FORMULATION AND IN VITRO EVALUATION OF ACEBUTOLOL HYDROCHLORIDE MICRO BALLOONS FOR SUSTAINED DRUG DELIVERY

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***ABSTRACT:** Acebutolol HCl is a cardio selective Beta Blocker, widely used in the management of hypertension. The micro particles can be prepared by using any one of the several techniques but choice of the technique mainly depends on the nature of the polymer used, the drug and the duration of the therapy. a sustained release Acebutolol HCl microspheres prepared by Emulsion-solvent diffusion technique which the different concentration ranges of Acebutolol HCl and Eudragit RLPO and Sodium alginate polymer was taken. there was no interaction between drug and the excipients. The microspheres were evaluated with respect to the yield, particle size, Drug entrapment efficiency, in vitro drug release and stability. Microspheres were characterized by FTIR studies. It was found that the particle size and Drug entrapment efficiency of microspheres increases with increasing drug-to-polymer ratio. The drug release was found to follow Higuchi kinetics with non-fickian diffusion mechanism, from all the batches and F3 formulation is the optimised formulation.*

***Key words:** Acebutolol HCl, polymers, Drug entrapment efficiency, in vitro drug release and stability*

I. INTRODUCTION

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. Gastric retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[1] Microballons are gastro-retentive drug delivery systems based on non-effervescent approach. These microspheres are characteristically free flowing powders having a size less than 200 μm and remain buoyant over gastric contents and for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.[2] 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. The aim of this study was to design microballoons containing Acebutalol hydrochloride with gastroretentive properties, with the purpose of improving oral bioavailability of the drug and also to provide sustained release.[3]

II. MATERIALS AND METHODS

2.1. Materials

Acebutolol HCl was obtained from Arudavis labs private limited (Tamilnadu, India).Eudragit RLPO, Sodium alginate, Dicloromethane and PVA were procured from Vijaya chemicals, Hyderabad and other chemicals and reagents used were of analytical grade.

2.2 Methods

Drug excipient compatibility studies[4]

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in high density polyethylene bags and low density poly ethylene bags.Glass vials were exposed to 60^0C and 40^0C/75 % relative humidity for 4 weeks and low density polyethylene bags were exposed to 40^0C±75 % relative humidity for 4 weeks. Samples were observed periodically for any physical change.

Preparation and evaluation of Acebutolol Hydrochloride Microballoons[5,6]

Formulation table:

Table-1: Formulation development of Acebutolol Hydrochloride Microballoons

F. no	Polymer	Drug and polymer ratio	Stirring speed
F1	Eudragit RLPO	1:1	1000
F2	Eudragit RLPO	1:2	1000
F3	Eudragit RLPO	1:3	1000
F4	Eudragit RLPO	1:4	1000
F5	Sodium alginate	1:1	1000
F6	Sodium alginate	1:2	1000
F7	Sodium alginate	1:3	1000
F8	Sodium alginate	1:4	1000

(Acebutolol Hydrochloride Drug taken is 100mg)

Method:

Emulsion-solvent diffusion technique with some modifications was used to prepare Eudragit RLPO, and sodium alginate Microballoonscontaining Acebutolol Hydrochloride. Briefly Acebutolol Hydrochloride was dissolved in 5 ml distilled water. Polymers was dissolved in Dichloromethane at various drug - polymer ratios (1:1, 1:2 and 1:3). Then these drug and polymer solutions were mixed and emulsified using a Remi Lab Magnetic stirrer at 500 rpm for about 10 min to form stable w/o emulsion. This stable w/o emulsion was slowly added to 200 ml aqueous solution containing 1 % PVA and stirred at 1000 rpm by a mechanical stirrer equipped with a three bladed propeller (Remi motors, India) at room temperature for 2 h to allow the solvent to evaporate completely. Microballoons were isolated by filtration and washed with distilled water several time to remove PVA. The produced Microballoons were dried at ambient temperature for 24 h and dried in vacuum chamber at 25 ^{0}C for 2 h to remove any residual solvent.

Evaluation of ofMicroballoons

Particle size analysis:[7]

Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of Microballoons were measured by using a set of standard sieves ranging from 14, 16, 18, 22, 30 and pan. The sieves were arranged in increasingorder from top to bottom. The Microballoons were passed through the set of sieves and amount retained on each sieve was weighed and calculate the % weight of Microballoons retained by each sieve. Mean particle size for all formulation was determined by dividing the total weight size of formulation to % total weight of Microballoons.

Floating Property of microsphere:[8]

100 mg of the microsphere were placed in 0.1 N HCI (300 ml) containing 0.02% Tween 20. The mixture was stirred with paddle at 100rpm. The layer of buoyant microballoons was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microballoons were dried in a desiccator over night.

The percentage of microballoons was calculated by the following equation :

$$\% \text{ microsphere} = \frac{\text{Weight of microsphere}}{\text{Initial weight of microsphere}} \times 100$$

Drug Entrapment efficiency:[9]

The various formulations of the Microballoons were subjected for drug content. 50 mg of Microballoons from all batches were accurately weighed and crushed. The powdered of Microballoons were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. Again from this solution 2 ml was taken out and diluted up to 10 m1 with 0.1 N HCI and the absorbance was measured against 0.1 N HCI as a blank.

The percentage drug entrapment was calculated as follows.

$$\text{\% Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Percentage Yield:[10]

The percentage yield of different formulations was determined by weighing the Microballoons after drying. The percentage yield was calculated as follows.

$$\% \text{ Yield} = \frac{\text{Total weight of Microballoons}}{\text{Total weight of drug and polymer}} \times 100$$

Shape and Surface Characterization by Scanning Electron Microscopy:[11]

From the formulated batches of Microballoons, formulation which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using scanning electron microscope Hitachi, Japan. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 20KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

In vitro drug release study[12]

In vitro drug release studies were carried out for all formulations in Franz diffusion cell. Microballoons equivalent to 10 mg of Acebutolol Hydrochloride were poured into 1 ml aliquots were withdrawn at a predetermined intervals and equal volume of dissolution medium was replaced to maintain sink conditions. The necessary dilutions were made with 1.2 pH buffer and the solution was analysed for the drug content spectrophotometrically using UV-Visible spectrophotometer.

Drug release kinetics[13]

In order to describe the Drug release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models:

Zero order, first order, and Higuchi respectively.

$$Qt = Q0 + K0\ t \text{……..}$$

where, Qt is the amount of drug released at time t; Q0 the amount of drug in the solution at t = 0, (usually, Q0 = 0) and K0 the zero order release constant.

$$\log Qt = \log Q\alpha + (K1 / 2.303)\ t \text{……..}$$

Qα being the total amount of drug in the matrix and K1 the first order kinetic constant.

$$Qt = KH.\ t\ ½ \text{…….}$$

where,

KH is the Higuchi rate constant.

Further, to better characterise the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Korsmeyer and Peppas.

$$Q\ (t-l)\ /Q\alpha = KK\ (t-l)n \text{…….}$$

where, Qt corresponds to the amount of drug released in time t, *l* is the lag time (*l* = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where $Q\ (t-l)/Q\alpha > 0.6$, were only used. If n approaches to 0.5, the release mechanism can be Fickian. If n approaches to 1, the release mechanism can be zero order and on the other hand if $0.5 < n < 1$, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ‘‘best model’’ was the one with the highest coefficient of determination (r^2).

Stability Study:[14]

From the prepared Microballoons which showed appropriate balance between the buoyancy and the percentage release was selected for stability studies. The prepared formulation were placed in borosilicate screw capped glass containers and stored at room temperature (27 ± 2° C), oven temperature (42±2° C) and in refrigerator (5-8° C) for a period of 90 days.

III. RESULTS & DISCUSSION

FT-IR Spectrum of Acebutolol Hydrochloride

FT-IR Spectra of Acebutolol Hydrochloride and F3 formulation were recorded. All these peaks have appearedin formulation and physical mixture, indicating nochemical interaction between Acebutolol Hydrochlorideand polymer. It also confirmed that the stability of drug during microencapsulation process.

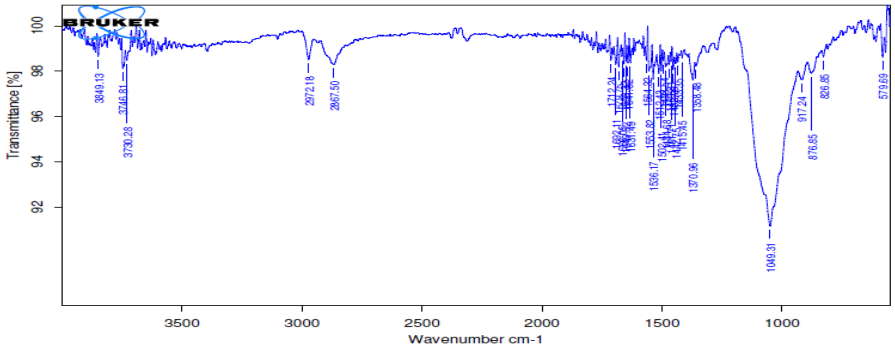

Fig. 1. FTIR Studies of Acebutolol Hydrochloride

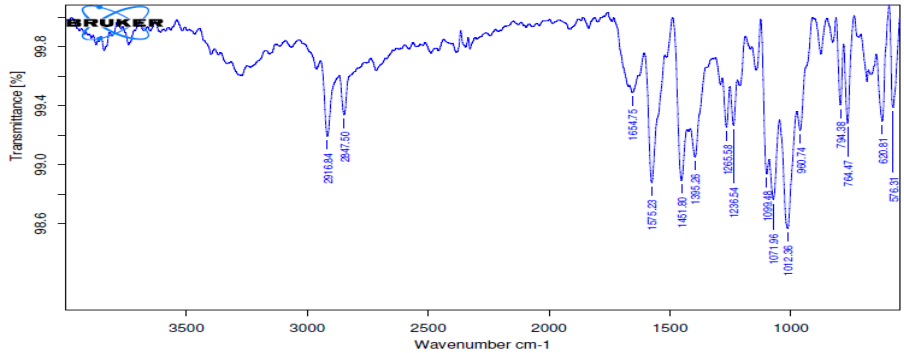

Fig. 2. FTIR Studies of optimized formulation

Results of the evaluation parameters of formulated sustained release Microballoons

The prepared sustained release Microballoons were evaluated for various parameters such as yield, drug entrapment efficiency, particle size, and in vitro drug release. And effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on particle size, yield, entrapment efficiency, and *in-vitro* release of Acebutolol Hydrochloride from sustained Microballoons were also studied.

Table-2: Effect of drug polymer ratio on Yield of Microballoons, Particle size, Drug entrapment efficiency

Formulation code	%yield	Particle size	Drug Entrapment efficiency
F1	82.96	223.7	70.69
F2	79.34	198.2	75.86
F3	85.45	202.38	83.55
F4	78.63	197.93	80.12
F5	84.92	202.14	78.53
F6	80.51	218.49	77.12
F7	79.93	214.36	81.23
F8	75.82	223.15	77.25

Characterization of Microballoons

A. Surface topography by scanning electron microscopy (SEM)

Figure 4.13 A shows SEM photograph of optimized Microballoons at 100× magnification, at 1000× magnification. SEM photographs showed discrete, spherical Microballoons. SEM photographs also showed the presence of drug crystal on the surface of Microballoons revealing that the Microballoons were having some rough surface**.** The drug crystals on Microballoons were may be due to the presence of un entrapped drug in dispersion medium.

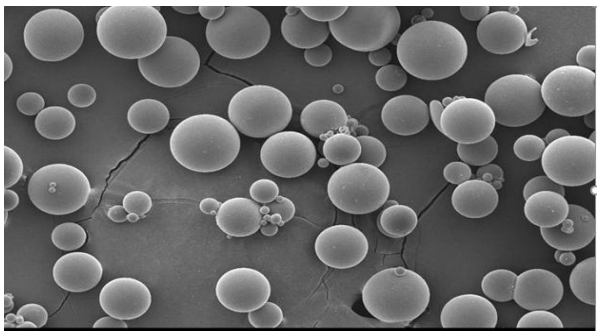

Fig.3. SEM photograph of Microballoons at 100x and 1000x magnification.

Drug release studies

Table-3: Drug release studies all formulations

TIME (hours)	F1	F 2	F3	F4	F5	F6	F7	F8
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	8.93	9.36	12.39	10.32	13.12	12.34	11.35	9.16
2	20.46	21.21	22.35	22.84	22.36	24.32	23.13	23.14
3	31.25	32.25	32.7	30.28	33.29	32.14	32.34	33.28
4	42.36	41.48	40.3	41.29	42.50	42.85	42.35	43.11
5	50.12	50.15	53.3	52.16	53.91	52.14	53.16	53.49
6	63.31	62.69	67.6	64.92	65.63	63.46	62.19	62.14
7	71.24	72.32	76	73.98	73.41	73.12	73.46	72.13
8	88.96	87.90	95.6	92.36	92.16	90.11	89.12	93.27

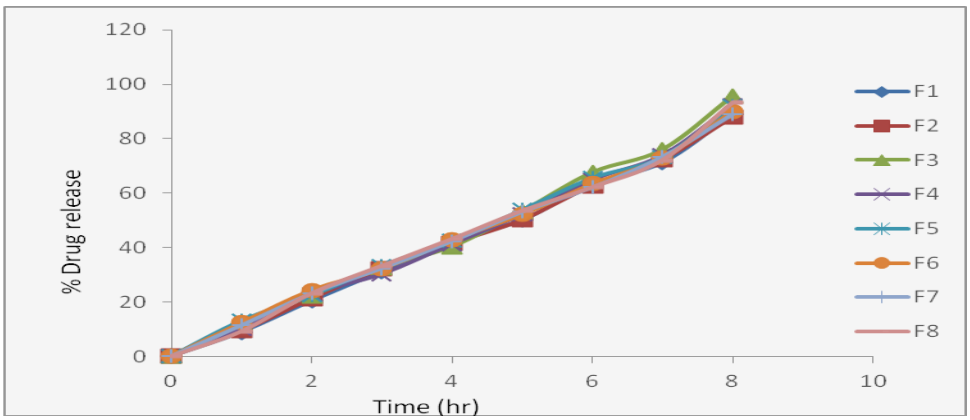

Fig.4. In vitro drug release studies of all formulation

Release kinetics

The mechanism of Acebutolol Hydrochloride release from Microballoons was studied by fitting the data obtained from *in-vitro* release studies into zero-order, first-order, Higuchi's, korsermeyerpeppas kinetic models. On application of different release kinetic models mentioned earlier, it was found that optimized formulations showed better fitting with the zero-order release and korsermeyerpeppas model.

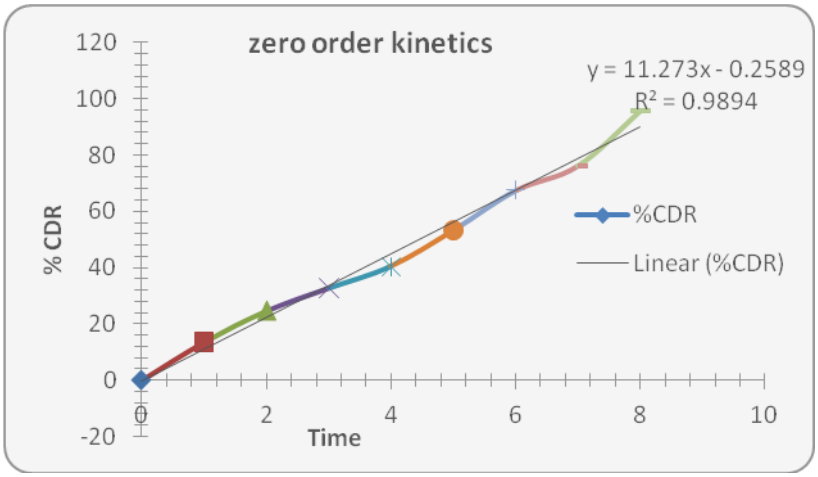

Fig.5. Drug release kinetics of zero order kinetics

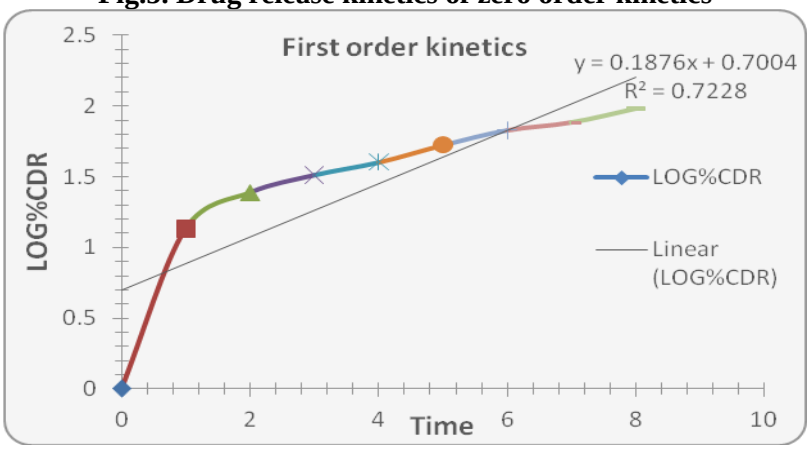

Fig.6. Drug release kinetics of First order kinetics

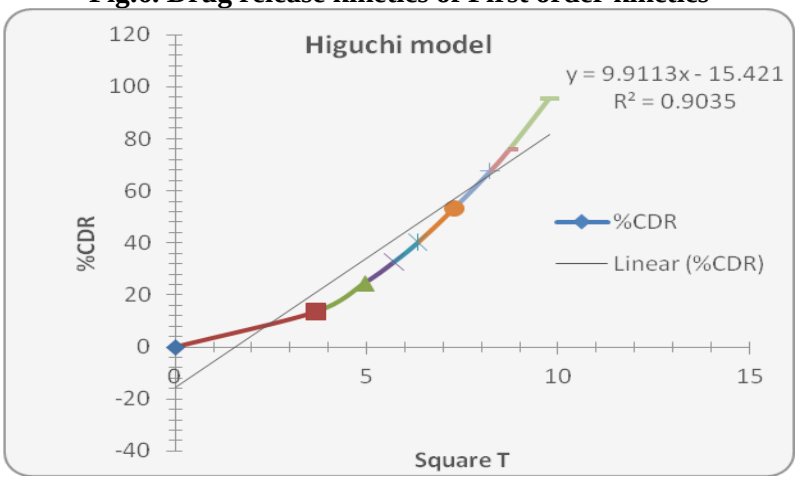

Fig.7. Drug release kinetics of Higuchi model

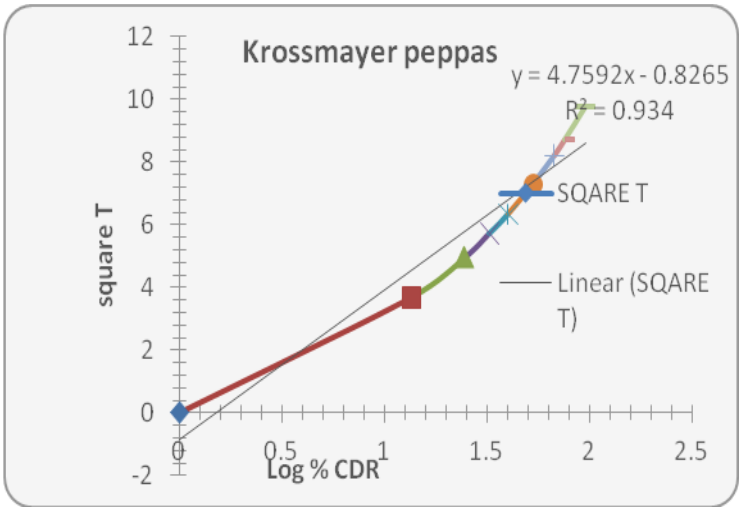

Fig.8. Drug release kinetics of Krossmayerpeppas

Stability studies

There was no significant change in physical and chemical properties of the Microballoonsoptimized formulation after 90 days. Parameters quantified at various time intervals were shown;

Table-4: Results of stability studies of optimized formulation

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	**25^0C/60%RH % Release**	95.63	95.10	94.29	93.12	**Not less than 85 %**
F-3	**30^0C/75% RH % Release**	95.63	95.06	94.38	93.11	**Not less than 85 %**
F-3	**40^0C/75% RH % Release**	95.63	95.01	94.12	93.08	**Not less than 85 %**

IV. CONCLUSION

Acebutolol HCl is a cardio selective Beta Blocker, widely used in the management of hypertension. The micro particles can be prepared by using any one of the several techniques but choice of the technique mainly depends on the nature of the polymer used, the drug and the duration of the therapy. In the present paper, a sustained release Acebutolol HCl microspheres prepared by Emulsion-solvent diffusion technique in which the different concentration ranges of polymers. All formulated 8 microspheres with different percentage of loading and magnetite content showed good entrapment (above 81%) and encapsulation efficiency (above 75%). The average particle size of magnetic microspheres meant for intravenous administration was 2.4 µm. The particle sizes of microspheres were well within the injectable range through desired routes with 20–27-gauge needle. The optical microscopy and SEM analysis revealed the spherical geometry of the microspheres. The SEM photographs showed the presence of magnetite particles on the surface of magnetic microspheres. The microspheres were compact, discrete and free flowing in nature. The FT-IR spectrum of microspheres loaded with drug showed many characteristics peaks of Acebutolol HCl and revealed the absence of drug carrier interaction. The SEM photographs of microsphere surfaces, which showed no crystalline drug particles, further supported the amorphous nature of Acebutolol HCl present in the microspheres. In conclusion, the microballons loaded with Acebutolol HCl showed promising results in reducing hypertension without drug induced toxicity.

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