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Research Article

Formulation Development and *In Vitro* Characterization of Gastroretentive Floating Microballoons Bearing Labetalol Hydrochloride

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ABSTRACT

The objective of present study was to develop Gastroretentive floating microballoons of Labetalol Hydrochloride in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. Gastroretentive Floating microballoons of Labetalol hydrochloride were prepared by emulsion solvent diffusion method using Ethyl Cellulose and Eudragit RS100 in varying compositions and ratios. The percentage yield, particle size, Scanning Electron Microscopy (SEM),*in vitro* buoyancy, drug entrapment efficiency, *in vitro* drug release, release kinetics and Stability studies were studied. The optimized formulation was filled in capsules and post formulation parameters of capsules were performed. Percentage yield of all formulations was in the range of48.33-86.25 %. The particle size of all formulations was distributed between 55.4µm - 219.33µm.Drug entrapment efficiency was in the range of80.5 to 97.2%, and *in vitro* buoyancy percentage was in the range of 76 - 94%. The best drug release profiles were seen with formulation F3 and F8 at the end of 12hrs.Scanning electron microscopy confirmed their spherical and circular shape with smooth surface. The release kinetics of the optimised formulation showed zero order kinetics. Stability studies indicated that the formulation is stable as per ICH guidelines. The data obtained in this study suggest that Gastroretentive floating microballoons of Labetalol Hydrochloride are promising for controlled drug delivery. It also shows that as increase in drug: polymer ratio affects the particle size, *in vitro* buoyancy and drug release.

INTRODUCTION

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time by using gastro-retentive dosage forms (GRDFs). It remains in the gastric region for several hours and hence prolongs the gastric residence time of drug. It has several advantages over immediate release dosage form including the minimization of fluctuations in drug concentration in plasma and at the site of action over prolonged period of time, resulting in optimized therapeutic efficiency and reduce the side effect, reduction of total dose administered and reduction of administration frequency leading to improved patient compliances.

Microballoons are gastro retentive drug-delivery systems with non-effervescent approach.

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Microballoons (Hollow microspheres) are in strict sense, empty particles of spherical shape without core. These microspheres are characteristically free flowing powders comprising of proteins or synthetic polymers, ideally having a size less than 200 micrometre [1].

Labetalol hydrochloride is an anti-hypertensive drug, belongs to the class of alpha and beta blocking agents which is used to treat high blood pressure. It is slightly soluble in water and is well absorbed from the GIT. Labetalol hydrochloride is rapidly absorbed following an oral dose but undergoes extensive first pass metabolism, resulting in only 25% oral bioavailability. The drug is eliminated rapidly, so repeated daily administration is required to maintain the effective plasma levels. The half-life of Labetalol hydrochloride is approximately 4-6 hours [2]. Thus, an attempt has been made to develop Gastroretentive Microballoons of Labetalol hydrochloride for controlled release of drug and thereby improving the bioavailability.

MATERIALS AND METHODS

Materials

Labetalol hydrochloride was supplied as a gift sample from Gland Pharma, Hyderabad. Ethyl cellulose obtained from Sai Mirra Innopharm Pvt Ltd., Chennai. Eudragit RS100 was purchased from Evonik India Pvt, Ltd. Mumbai. Polyvinyl Alcohol as a gift sample from Signet Chemicals Pvt Ltd., Mumbai. All the reagents used were of analytical grade.

Methods

Preparation of Calibration Curve using 0.1N HCl

Accurately weighed 100 mg of Labetalol Hydrochloride is dissolved in 100 ml of 0.1 N HCl which gives 100µg/ml standard stock solution. From standard stock solution of 100µg/ml, 20ml is taken into a volumetric flasks and volume is made up to 100 ml with 0.1 N HCl so as to get drug concentration of 200µg/ml. From this, 10, 20, 30, 40, 50 ml is taken into different volumetric flasks and volume is made up to 100 ml with 0.1 N HCl so as to get drug concentrations of 20, 40, 60, 80 and 100µg/ml. The absorbencies of these drug solutions are estimated at λ_{max} 302 nm [3-5].

Formulation of Gastroretentive Labetalol Hydrochloride Microballoons:

Labetalol Hydrochloride floating microballoons were prepared by Emulsion solvent diffusion method using polymers like Eudragit RS 100 and Ethyl cellulose at varying drug to polymer compositions ratios and Polyvinyl Alcohol as Stabilizing agent as shown in table 1. Labetalol Hydrochloride, Eudragit RS100 and/or Ethyl Cellulose were dissolved in a mixture of ethanol and dichloromethane. The resulting solution was added slowly to 100 ml of aqueous solution of 0.50% (w/v) PVA at 40°C temperature kept under magnetic stirring. The stirring was done for 2 hours at 1000-1200 rpm by mechanical stirrer, to evaporate the volatile solvent. After evaporation of solvent, microballoons were collected by filtration, washed with water and dried at room temperature in a desiccator for 24 hours [6].

In Vitro Characterization

Particle Size Analysis

The particle size, of the Microballoons is evaluated using an optical microscope fitted with a calibrated eyepiece micrometer. It randomly measures the particle diameters of about 300 Microballoons and the average particle size was determined using the Edmondson's equation:

$$d_{mean} = \Sigma nd / \Sigma n$$

Where,

"n" stands for the number of counted Microballoons, "d" for the mean size range.

Surface Morphology Analysis

Scanning electron microscope (SEM) is used to study the shape and surface morphology of the Microballoons.

Percentage Yield

The percentage yield was determined for all the formulations based on the dry weight of the drug and the polymers taken. The percentage yield can be calculated using the following equation:

$$\text{Percentage yield} = \frac{\text{Total weight of floating microspheres}}{\text{Total weight of drug and polymers taken}} X\ 100$$

Percentage Drug Entrapment Efficiency:

Hundred milligrams of microballoons are dissolved in 10ml ethanol. The samples were then assayed using UV spectrophotometer at 302nm after suitable dilution using 0.1N HCl for drug content. Percentage drug entrapment efficiency is then calculated using the following equation:

$$\text{Percentage drug entrapment efficiency} = \frac{Calculated\ drug\ concentration}{Theoretical\ drug\ concentration}\ x100$$

In vitro Buoyancy

Floating behavior of Labetalol Hydrochloride microballoons is studied using USP dissolution test apparatus II. The microballoons (100 mg) re spread on 900ml of 0.1 mol/l HCl containing the surfactant Tween-80 at a concentration of 0.02%. The medium is agitated at 100 rpm with a paddle, and the temperature is maintained at 37°C. After 12 h, both the settled and floating portions of microballoons are collected separately. Then the microballoons are dried and weighed. The percentage of microballoons is calculated using the following equation:

$$\text{Percentage buoyancy} = \frac{\text{Weight of Microballoons}}{\text{Initial weight of Microballoons}} X100$$

In Vitro Drug Release Study

Labetalol Hydrochloride floating microballoons are evaluated for the *in vitro* drug release studies in simulated gastric fluid. USP dissolution test apparatus II (Paddle type) is used to find out the drug release rate from microballoons.

Table 1: Composition of Labetalol Hydrochloride Microballoons

F. CODE	Labetalol Hydrochloride (mg)	Ethyl Cellulose (mg)	Eudragit RS100 (mg)	Polyvinyl Alcohol (0.5%w/v)	Ethanol: Dichloromethane (1:1)(ml)
F1	100	100	--	100	10:10
F2	100	200	--	100	10:10
F3	100	300	--	100	10:10
F4	100	--	100	100	10:10
F5	100	--	200	100	10:10
F6	100	--	300	100	10:10
F7	100	100	100	100	10:10
F8	100	200	100	100	10:10
F9	100	100	200	100	10:10

The dissolution test was performed using 900 ml of 0.1N HCl, at 37°C ±0.5°C and 100 rpm. Microballoons equivalent to 100 mg Labetalol Hydrochloride were accurately weighed and filled in a hard gelatin Capsule and added to the dissolution medium, aliquots (10 ml) are withdrawn at hourly intervals for a period of 12 h. Perfect sink condition is established during the drug dissolution study period by replacing an equivalent volume of dissolution medium. The samples are filtered, and solutions are analyzed at 302 nm using a UV Spectrophotometer [7].

Preformulation Study of Optimized Microballoons

Flow Property Measurements

The flow properties are critical for an efficient tableting and capsule filling operation. A good flow of the powder or granules is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets and capsules. The flow property measurements include bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. The flow property measurements of Labetalol Hydrochloride microballoons are determined [8].

Bulk Density (ρb)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$$\rho b = M/V_b$$

Where, M and V_b are mass of powder and bulk volume of the powder respectively.

Tapped Density (ρ_t)

It is the ratio of weight of the powder to the tapped volume of powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for 300 times on a wooden surface at 2 sec interval and the volume attained is the tapped volume.

$$\rho_t = m/V_t$$

Angle of Repose (θ)

The flow properties were characterized in terms of angle of repose, Carr's index and Hausner's ratio. For determination of angle of repose, the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The drug or the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$$\theta = \tan^{-1} (h/r)$$

Where, h= height of pile in cm; r = radius of pile in cm.

Carr's Index or % Compressibility

It indicates powder flow properties. It is measured for determining the relative importance of inter particulate interactions. It is expressed in percentage and is given by

$$CI = \frac{\rho t - \rho b}{\rho t}$$

Where, ρ_t and ρb are tapped density and bulk density respectively.

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$HR = \rho_t / \rho_b$$

Where, $\rho_t$and $\rho_b$are tapped density and bulk density respectively.

Optimized Microballoons Filled in Hard Gelatin Capsules

The optimized Labetalol Hydrochloride Microballoons is filled into "0" size hard gelatin capsules and each capsule containing 100 mg equivalent of Labetalol Hydrochloride [9].

Evaluation of Optimized Capsules

Uniformity of Weight

Intact capsules were weighed. The capsules were opened without losing any part of the shell and contents were removed as completely as possible. The shell was washed with ether and the shell allowed to stand until the odour of the solvent was no longer detectable. The empty shell was weighed. The procedure was repeated with further 19 capsules. The average weight was determined. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation and none deviates by more than twice that percentage.

Disintegration Test

One capsule introduced in to each tube of the disintegration test apparatus, a disc was added to each tube. The basket rack assembly is suspended in the beaker containing the liquid medium. The apparatus is operated and the time for disintegration is noted.

Drug Content

Five capsules were selected randomly and the average weight was calculated. The powder is removed completely from capsule. An amount of powder was equivalent to 100 mg made up to 100 ml with acid buffer pH 1.2. It was kept for overnight. 1 ml of solution was diluted to 100 ml using acid buffer pH 1.2 in separate standard flask. The absorbance of solution was recorded at 302 nm.

***In Vitro* Drug Release Studies**

Labetalol Hydrochloride floating Microballoons are evaluated for the *in vitro* drug release studies in simulated gastric fluid. USP dissolution test apparatus II (Paddle type) is used to find out the drug release rate from Microballoons. The dissolution test was performed using 900 ml of 0.1N HCl, at 37°C ±0.5°C and 100 rpm. Microballoons equivalent to 100 mg Labetalol Hydrochlorides were accurately weighed and filled in a hard gelatin Capsule and added to the dissolution medium, aliquots (10 ml) are withdrawn at hourly intervals for a period of 12 hr. Perfect sink condition is established during the drug dissolution study period by replacing an equivalent volume of dissolution medium. The samples are filtered, and solutions are analyzed at 302 nm using a UV Spectrophotometer [10].

Release Kinetics Study

The drug release kinetics was studied by various kinetic models such as Korsmeyer-Peppas, Higuchi plot, Hixson and Crowell law of cube root, First order plot and Zero order plot. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models. Zero order as cumulative amount of drug released Vs time, first order as log cumulative percentage of drug remaining Vs time, Hixson and Crowell as cube root of percentage drug remaining vs. time in hours and Higuchi's model as cumulative percentage of drug released Vs square root of time. The best fit model was confirmed by the value of correlation coefficient near to 1. The data was presented for the most appropriate model. If n value is 0.45 or less, the release mechanism follows "Fickian diffusion" and higher values of 0.45 to 0.89 for mass transfer follow a non-fickian model (anomalous transport). The drug release follows Higuchi model of drug release and case II transport if the n value is 0.89. For the values of n higher than 0.89, the mechanism of drug release is regarded as super case II transport [11-13].

Stability Study

The optimized Labetalol Hydrochloride Microballoons filled in hard gelatin capsules and kept under accelerated conditions (temperature 40°C±2°C and RH 75±5%) according to ICH guidelines using stability chamber for the period of one month. The samples were withdrawn at 15 days of predetermined intervals and evaluated for their physical appearance, entrapment efficiency, *in vitro* buoyancy and disintegration test of capsules [14].

RESULTS AND DISCUSSION

Standard Curve for Labetalol Hydrochloride

Labetalol hydrochloride in acid buffer pH 1.2 shows linearity (R^2=0.999) in absorbance at concentrations of 20 to 100 mcg/ml as shown in Table 2 and Fig. 1 and obeys Beer Lambert's Law.

Table 2: Data for standard curve of Labetalol Hydrochloride

S.No	Concentration (mcg/ml)	Absorbance at 302 nm*
1	0	0
2	20	0.1540±0.003
3	40	0.3105±0.001
4	60	0.4587±0.001
5	80	0.6063±0.002
6	100	0.7892±0.002

*n=3

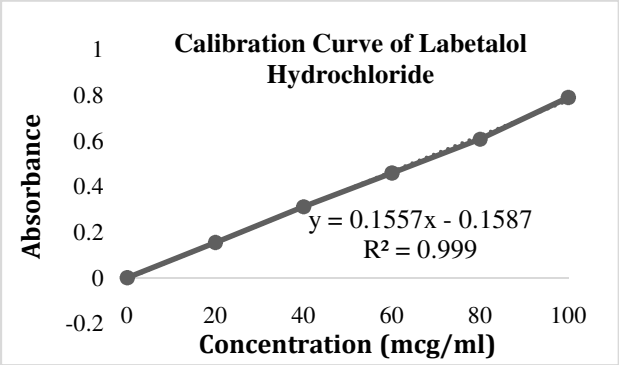

Figure 1: Calibration Curve of Labetalol Hydrochloride in pH 1.2

Formulation of Gastroretentive Floating Microballoons of Labetalol Hydrochloride

Labetalol Hydrochloride Microballoons were prepared by Emulsion solvent diffusion method using polymers like Eudragit RS 100 and Ethyl cellulose at different drug to polymer ratios and compositions and Polyvinyl Alcohol as Stabilizing agent shown in Fig. 2.

Figure 2: Labetalol Hydrochloride Microballoons

Surface Morphology Analysis

The particle size of microballoons was found in the range of 55.4µm - 219.33µm. The particle size of the microspheres increases with increase in polymer concentration respectively. This is because the viscosity of polymer solution increases with increasing polymer concentration resulting in enhanced interfacial tension, which in turn decreases the stirring efficiency, which results in increased particle size.

The shape and surface morphology of optimized formulations F3 and F8 were observed in scanning electron microscope. It shows spherical and circular shape with smooth surface as shown in Fig. 3 and 4.

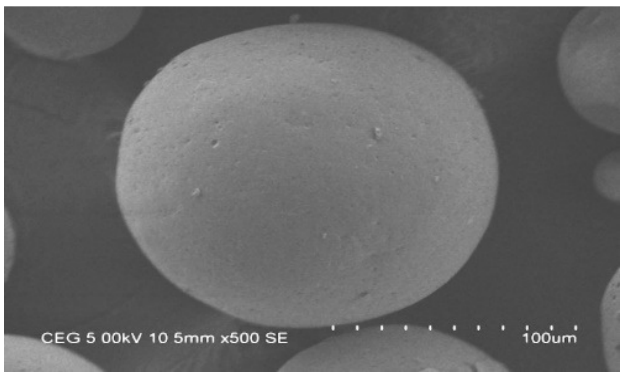

Figure 3: SEM Image of optimized formulation F3

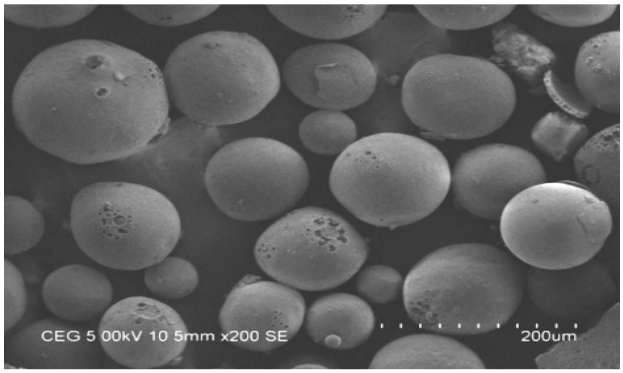

Figure 4: SEM Image of optimized formulation F8

Evaluation Parameters

The Percentage yield of microballoons was found in the range of 48.33-86.25 % shown in Table 3. It was observed that with the increase in the polymer concentration in the formulation, the product yield increased.

The drug entrapment efficiency of all formulations was found to be in the range between 80.5 to 97.2% shown in Table 3. With the increase in polymer concentration, increased entrapment efficiency was seen because with increasing polymer content, more particles of drug would be coated leading to higher encapsulation efficiency.

The buoyancy of all the formulations was found to be in the range of 76 - 94% shown in Table 3. Formulation F4 showed least percentage buoyancy of 76%, while F8 showed highest buoyancy of 94%. In the test of floating time, microballoons remained floating for more than 12 hours. The good buoyancy behavior of the microspheres may be attributed to the hollow nature of the microspheres. As the concentration of polymers increases, buoyancy also increases.

In Vitro Drug Release Study

The *in vitro* drug release profile for formulated Labetalol Hydrochloride Microballoons obtained for F1-F9 formulations were shown in Fig. 5, 6 & 7. Among these the formulations F3 and F8 formulation shows controlled release up to 12thh.The entrapment efficiency was found to be higher in F3-93.4% and F8-97.2% comparatively with other formulations. Therefore, F3 and F8 were selected as optimized formulations.

Table 3: Evaluation Parameters

Formulation Code	Average Particle Size (µm)	Percentage yield (%)	Entrapment efficiency (%) *	*In vitro* Buoyancy (%)
F1	55.4	69.00	86.9±1.33	86.0±1.63
F2	85.56	77.3	90.8± 0.45	84.0±1.25
F3	**136.65**	**81.75**	**93.4±0.21**	**90.0±1.25**
F4	85.46	49.0	80.5±0.52	76.0±1.63
F5	105.69	48.33	85.7±0.57	88.0±1.25
F6	135.19	70.5	89.5±0.94	80.0±0.82
F7	143.77	62.0	92.1±0.52	88.0±0.47
F8	**219.33**	**86.25**	**97.2±1.07**	**94.0±1.25**
F9	191.77	78.0	94.7±0.78	92.0±1.25

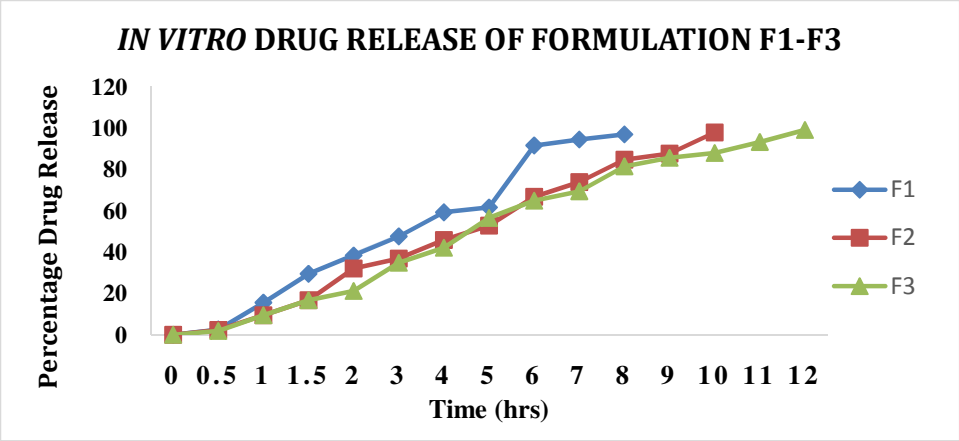

Figure 5: *In vitro* release of formulations F1-F3

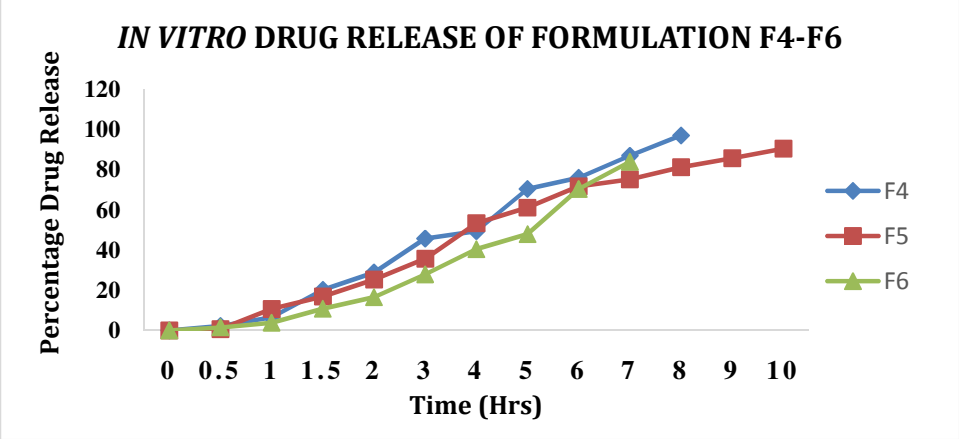

Figure 6: *In vitro* release of formulations F4-F6

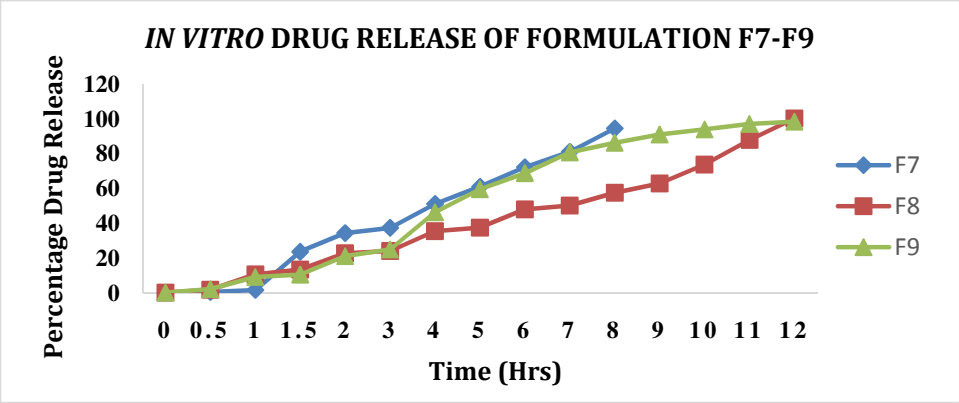

Figure 7: *In vitro* release of formulations F7-F9

Table 4: Flow property measurements of optimized Microballoons

F. code	Bulk density (g/ml) *	Tapped density (g/ml) *	Carr's Index (%) *	Hausner's ratio	Angle of repose (θ)
F3	0.47 ±0.03	0.52 ± 0.02	10.63 ± 0.03	1.11	25°41'
F8	0.49 ±0.01	0.54 ± 0.01	10.20 ± 0.02	1.10	33°50'

* n= 3

Table 5: Evaluation Parameters

Formulation code	Average weight of capsules (g)^	Disintegration Time*	Drug content (%) *
F3	0.532±0.083	10 min 16 sec±0.060	97.88±1.025
F8	0.534±0.084	10 min 02 sec±0.032	99.37±0.826

^n= 20, *n= 3

Preformulation Studies of Optimized Labetalol Hydrochloride Microballoons

The optimized formulations F3 and F8 showed good flow property, which are studied from Table 4.

Optimized Labetalol Hydrochloride Microballoons filled in Capsules

The optimized Labetalol Hydrochloride microballoons were filled into "0" size hard gelatin capsules without adding glidant or excipients because of good flow property. Each capsule containing sufficient quantity of Labetalol Hydrochloride Microballoons which is equivalent to 100 mg as shown in Fig. 8.

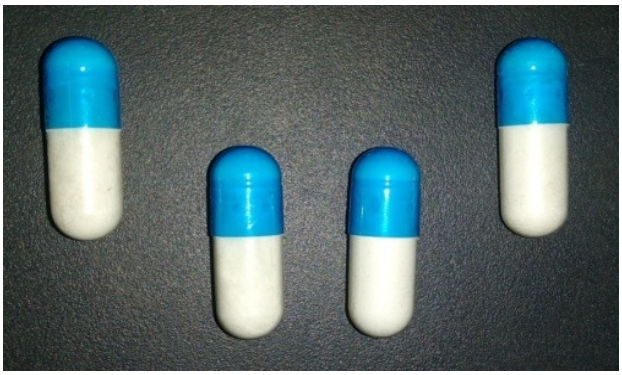

Figure 8: Labetalol Hydrochloride Microballoons filled in Hard Gelatin Capsules

Post Formulation Studies for Labetalol Hydrochloride Microballoons Capsules

The Labetalol Hydrochloride Microballoons capsules comply with the official test for Uniformity of weight, Disintegration test, Drug content and drug release shown in Table 5 and 6.

Table 6: *In vitro* release study of Microballoons capsules

Time (hours)	Percentage drug release (%) *	
	C-F3	C-F8
0	0	0
0.5	0.98±0.373	1.56±0.075
1	7.41±0.837	10.66±0.282
1.5	17.52±0.606	14.29±0.531
2	24.26±1.769	20.5±0.865
3	34.02±1.505	25.02±0.461
4	48.35±2.572	35.04±0.391
5	55.26±1.378	36.52±0.381
6	62.19±1.680	48.52±0.799
7	77.82±3.476	50.87±0.357
8	84.56±1.293	57.56±0.299
9	87.24±0.692	64.03±1.223
10	89.26±0.566	73.05±0.417
11	96.72±1.480	88.05±0.822
12	99.76±0.418	100.03±0.135

* n= 3

Kinetic Study of Optimized Formulations

In vitro release of F3 was fit into various kinetic models to find out the mechanism of drug release as shown in Table 7. Among all the models, highest correlation coefficient was observed in Zero order kinetics (R^2=0.972) followed by Hixson Crowell cube root Law (R^2=0.972). The slope of the Korsmeyer-Peppas plot (n=0.927) was found to be more than 0.89 indicating Super Case II Transport. *In vitro* release of F8 was fit into various kinetic models to find out the mechanism of drug release. Among all the models, highest correlation coefficient was shown in Zero order kinetics (R^2=0.982) followed by Hixson Crowell cube root Law (R^2=0.937). The slope of the Korsmeyer-Peppas plot (n=0.860) was found to be more than 0.5 indicating the diffusion was anomalous diffusion (Non Fickian diffusion).

Table 7: Data for R^2 value

Kinetic models	Coefficient determination for C-F3(R^2)	Coefficient determination for C-F8(R^2)
Zero order	0.972	0.982
First order	0.850	0.638
Higuchi	0.966	0.917
Korsmeyer-Peppas	0.984	0.981
Hixson Crowell	0.972	0.937

Stability Studies

The optimized formulations (C-F3 & C-F8) subjected to stability studies and shown in Table 8. No significant changes in appearance, entrapment efficiency, *in vitro* buoyancy and disintegration time were observed after the end of 0, 15 and 30 days and found identical in stability studies.

Table 8: Stability data for Optimized capsules

F. code	Physical appearance			Entrapment Efficiency (%)			*In vitro* Buoyancy (%)			Disintegration time		
	Zero day	15th day	30th day	Zero day	15th day	30th day	Zero day	15th day	30th day	Zero day	15th day	30th day
C-F3	NC	NC	NC	93.4	92.5	91.5	90.0	89.0	88.0	10 min 20 sec	10 min 11 sec	10 min 2 sec
C-F8	NC	NC	NC	97.2	95.3	95.1	94.0	93.0	91.0	10 min 17 sec	10 min 10 sec	10 min

*NC-No change

CONCLUSION

The microballoons so prepared will remain buoyant on the surface of gastric fluid releasing Labetalol Hydrochloride in a controlled manner. Inferences drawn from *in vitro* studies suggest that microballoons may prove as potential delivery system for Labetalol Hydrochloride by improving bioavailability in comparison to conventional dosage forms.

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