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Research Article

Formulation and *In Vitro* Evaluation of Acebutolol Hydrochloride Microballoons for Sustained Drug Delivery

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ABSTRACT

A sustained release drug delivery system for acebutolol hydrochloride was designed to increase its residence time in the stomach without establishing contact with the mucosa. This was made possible through the preparation of microballoons by emulsion solvent diffusion-evaporation technique. The prepared microballoons were characterized for physical characteristics such as particle size, particle shape and surface morphology by scanning electron microscopy. Further, percentage yield determination, drug entrapment efficiency, *in vitro* buoyancy test, micromeritic investigations and *in vitro* drug release studies were carried out. The obtained microspheres were free flowing, spherical and displayed a particle size ranging from 52.37 to 67.5µm suitable for oral delivery. The drug entrapped in the hollow microspheres increased with the increase in eudragit RSPO content. Scanning electron microscopy and particle size analysis revealed differences in the formulations in respect to their appearance and size distribution. The Fourier Transform Infrared spectroscopy technique and Differential Scanning Calorimetry were carried out to rule out drug – excipients interactions. From the results obtained, it was concluded that there was no interaction between drug and the excipients. The formulation containing acebutolol: eudragit RSPO (1:3 and 1:4) exhibited higher percentage values for buoyancy time. The drug release was found to follow Higuchi kinetics with non-fickian diffusion mechanism, from all the four batches. These preliminary results indicate that acebutolol hydrochloride loaded microballoons could be effective in sustaining drug release for prolonged periods of time.

INTRODUCTION

Recently in the field of pharmaceutical technology, great efforts are being made towards the re-fabrication of existing drug molecules in a dosage form, capable of overcoming problems related to poor water solubility, poor bioavailability, dosing problem, stability, toxicity etc. This trend of working has led to the development of novel drug delivery systems.

Even today, conventional drug delivery systems are primary pharmaceutical products commonly seen in prescriptions and 'over the counter' marketed products. They provide prompt release of the drug but in order to achieve and as well as to maintain drug concentration within therapeutically acceptable range, it is often necessary to administer the dosage form several times a day.

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Conventional drug therapy results in significant fluctuations of drug concentration in systemic circulation causing either lethal effect or no therapeutic action [1].

Basic goal of drug therapy is to provide therapeutic amount of drug to proper site in body which is to be promptly achieved and then to maintain desired drug concentration. This idealized objective points out to two most important aspects related to drug delivery, namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to specific organ or tissue while temporal delivery refers to controlling rate of drug delivery to that specific organ or tissue [2].

Despite tremendous advancement in drug delivery, oral route remains to be the most preferred route for administration [3]. Oral controlled release dosage forms have been developed over past three decades. These drug

delivery system have a great potential of solving problems associated with conventional multiple dosing system like strict adherence to timely dosing, flip flop plasma concentration, associated side effects due to systemic accumulation of drug. Thus, there are numerous advantages such as improved efficacy, reduced toxicity, improved patient compliance and convenience, reduction in health care cost etc [4].

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug wastage, and improves solubility for drugs that are less soluble at a higher pH. Also it has applications for the local drug delivery to the stomach and proximal small intestine. Gastricretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [5].

Several approaches are being designed and developed for increasing the residence time of dosage form in the GIT such as: high density (sinking) systems that is retained in the bottom of the stomach; low density (floating) systems that cause buoyancy in gastric fluid [6], mucoadhesive systems, unfoldable, extendible, or swellable systems, superporous hydrogel systems [7], magnetic systems [8] etc. The other various floating preparations such as microballoons, granules, foam powders [9], capsules, tablets, *in situ* gelling systems [10] and laminated films are also being investigated. An excellent concept of floating system suffers from the disadvantage in that it is effective only when the fluid level in stomach is sufficiently high, however, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded [11]. Therefore, a synergic drug delivery system combining buoyancy and microballoons may overcome these problems and prove more effective in treating gastric disease.

Floating and microballoon drug delivery systems offer the advantages of increased gastric retention time, more effective absorption and bioavailability of drugs with absorption windows near to the proximal intestine and stomach, leading to low dosing frequencies [12]. Amongst the various floating drug delivery approaches, microballoons or hollow microspheres is an attractive concept in which the dosage form remains buoyant in the stomach, prolonging the drug residence time in the GI tract and thereby able to release the loaded drug in a sustained manner.

Acebutolol hydrochloride (AH) is a cardioselective beta blocker with intrinsic sympathomimetic activity. It is therefore more suitable than non cardioselective beta blockers, particularly if a patient with asthma or chronic obstructive pulmonary disease needs treatment with a beta blocker. The plasma elimination half-life of AH is approximately 3 to 4 h, while that of its metabolite, diacetolol, is 8 to 13 h. The time to attain peak plasma concentration for AH is 2.5 h and for diacetolol, after oral administration of AH, is 3.5 h [13]. The polymer used was Eudragit RSPO which is a co-polymer of methacrylic acid and ethyl acrylate (1:1) having a mean relative molecular mass of about 2, 50,000 [14].

The aim of this study was to design microballoons containing AH with gastroretentive properties, with the purpose of improving oral bioavailability of the drug and also to provide sustained release.

MATERIALS AND METHODS

AH was obtained as a gift sample from Hikal Pharmaceuticals, Bangalore. Eudragit RSPO was gifted to us from Evonik Industries, Mumbai. Polyvinyl alcohol and Tween 20 of Thermofischer Scientific India and Merck Specialities Private Limited, Mumbai, respectively were used. All other reagents used were of analytical grade.

Preparation of Microballoons

AH loaded Eudragit RSPO microballoons were prepared by employing emulsion solvent diffusion-evaporation technique [15]. Weighed amount of AH was mixed with Eudragit RSPO (in ratios of 1:1, 1:2, 1:3 and 1:4) in a solvent mixture of dichloromethane and ethanol (1:1) at room temperature. The resulting drug-polymer solution was poured gradually into 200 mL of water containing 0.75% w/v polyvinyl alcohol and the preparation was stirred at 400 rpm for 3 h at 40^0C. The finely formed microballoons were then filtered, washed with water and dried overnight at room temperature. The composition of the formulations is displayed in Table 1.

Evaluation of Microballoons

Investigation of drug polymer compatibility

Fourier transform Infrared spectroscopy (FTIR) of pure drug AH and mixture of AH with Eudragit RSPO were taken using Shimadzu FTIR 8400 spectrophotometer to determine drug polymer

Table 1: Formulation compositions of AH microballoons

Formulation code	Polymer to drug ratio	Solvent mixture	Concentration of PVA (%w/v)	Stirring speed (rpm)
MB1	1:1	1:1	0.75	400
MB2	2:1	1:1	0.75	400
MB3	3:1	1:1	0.75	400
MB4	4:1	1:1	0.75	400

Solvent mixture (Dichlomethane and Ethanol); PVA: Polyvinyl alcohol

Table.2: Physicochemical Characterization of microballoons

Formulation code	% yield	Entrapment efficiency (%)	Angle of repose (degrees)	Buoyancy (%)
MB1	86.0	80.65	32.5^0	82.0
MB2	82.0	82.04	31.3^0	84.2
MB3	89.0	95.19	31.2^0	86.2
MB4	85.0	97.62	30.8^0	91.8

Table.3: Micromeritic properties of microballoons

Formulation	Particle size (µm)	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's Index
MB1	52.37	0.439±0.008	0.494±0.016	1.125	11.1
MB2	61.62	0.492±0.005	0.539±0.007	1.095	8.71
MB3	63.5	0.532±0.008	0.577±0.014	1.084	7.79
MB4	67.5	0.539±0.004	0.587±0.003	1.089	8.17

Table 4: Model fitting for drug release rates

Formulation	Zero order	First order	Higuchi	Korsmeyer peppas	n value
	R^2	R^2	R^2	R^2	
MB1	0.8368	0.9718	0.9790	0.9562	0.5213
MB2	0.8717	0.9667	0.9877	0.9812	0.5277
MB3	0.8437	0.9356	0.9769	0.9256	0.5133
MB4	0.8723	0.9602	0.9768	0.9780	0.5341

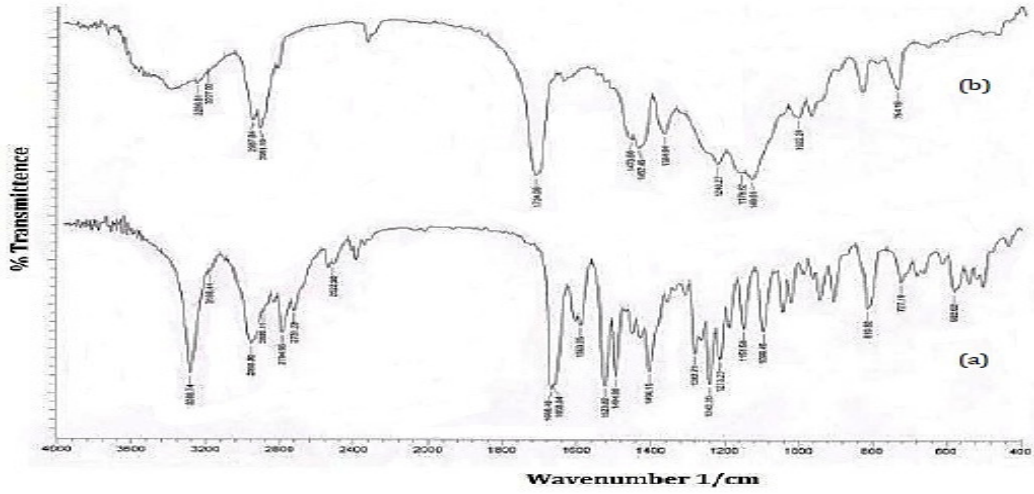

Figure 1: FT-IR spectra of (a) Drug-polymer mixture (b) pure AH

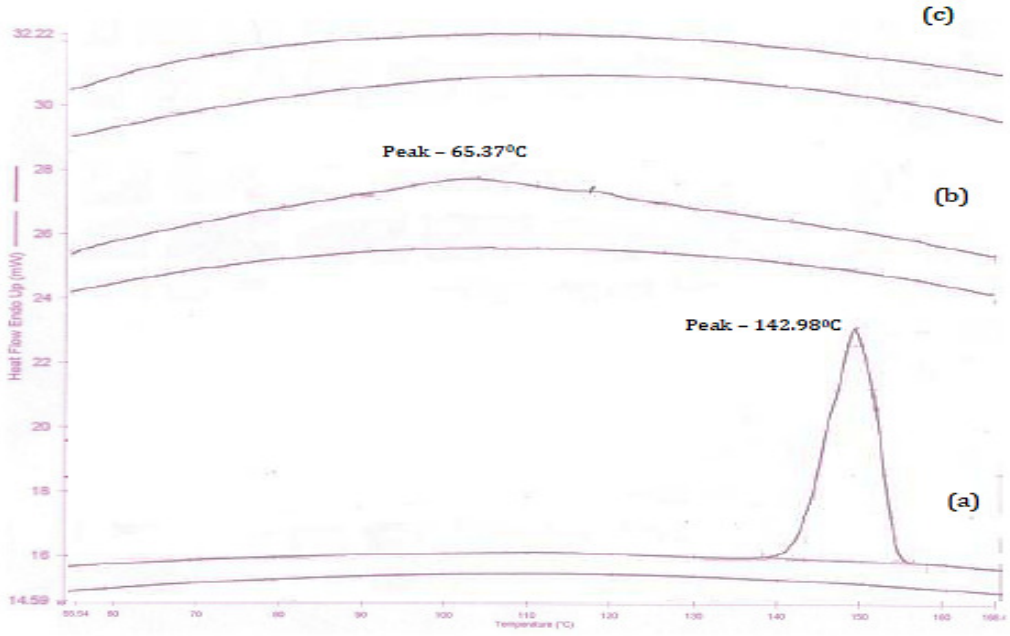

Figure 2: DSC thermogram of (a) AH (b) Eudragit RSPO and (c) formulation MB4

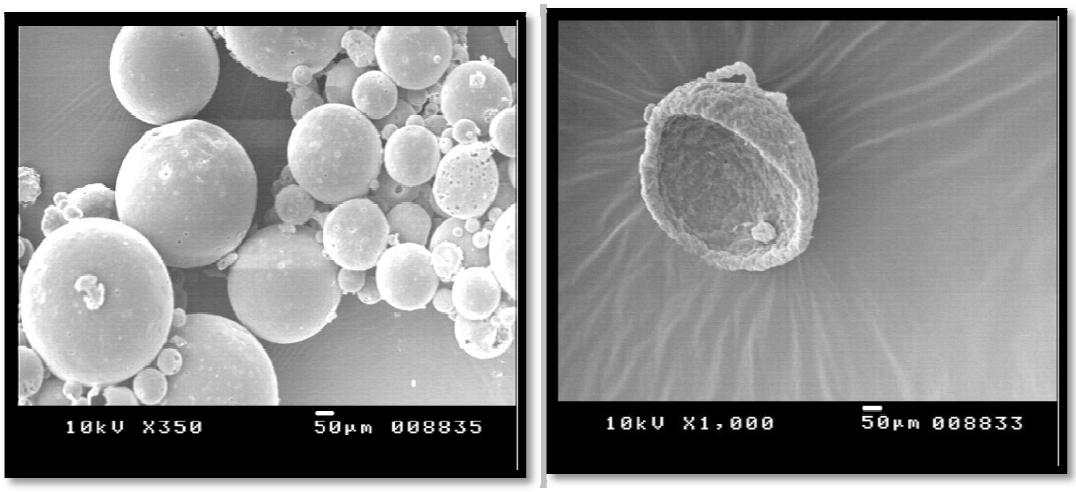

Figure 3: SEM photographs of Microballoons

compatibility. Samples were prepared with potassium bromide and the spectral data was recorded over a spectral range of 400 to 4500 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC (Mettler-7, Germany) was performed to study the thermal behaviour of drug alone and mixture of drug and polymer. Scans of final formulae were done at 50 to 300°C with a heating range of 10°C/min.

Percentage Yield

The prepared microballoons were collected and weighed. The measured weight was divided by the total amount of drug and polymer (plus other ingredients if any) which were used for the preparation of the microballoons [16].

$$\% \text{ Yield} = \frac{\text{Practical mass (Microspheres)}}{\text{Theoretical mass (Polymer + Drug)}} \text{ X } 100$$

Determination of drug entrapment efficiency

10 mg of the microspheres were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 50 mL volumetric flask and the volume was made up using 0.1N HCl. From above stock solution, 1mL was withdrawn and transferred to 10mL volumetric flask and the volume was made up with 0.1N HCl. The absorbance was recorded

using Elico SL-159 UV-Visible spectrophotometer at 233.2 nm [16].

$$\% \text{ Drug entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \text{ X } 100$$

Shape and Surface morphology

The shape and surface characteristics of the microspheres were evaluated by means of scanning electron microscopy (JEOL – JSM - 840A, Japan). The samples were prepared by gently sprinkling the microspheres on a double adhesive tape, which is stuck to an aluminium stub. The stubs were then coated with gold using a sputter coater (JEOL Fine coat JFC 1100E, ion sputtering device) under high vacuum and high voltage to achieve a film thickness of 30 nm. The samples were then imaged using a 20 KV electron beam [17].

Particle size analysis

Particle size of the floating microspheres was determined by optical microscopy [17]. The eye piece micrometer was calibrated with the help of a stage micrometer. The particle diameters of more than 200 microspheres were measured randomly. The average particle size of the microspheres was determined by using Edmondson's equation.

$$D_{mean} = \frac{\sum nd}{\sum n}$$

Where, n = Number of microspheres checked; d =Mean size range

Micromeritic Studies [18]

Bulk density:

In this method microballoons were transferred to a measuring cylinder and the volume was recorded. This volume is bulk volume and it includes true volume of the powder and the void space amongst the microballoons.

$$D_b = \frac{M}{V_b}$$

Where, M= is the mass of powder. V_b= is the bulk volume of the microballoons

Tapped density:

In this method microballoons were transferred to a measuring cylinder and tapped for 100 times. After tapping volume of microballoons was visually examined. The ratio of mass of microballoons to volume of microballoons after tapping gives tapped density of microballoons.

$$D_t = \frac{M}{V_t}$$

Where, M = is the mass of powder. V_t = is the tapped volume of the powder.

Carr's Compressibility Index:

Carr's index is calculated using following equation**:**

$$\text{Carr}'\text{s index} = \frac{D_t - D_b}{D_t} \text{ x } 100$$

Hausner's ratio:

It is an index of ease for powder flow. It is calculated by the following formula,

$$\text{Hausner}'\text{s ratio} = \frac{D_t}{D_b}$$

Where, D_t is the tapped density, D_b is the bulk density.

Percentage Buoyancy (Floating Behaviour)

Approximately 100 mg of microballoons were spread over the surface of a USP dissolution apparatus (type II) filled with 500 mL 0.1 N HCl (pH 1.2) containing 0.02% Tween 20 as a surfactant [19]. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of hollow microspheres were recovered separately. Then the hollow microspheres were dried and weighed. Buoyancy percentage was calculated using formula given below:

$$\% \text{ Buoyancy} = \frac{\text{Total weight of floating microballoons}}{\text{Initial weight of microballoons}} \text{ X } 100$$

***In vitro* drug release study**

The release rate of AH from the microballoons was determined using USP dissolution testing apparatus I (Basket type). The dissolution test was performed using 500 ml of 0.1 N HCl, containing 0.02% Tween 20 at 37 ± 0.5°C and 100 rpm. Microballoons equivalent to 200 mg AH were used for the test. Aliquots (5mL) were withdrawn at hourly intervals for 12 h. Samples were replaced by its equivalent volume of dissolution medium. The samples were analyzed at 233. 2 nm using Elico Sl-159 UV-Visible spectrophotometer [16].

***In vitro* drug release kinetics**

In order to investigate the drug release mechanism and release rate kinetics [20] from the dosage form, the data obtained was analysed with software (PCP - Disso V2.08) equipped with zero order, first order, Higuchi matrix, Hixon Crowell and Korsmeyer –Peppas model kinetics. By analyzing the R values, the best fit model was arrived at.

RESULTS AND DISCUSSION

The FT-IR spectra of the drug – polymer mixture and pure AH are portrayed in Fig.1. The IR spectra of drug-polymer mixture exhibited distinctive peaks at 3286.8 cm^{-1} due to OH stretch, 3227.0 cm^{-1} due to NH stretch. The FT-IR spectra of AH displayed characteristic peak at 3670 – 3580 cm^{-1} due to OH stretching and at 3389.0 cm^{-1} due to – to NH stretch. From the above characteristic peaks, it can be noted that there is no significant change in the wavenumbers indicating the absence of incompatibility between the drug and the excipients.

DSC study of AH, Eudragit RSPO and drug-loaded microballoons were carried out to study the stability of the drug during the formulation storage and Any abrupt or drastic change in the thermal behaviour of either the drug or polymers is tracked in the DSC thermograms which are portrayed in Fig. 2. DSC curve of AH showed a sharp endothermic peak at 142.98^{o}C, corresponding to its melting point. The polymer revealed an endothermic peak at 65.37^{o}C indicating melting temperature of the polymer, whereas drug-loaded microballoons did not show any characteristic peak at 142.98^{o}C suggesting that AH existed as a molecular dispersion in the polymer matrix.

As the drug to polymer ratio was increased, the yield of the product also increased. The low percentage yield in some formulations may be due to microballoons lost during the washing process. The percentage yield was found to be in the range of 82 - 89%. The % Drug entrapment efficiency of AH ranged from 80.65% to 97.62%. The drug entrapment efficiency of the prepared microspheres increased progressively with increase in proportion of the polymer. Increase in the polymer concentration increases the viscosity of the dispersed phase. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The percentage yield and % drug entrapment efficiency are displayed in Table 2.

Morphology of the microspheres was investigated by Scanning electron microscopy. The photographs of the optimized formulations taken by scanning electron microscope are shown in the Fig.3. Surface topography of the spherical microballoons revealed a porous texture, thereby suggesting the possible drug release mechanism to occur by diffusion.

The mean particle size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased emulsion droplet size and finally a higher microballoon size. AH microballoons had a mean particle size in the range of 52.37µm to 67.5µm. The microballoons revealed angle of repose values in the range of 30.8^{0} to 32.5^{0} with Carr's index value ranging from 7.79 to 11.13 indicating good flow properties. Further, the microballoons revealed Hausner's ratio values in the range of 1.084 to 1.125 indicating good flow characteristics and not necessitating the incorporation of a glidant. The Micromeritic properties of the microballoons are enlisted in Table 2 and Table 3.

The *In vitro* release of AH from the prepared microballoons exhibited a biphasic mechanism. The release of AH from the microballoons was characterized by an initial phase of burst effect (higher release), which was due to the presence of drug particles on the surface of the microballoons followed by a second phase of moderate release. The initial burst effect may be attributed as a desired effect to ensure initial therapeutic plasma concentration of the drug. The biphasic pattern of release is a characteristic feature of matrix diffusion kinetics. The initial burst effect was considerably reduced with increase in polymer concentration. The fact that increase in the polymer concentration resulted in better incorporation efficiency could be the reason for the observed decrease in burst effect, since the amount of surface associated drug decreases with an increase in entrapment efficiency.

As the polymer to drug ratio was increased, the extent of drug release decreased. A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The release of the drug has been controlled by swelling control release mechanism. Additionally, the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release. With the increase in polymer to drug ratio, the formulations MB1, MB2, MB3 and MB4 exhibited a % cumulative drug release of 47.29 respectively at the end of 12 h. The drug release profiles are displayed in Fig.4.

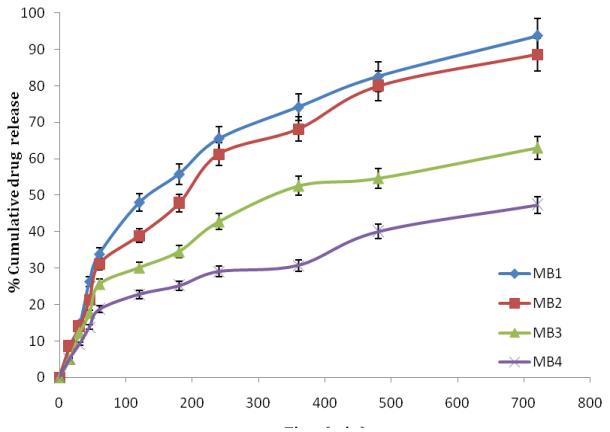

Figure 4: Comparison of *in vitro* drug dissolution profile for MB1, MB2, MB3, and MB4.

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the obtained *in vitro* drug release data were fitted to various mathematical models such as zero order, First order, Higuchi matrix, Korsmeyer-Peppas model and Hixson-Crowell model using software (PCP-Disso-V2.08). The resultant kinetic values are compiled in Table 4. Higuchi plot for different microballoon formulations is projected in Figure 5. The n values have been found to be in the range of 0.5133 – 0.5341, which is indicative of non-Fickian diffusion mechanism. The obtained R^2 values are closer in case of Higuchi model. Therefore the drug release occurs by matrix diffusion controlled mechanism. Higuchi plot for the drug release from different microballoon formulations is presented in Fig.5.

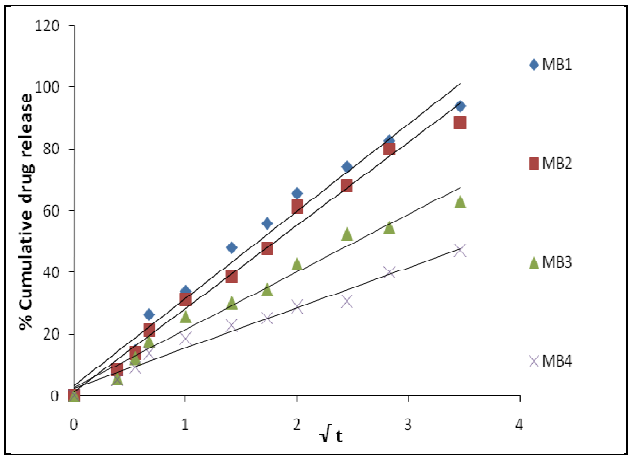

Figure 5: Higuchi Plot

CONCLUSION

In this investigation, we were able to successfully formulate gastroretentive hollow microballoons of AH. The procedure was simple, reproducible yielding hollow microballoons with a porous surface texture. The drug release from the formulation occurred by non-Fickian Higuchi matrix diffusion controlled mechanism sustaining the drug release for a period of upto 12 h. Based on the results of evaluation tests it could be concluded that MB3 and MB4 were the best formulations for oral sustained delivery of AH. The microballoons filled in a capsule need to be administered with a glass of water to provide suitable floatation. Thus the objective of designing a floating drug delivery system of AH has been achieved with success.

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