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FORMULATION AND OPTIMIZATION OF PROPRANOLOL HYDROCHLORIDE MICROBALLONS USING DESIGN OF EXPERIMENTS

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ABSTRACT

The formulation of Propranolol Hydrochloride loaded micro balloons involved the use of Ethyl Cellulose as Coating Agent, HPMC as a polymer, and Tween 80 as a Dispersing agent, Isopropyl alcohol as solvent. The micro balloons were prepared by an Solvent evaporation Technique using liquid paraffin, Hydrophilic non-ionic Surfactants, Methanol, as a processing medium. The Full Factorial design of experiments was utilized to get optimized formulation using a concentration of HPMC, Concentration of Ethyl Cellulose, Concentration of surfactant (C), and stirring speed (D) as an independent parameter while, Particle size (Y1), entrapment efficiency (Y2) and %buoyancy (Y3) using as a dependent parameter. For the optimized formulation, the mean particle size was 83.788 µm, entrapment efficiency was 88.70%, and buoyancy was 88% found. An image of the formulation taken using a scanning electron microscope (SEM) reveals discrete particles with a smooth surface texture, a hollow interior, a spherical shape, and a particle size of less than 200 µm. The FTIR study confirms there was no interaction between the drug and excipients. The *in-vitro* drug release study found that Propranolol Hydrochloride loaded micro balloons released the drug for up to 12 hours as compared to the pure drug. This was due to increasing the gastric residence time and absorption area in the stomach. The drug release kinetic study reveals that it follows the Higuchi model and the drug release mechanism was type II transport which was obtained from the Korsmeyer Peppas model. The stability study shows that there is no significant change in the optimized micro balloons for 30 days as per ICH guidelines.

KEYWORDS: Drug release, Emulsion Solvent Diffusion, In-vitro drug release kinetics, Microballons, Scanning electron microscope.

INTRODUCTION

A Medication administration route is often classified by the location at which the drug isadministered. The choice of route in which the medication is given depends not only on convenience and compliance but also on the drug on the drug's pharmacokinetic and pharmacodynamics profile. Compared to other route of drug administration, oral drug administration still remains the preferred choice for delivery of drugs into systemic circulation due to ease of dosing administration, patient compliance and flexibility in formulation. Oral controlled release dosage form (CRDF) has been extensively used to improve therapy of many important medications.

The GRDDS One of the most feasible approaches for achieving a prolonged and predictable drug delivery. Profiles in the GIT is to control the gastric residence time, using gastro –retentive dosage form (GRDF). GRDF are the drug delivery system that are designed to be retained in the stomach for a prolonged time and release their active materials and thereby enable sustained input of the drug to the upper part of the GIT. This technology has generated enormous attention over the last few decades owing to its potential applications to improve the oral delivery of some important drugs for which prolonged retention in the upper GIT can greatly improve their oral bioavailability and /or their therapeutic outcome.

- From the formulation and technological point of view the floating drug delivery system (FDDS) is considerably easy and logical approach in the development of GRDF. Floating drug delivery system float on the gastric only when it has density less than of gastric fluids. Usually, floating formulation are prepared from hydrophilic matrices that either have a density lower than one or their density drops low after immersion in the gastric fluids owing to swelling. There are several formulation approaches used for designing GRDDS. These include swelling and expanding system, which are retained in the gastric region due to their large size gained after swelling. Floating system are retained in the gastric region due to their floating

ability on the gastric fluid The floating system is further divided into effervescent and non-effervescent floating system based on their mechanism of floating. Bio adhesive system adheres to the gastric mucosa due to which they are retained in the gastric region. Micro balloons are a type of floating drug delivery system that consist of small spherical particle made of biocompatible polymers. The particles are typically between 10 to 200 microns in size. Micro balloons are designed to be administered orally and they are intended to release their content slowly over time. Gastro retentive floating microspheres are very effective in the reduction of adverse effect of gastric irritation. Floating micro balloons are very effective approach in delivery of drug that have poor bioavailability because of their limited absorption in the upper GIT. The higher dose of drug can reduce due to increase in gastric retention time which lead to low dose frequency.

MATERIALS AND METHODS

Materials

Propranolol Hydrochloride was obtained as a gift sample from Cadila Pharmaceuticals, Ahmedabad, India. Synthetic and semi-synthetic polymers like Ethyl cellulose, HPMC K4 M, Eudragit RS 100, and Eudragit L 100 were obtained from ChemDyes Corporation. Natural polymers like Xanthan gum from ChemDyes Corporation, guar gum from Oxford Laboratory Reagent, and chitosan from AnaChem Laboratories were obtained. Solvents like chloroform, dichloromethane (DCM), acetone, and acetonitrile were obtained from ChemDyes Corporation and also methanol was obtained from the RANKEM laboratory agent. Surfactants like Span 80 and Tween 80 from ChemDyes Corporation. Liquid paraffin as a processing medium was obtained from ChemDyes Corporation.

Methods

Solubility analysis: Solubility analysis was done to select suitable solvents to dissolve the drug, polymer as well as various excipients used for the formulation of micro balloons.

Determination of ƛmax: 100 of Propranolol hydrochloride was dissolved in methanol and diluted to 100ml with the 0.1N HCL 1ml of this solution was diluted to 10ml 0.1N HCL this gives the solution of concentration 100mcg/ml. from this 1ml solution was transferred in 10ml volumetric flask and dilute with 0.1N HCL this gives the solution of concentration 10mcg/ml and this solution was examined between 290nm

Standard Calibration Curve For Propranolol Hydrochloride

In simulated gastric fluid (acidic buffer) pH1.2

Weighed quantity of propranolol hydrochloride (100mg) was dissolved in pH1.2 buffer and the volume were made up to 100ml with the same medium from this stock solution serial dilutions were made to obtain solution in concentration ranging from 5-60µg/ml. The absorbance was measured at 290nm

Trial and error method: (preliminary experiments)

Previously many trails were run for the preparation of floating micro balloons of propranolol, concentration of the ethyl cellulose, hydroxy propyl methyl cellulose and propranolol hydrochloride by solvent evaporation technique. Trails were made by changing the temperature, stirring speed. After so many trails, it was concluded that temperature play varies critical role in the formation of floating micro balloons, it is a continuous process of stirring, with the combination of hydrophilic non- ionic surfactants and ethyl cellulose as release retarding polymer and hydroxy propyl methylcellulose as pore former. Every step in the process was optimized by performing experiments through trail and error method.

DOE

A full 2 factorial design was introduced to optimize the formulation of PROPRANOLOL loaded Ethyl cellulose + HPMC Micro balloons using the Solvent Evaporation Technique. Entrapment Efficiency was considered as a measurable parameter for this study. A design matrix comprising of 8 experimental runs was constructed using DOE. On the response variable i.e., % drug release at 1 hour and % of drug release at 8 hours were considered as measurable parameters. Volume of solvent (50ml) ratio of IPA and Acetone (1:1), volume of aqueous phase (500ml) concentration of Tween (2.5ml), stirring speed (50 rpm) and temperature werekept constant.

Table 7: Full Factorial Doe Floating Micro Balloons of Propranolol Hydrochloride.

Formulation	Propranolol	Ethyl cellulose	HPMC
F1	L	L	L
F2	L	L	H
F3	L	H	L
F4	L	H	H
F5	H	L	L
F6	H	L	H
F7	H	H	L
F8	H	H	H

L- Low and **H**- high.

DOE (mg/units)

S.no	Ingredients	LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
		F1	F2	F3	F4	F5	F6	F7	F8
1	PROPRANOLOL	100	100	100	100	100	100	100	100
2	EC	200	200	500	500	200	200	500	500
3	HPMC	200	500	200	500	200	500	200	500

PROPRANOLOL: L-100mg, H-500 mg ETHYL CELLULOSE: L-200mg, H-500mg
HPMC: L-200mg, H-500mg.

▸ CHARACTERIZATION OF THE PROPRANOLO HYDROCHLORIDE FLOATING MICROBALLONS

Particle size

Determination of average particle size of propranolol hydrochloride floating micro balloons was carried out by optical microscopy in which stage micro meter was employed. A minute quantity of micro balloons was suspended in liquid paraffin and spread on a clean glass slide and average size of 100mg was determined in each batch.

Drug Entrapment Efficiency

The micro balloons sample was powdered using mortar and pestle. An accurately weighed sample of 20mg of micro balloons was dispersed in 47.5ml of 0.1N HCL and 2.5ml of methanol, and sonicated for 30 mins at a temperature of 37.5℃. The resultantsolution was filtered, and the filtrate was suitably diluted with 0.1N HCL. Absorbance was measured at 290nm by using UV Spectroscopy.

$$\% \text{ Entrapment efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

Estimation of drug content

Drug content in the microcapsules was calculated by UV Spectrophotometric method. A sample of micro balloons equivalent to 100 mg was dissolved in 25ml of methanol and the volume was adjusted up to 100ml using 0.1N HCL. The solution was filtered through What man filter paper. Then the filtrate was assayed for drug content by measuring the absorbance at 290 nm after suitable dilution

➢ PERCENTAGE YIELD

The percentage yield of the prepared micro balloons was determined by using theformula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

In-vitro dissolution

- ❖ Dissolution is the main evaluation study conducted for the estimation of the drug releasefrom the dosage form.
- ❖ USP-TYPE II apparatus was selected for the study
- ❖ Formulation with efficiency more than 65% were selected for the study.
- ❖ The microballoons equivalent to 100mg of drug were weighed accurately and filled in the capsule shells.
- ❖ Dissolution profiles were carried out in the following media:

1. 0.1N HCL for 2hours

The parameters for dissolution apparatus for all the above runs were kept constant asdescribed below

Type of apparatus: USP II

RPM: 50rpm

Temperature: 37.5 ± 0.5℃.

▸ Preparation of buffer solution

1. **Preparation of pH1.2 buffer:** place 8.5ml of HCL in 1000ml 0f distilled water.

▸ METHOD FOR DISSOLUTION

- ❖ A total of 8 formulations were selected for the dissolution with drug entrapment more than 65%. These formulations were taken as n= 8 for the dissolution In-vitro dissolutiontesting was conducted on microballoons equivalent to 100mg of propranolol hydrochloride.
- ❖ Microballoons were filled in hard gelatin capsule shell
- ❖ USP Type II apparatus was used
- ❖ Media: 900ml 0.1N HCL
- ❖ RPM:50rpm
- ❖ Time points:0.05,1,2,4,5 hours
- ❖ Estimation by UV spectrophotometry.
- ❖ The dissolution vessels must be filled with the respective dissolution media. The dissolution parameter such as temperature, stirring speed must be set before starting ofthe dissolution.
- ❖ As the dissolution assembly reaches the temperature, sometime must be allowed for the paddles to rotate, after which the sample should be dropped carefully and the time mustbe noted.
- ❖ At the prescribed time intervals, aliquots(5ml) must be withdrawn with sampling tubes, at the same time equal quantity(5ml) of dissolution medium must replace to maintain the volume of the medium.
- ❖ Withdrawn aliquots must be suitably diluted with the dissolution medium, and analyzed spectrophotometrically. Drug release was calculated and tabulated

MECHANISM OF DRUG RELEASE

To analyse the mechanism of the drug release rate kinetics of the dosage form, the data obtainedwere plotted as

1. Cumulative percentage drug released Vs time (in-vitro drug release plots)
2. Cumulative percentage drug release Vs square root of time (Higuchi's plot)
3. Log cumulative percentage drug remaining Vs time (first order plot)
4. Log percentage drug release Vs log time (Peppas plots)

Zero order release rate kinetics

To study the zero-order release kinetics the release

rate data are fitted to the followingequation.

$F=K_0t$

Where 'F' is the fraction of drug release, 'K_0' is the release rate constant and
't' is the release time.

When the data is plotted as cumulative percentage drug release Vs time, if the plot is linear then the data obeys zero – order release kinetics, with a slope equal to K_0.

First order model

This model has also been used to describe absorption and /or elimination of some drug, therelease of the drug which followed first order kinetics can be expressed by the equation:

$$\text{Log } C = \log C_0 - Kt/2.303$$

Where C_0 is the initial concentration of drug, k is the first order rate constant, and it is time.

Higuchi release model

To study the Higuchi release kinetics, the release rate data was fitted to the following equation.

$F = K_H.t^{1/2}$

Where 'F' is the amount of drug release. 'K_H' is the release rate constant, and
't' is the release time

When the data is plotted as a cumulative percentage drug release Vs square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equalto 'K'.

Korsemeyer and peppas release model

The release rate data were fitted to the following equation,$Mt / M\infty = K_M. t^n$

Where, $Mt / M\infty$ is the fraction of drug release,

'K_M' is the release constant,

't' is the release time, 'n' is the diffusional exponent for the drug release that depends on the shape of the matrix dosage form. When the data is plotted as log percentage release Vs log time, yields as straight line with a slope equal to 'n' and 'K' can be obtained from Y- intercept,for non-fickian release the 'n' values falls between 0.5 and 1.0 while for Fickian (case I) diffusion n= 0.5 and zero release (case- II transport) n= 1.0

MECHANISM OF DRUG RELEASE

To analyse the mechanism of the drug release rate kinetics of the dosage form, the data obtainedwere plotted as

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2. Cumulative percentage drug release Vs square root of time (Higuchi's plot)
3. Log cumulative percentage drug remaining Vs time (first order plot)
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When the data is plotted as a cumulative percentage drug release Vs square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equalto 'K'.

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RELEASE EXPONENT (n) VALUSES AND DRUG TRANSPORTMECHANISM

Release exponent(n)	Drug Transport Mechanism
0.5	Fickian diffusion (Higuchi matrix)
0.45<n<0.89	Non – fickian diffusion
0.89	Case II transport
Higher than 0.89	Super case II transport

RESULTS AND DISCUSSION

A total of eight formulations of propranolol hydrochloride floating micro balloons were formulated by solvent evaporation technique using Design of Experiment approach. The Formulations were subjected to evaluation parameters like solubility, compressibility index, angle of repose, Drug entrapment efficiency, in-intro drug release studies.

Table Showing The Compressibility Index For Each Formulation.

Formulation	Carr's index
f1	12.2
f2	14.5
f3	13.9
f4	14.4
f5	13.3
f6	12.6
f7	14.5
f8	14.1

: Compressibility Index of every formulation i.e., F1-F8 shows good flow ability.

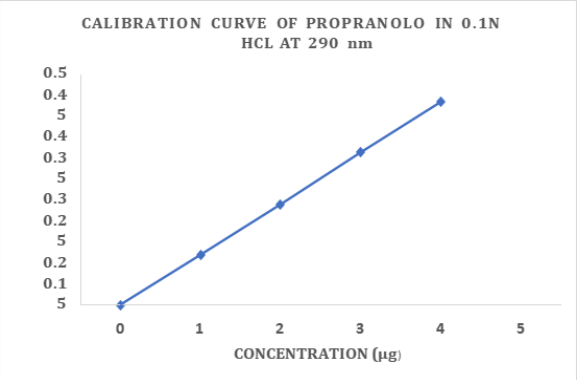
Formulation and their respective angle of repose

Formulation	Angle of repose
F1	8.28
F2	8.56
F3	7.98
F4	8.76
F5	8.88
F6	7.54
F7	8.78
F8	8.94

Angle of repose for formulation F1-F8 shows excellent flow property.

CALIBRATION VALUES OF PRORANOLOL HYDROCHLORIDE in 0.1N HCL.

S. no	Concentration (µg/ml)	Absorbance (nm)
1	1	0.280
2	2	0.305
3	3	0.388
4	4	0.505
5	5	0.604



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4	4	0.505
5	5	0.604

PERCENTAGE YIELD OF FORMULATION

Formulation	Percentage yield (%w/w)
F1	44.82
F2	54.76
F3	77.96
F4	80.34
F5	49.65
F6	69.96
F7	75.97
F8	78.65

The yield of microballoons seems to depend on the concentration of polymer in the preparation. For formulation F3, F4, F7 and F8 where the ethyl cellulose concentration is 500 mg, the yieldis >60%.

For formulation with low ethyl cellulose concentration, the yield is in the range of 45 to 55%.

Mean particle size of the microballoons of the formulations.

FORMULATION	MEAN PARTICLE SIZE (nm)
F1	356.87
F2	343.85
F3	276.92
F4	329.77
F5	355.28
F6	282.87
F7	384.54
F8	283.21

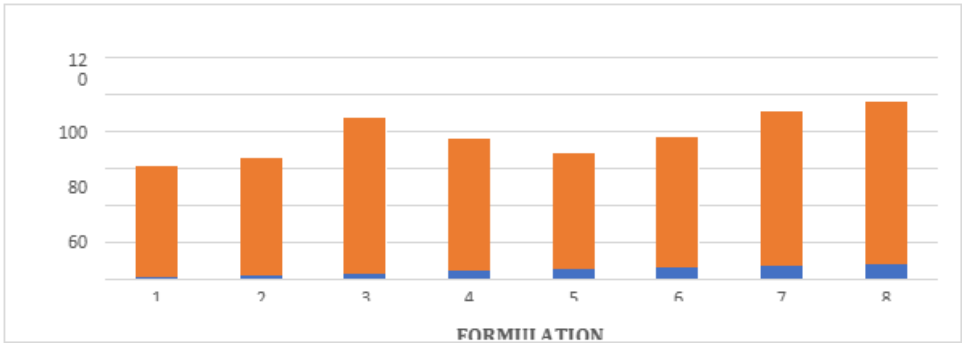
Mean particle size of the microballoons using optical microscopy

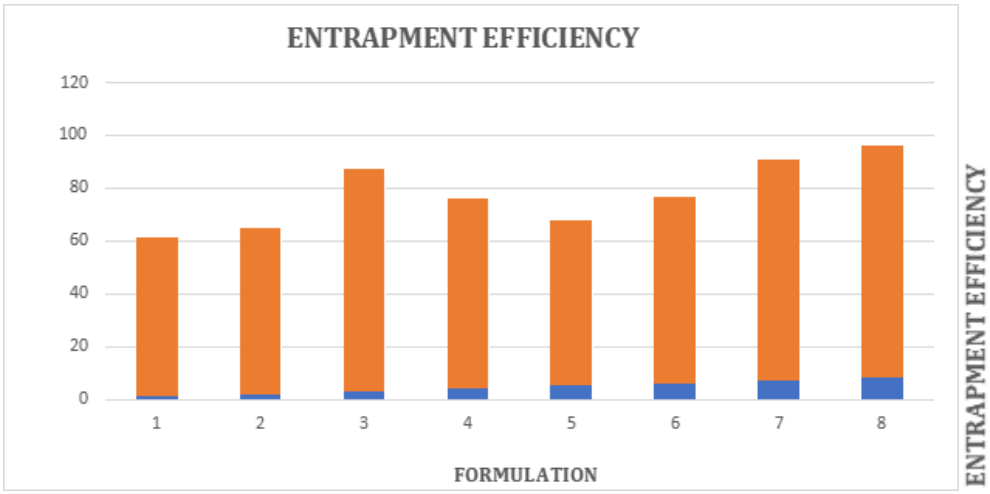
For all formulations, the microballoons are in the average particle size range of 278 to386µm.

The particle size distribution is independent on the formulation and is dependent moreon the Followed

Entrapment Efficiency of The Formulations

Formulation	Entrapment Efficiency
F1	60.30
F2	62.85
F3	84.00
F4	71.54
F5	62.79
F6	70.32
F7	83.24
F8	87.70





Discussion

The drug entrapment efficiency is dependent on the level of ethyl cellulose in the formulation. For formulation with ethyl cellulose is 500mg, the entrapment efficiency is >80%. For formulation with ethyl cellulose levels at 200mg, the efficiency is around 60 to75%.

▸ IN VITRO BUOYANCY STUDIES

The duration of floatation for all the batches of microballoons was evaluated as follows:

- ❖ Quantity of microballoons equivalent to 100mg of propranolol hydrochloride was accurately weighed out for each batch.
- ❖ This amount was added to a 500ml glass beaker containing 250ml of
- ❖ 0.1N HCL(medium). A three blade remi stirrer was fitted into the medium.
- ❖ The medium was stirred at 50 rpm for a period of 12 hours.
- ❖ The behavior of the micro balloons were observed at 2,4,8 and 12 hours interval and the visual observations were noted.

In- vitro buoyancy study F1-F8.

S.NO	Formulation no	Time (hours)				
		0	2	4	6	8
1	F1-F2	floating without clumping	floating without clumping	floating without clumping	floating without clumping	The clumps of ethylcelluloseare formed on the surface
2	F3-F4	floating without clumping	floating without clumping	floating without clumping	floating without clumping	floating without clumping
3	F5-F6	floating without clumping	floating without clumping	The clumps of ethylcellulose are formed on the surface	The clumps of ethylcellulose are formed on the surface	The clumps of ethylcellulose are formed on the surface
4	F7-F8	floating without clumping	floating without clumping	floating without clumping	floating without clumping	The clumps of ethylcellulose are formed on the surface

IN-VITRO DISSOLUTION STUDIES

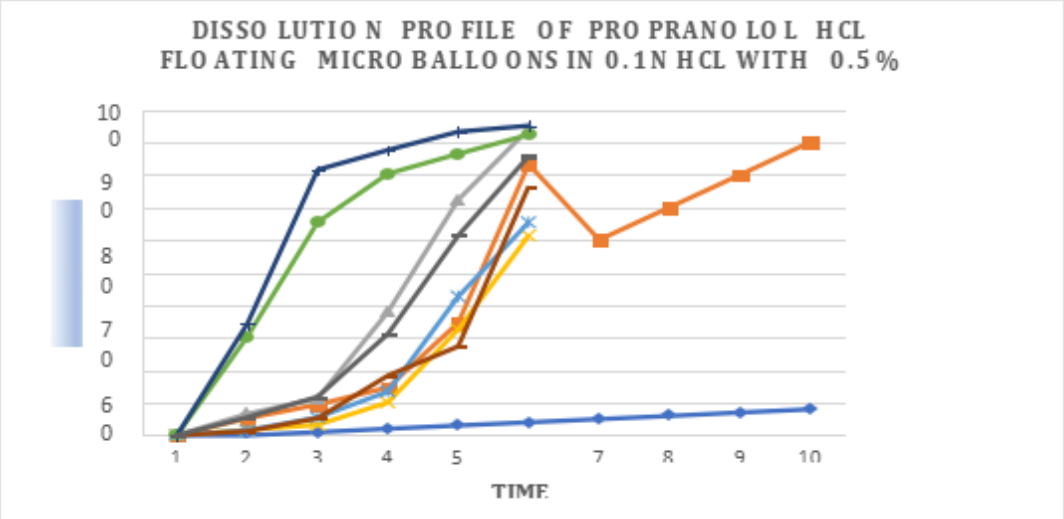
In vitro release study of propranolol hydrochloride floating micro balloons were performed inthe following pH media (pH 1.2) at 37°C±0.5°C.

In vitro dissolution testing was conducted on micro balloons equivalent to 100mg of propranolol hydrochloride. Micro balloons were filled in hard gelatin capsules shells. USP type I apparatus was used. Media 900ml 0.1N HCL with 0.5% sodium lauryl sulphate. RPM:50rpm, Time points: 0, 0.5, 1, 2, 4 and 8hours, Estimation by UV spectrophotometry.

DISSOLUTION PROFILE AT pH 1.2

TIME		DISSOLUTION PROFILE FOR PROPRANOLOL HCL FLOATING MICROBALLOONS						
	LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	5.22	6.54	1.65	1.54	30.32	34.21	1.23	5.54
1	9.43	11.34	3.23	5.44	65.43	81.54	5.28	11.78
2	14.65	37.87	10.10	13.44	80.32	87.56	18.32	31.12
4	34.56	72.34	32.54	42.65	86.45	93.21	27.34	61.34
8	83.23	94.09	61.34	65.43	92.32	95.06	76.50	85.76

The in-vitro release profile of propranolol hydrochloride floating microballoons were shownbelow



Discussion

The drug releases rate and extent are dependent of the ratio of the drug and ethyl cellulose as well as the pore former concentration.

For formulations with drug to polymer ratio 1:1 (F1, F2, F7 and F8) the release is dependent on concentration of HPMC (faster release for higher HPMC level) slow (<70% in 8 hours)

For formulations with drug to polymer ratio 4:1 (F5 and F6) the release is very fast (>80% in 2 hours).

Release Kinetics

Korsemeyer- peppas model indicates that the release mechanism is not well known or more than type of release phenomena could be involved. The 'n' value could be used to characterize different releasemechanism as:

Release exponent (n) values and drug transport mechanism

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion (Higuchi matrix)
0.45<n<0.89	Non – fickian diffusion
0.89	Case II transport
Higher than 0.89	Super case II transport

FORMULATION	Zero	First	Higuchi	Peppas	
F1	0.9981	0.9646	0.9272	0.9991	0.943
F2	0.9080	0.9964	0.9524	0.9659	0.874
F3	0.9867	0.9800	0.8689	0.9885	1.353
F4	0.9876	0.9918	0.9165	0.9915	1.146
F5	0.5225	0.9057	0.7911	0.7384	0.322
F6	0.4127	0.7461	0.6958	0.6188	0.244
F7	0.9981	0.9491	0.8834	0.9949	1.091
F8	0.9420	0.9946	0.9491	0.9803	0.927

RELEASE RATE OF PROPRANOLOL HCL FROM FORMULATION(F1-F8)

In order to understand the mechanism of drug release from the microballoons, the in- vitro drug release data were fitted to korsemeyer and peppas release model interpretation of release exponent values enlighten in understanding the release mechanism from the dosage form. The release exponents thus obtained were from 0.874 to 1.353 for the formulation F1- F4 and F7-F8.

Based on the values we can say that formulation exhibited super case II transport. Therelease exponents formulation F6 and F5 was found to be 0.244 and 0.322 based om these values we can say that formulations exhibited anomalous diffusion mechanism (non fickian transport).

The formulation F1 and F3 showed Higuchi r values for korsemeyer and peppas release plot indicating that the drug release from this formulation exhibited anomalous diffusion mechanism. Also, the remaining formulations showed higher r values for firstorder plot indicating that the drug release followed first order kinetics and also the drug release from the microballoons were by both diffusion and erosion.

Discussion

The release of propranolol hydrochloride at 1 hour and 8-hour time points weretaken as the measurable parameters for running the DOE experiments. The 1- hour time point indicates the rate of release and the 8- hour time point is a measure the extent of release. The following are for both 1-hour and 8- hours, there is a strong positive interaction between the drug to ethyl cellulose ratio and the rate and extent of drug release.

HPMC 6 cps which is added as the pore former, does not show either Positive or negative impact on drug release. However, for formulations having HPMC in higher concentrations, the drug release is more complete (at higher ethyl cellulose level) than formulation having low level of HPMC.

SUMMARY AND CONCLUSION

The hydro dynamically balanced modified release dosage form of propranolol Hydrochloride as targeted to be developed using a unique microballoons platform.

Microballoons were formulated using ethyl cellulose 7cps as the controlled release polymer hydroxyl propyl methyl cellulose 6cps as the former and acetone and isopropyl alcohol as solvents for the drug and polymer. Water with 1%Tween80 was used as the continuous phase.

The formulation showed that the drug content, entrapment efficiency and particle size distribution were not the dependent variable. There were no significant differences in any of the above paraments in all the 8 experiments.

However, in case of in- vitro dissolution studies the rate and extent of the release profile was strongly dependent of the drug and polymer ratio as well as on the pore former concentration.

Preformulation testing is the first step in the rationale development of dosage forms of a drug substance. It can be defined as the investigations of pysico- chemical properties of a new drug substance alone and when combined with the excipients to generate data useful to theformulator in developing safe potent bioavailable and efficacious dosage form which can be mass produced.

A full factorial design 14-15 was introduced for the formulation of propranolol hydrochloride microballoons using the solvent evaporation technique.

Entrapment efficiency was considered as a measurable parameter for this study. On the response variable i.e., %drug release at 1hour and percentage of drug release at 8hours were considered as measurable parameters.

In-vitro release study of propranolol hydrochloride at 1hour and 8hours time points were performed for running the DOE experiments.

The DOE charts were obtained by feeding the entrapment efficiency data in the DOE pro XL software.

All the formulations showed higher r values for first order plot indicating that the drug release followed first order kinetics and the drug release from microballoons were by both diffusion and erosion.

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