalakrishnan S, Chenthinlnathan A. Floating Drug Delivery system: a review, Journal of Pharmaceutical Science and Technology 2011; 3(2)
5. Gowramma A, A. Mounika, A. Vinod babu, P. Ratna kala, B. Prathibha, E. Susanna, P. Siva kumara Formulation and Evaluation of Valsartan Microballoons pharma research library Harrigan RM. Drug delivery device for preventing contact of un dissolved drug with the stomach lining. US Patent 405 5178; 25, 1977.
6. Hilton AK, Deasy PB. In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxicillin trihydrate. Int J Pharm 1992; 86: 79-88.
7. Gattani, YS, Kawtikwar PS, Sakarkar DM. Formulation and evaluation of gastroretentive multiparticulate drug delivery system of aceclofenac. Int. J. Chem. Tech. Res. 2009; 1:1-10.
8. Girish Kumar Tripathi, Satyawan Singh,Gopal Nath Evaluation of pH trigger oil entrapped buoyant beads of acetohydroxamic acid for eradication of Helicobacter pylori Int.J. Pharm Tech Res.2011,3(3)
9. Girish Kumar Tripathi, Satyawan Singh, Kiran Kushoha, Archana Singh. U.V. Spectroscopy tchnique for analysis to Acetohydroxamic acid for gastric p H sensitive formulation. Scholars Research Library 2014, 6 (1):214-218
10. Gopala krishnan S, Chenthinlnathan A. Floating Drug Delivery system: a review, Journal of Pharmaceutical Science and Technology 2011; 3(2)
11. Vasoya A, Shah SK, Tyagi CK, Formulation, Development and Evaluation of Chewable Bi-layered Tablets for Treating Gastro Esophageal Reflux Disease Journal of Drug Delivery & Therapeutics. 2020; 10(4-s):92-99.
12. Harrigan RM. Drug delivery device for preventing contact of undissolved drug with the stomach lining. US Patent 405 5178; October 25, 1977.
13. Hilton AK, D easy PB. In vitro and in vivo evaluation of an oral sustained release floating dosage form of amoxicillin trihydrate. Int J Pharm 1992; 86: 79-88.
14. Jiang Q, Zheng J and Yang W: Gastro retentive Drug Delivery System, Preparation Method and Use Thereof. US Patent 2011/0171275
15. Jiang Q. Gastric retention drug delivery system, preparation method and use thereof. European Patent 2329810A1. 2011.
16. Jinal N. Tandel. Development and Validation of RP-HPLC Method for The Simultaneous Determination Of Amiloride Hydrochloride and Furosemide In Pure And Pharmaceutical Dosage Form. Eurasian Journal of Analytical Chemistry. 2017 12(4):385-394.

17. Sharma HK Shah SK*, Kumar N, Choubey N, Tyagi CK, Formulation and Optimization of Expandable Gastro Retentive Floating Matrix Tablet of Mosapridecitrate Using Factorial Design, 2018:12(1):77-96.
18. International Journal of Research in Pharmacy and Chemistry (IJRPC).2011;1(3):362-375.
Joshi VK, Jaimini M. Microballons drug deliverysystem: Areview. AJPRD. 2013;1(1): 7 –16.
19. 17.Joydeep Dutta, G.Ganesh Kumar , Vikas Dash , Savendu Saha Formulation and Evaluation of Gastroretentive Floating Microballoons of Norfloxacin Indo American Journal of Pharmaceutical Research. 2011;1(4):332-342.
20. Kawashima Y, Niwa T, Takenchi H, HinoT, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J. Pharm. Sci. 1992; 81: 135-140.
21. Kikani H. N, "A Thesis on, Floating Drug Delivery System", The North Gujarat University, Patan, 2000-2001; 11-12.
22. Klausner, E. A., Lavy E., Friedman, M., Hoffman, A., (2003) Expandable gastrore tentive dosage forms. J. Control. Release 90, 143–162. 23.
23. Klusner EA, Lavy E, Barta M, Cserepes E, Friedman M, Hoffman A. Novel gastroretentive dosage form:evaluation of gastroretentivity and its effect on levodopa absorption in humans. Pharm Res 2003; 20(9): 1466-73.
24. Klusner E A, Lavy E, Stepensley D, Friedman M, Hoffman A. Novel gasrtroretentive dosage form: evaluation of gastroretentivity and its effect on riboflavin absorption in dogs. Pharm Res 2002; 19:1516-23.
25. Koner P, Saudagar RB, Dharwal J. Gastro-retentive drugs a novel approach towards floating approach towards floating therapy/, 2007.
26. Krogel I, Bodmeier R. Development of a multifunctional matrix drug delivery system surrounded by an impermeable cylinder. J Control release 1999; 61: 43-50.
27. Kumar K, Rai AK. Development and Evaluation of Floating Microspheres of Curcumin. Tropical Journal of Pharmaceutical Research.2012;11 (5):713-719.
28. Kumar R and Philip A. Gastro retentive dosage forms for prolonging gastric residence time. Int J Pharm Med. 2007; 21(2): 157-171.
29. Kumar, P., Singh, S., Mishra, B. 2008. Floating osmotic drug delivery system of ranitidine hydrochloride: development and evaluation-a technicalnote.AAPSPharmSciTech.9,480– 485.
30. Kunchu K, Raje VA et al. Albumin Microspheres: A Unique system as drug delivery carriers Forn on steroidal anti-inflammatory drugs. 2010; 5(2): 12.
31. Mahejabeen Syeda, Shahnaz Shaik Formulation and in-vitro evaluation of gastroretentive microballoons of riboflavin Int. J. of Pharmacy and Analytical ResearchVol-5(3)2016377-387.
32. Mali AD, Bathe RS. An updated review on microballoons for better approach in gastroretnton. Asian J. Res. Pharm. Sci. 2015; 5(3):188-192.
33. Negi M, Shukla VK. Preparation and evaluation of Ofloxacin sustained released gastro retentive floating microspheres. UKJPB. 2014; 2(4): 19-24.
34. Nilkhumhang N, Basit AW. The robustness and flexibility of an emulsion solvent evaporation method to prepare pH-responsive microparticles.Int.J.Pharm.2009;377:135-141.
35. P. S. Rajinikanth and B. Mishra: Preparation and in vitro characterization of gellan based floating beads of acetohydroxamic acid for eradication of H. pylori, Acta Pharm. 57 (2007) 413–427.
36. Patel DM, Patel MJ, Patel CN. Multi Particulate System: A Novel Approach in Gastroretentive Drug Delivery. IJAPR. 2011; 2(4): 96-106.