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DEVELOPMENT AND OPTIMIZATION OF CIPROFLOXACIN HCL HOLLOW MICROSPHERES (MICRO BALLONS) BY USING FACTORIAL DESIGN

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ABSTRACT

In the present study, a gastro retentive micro particulate system was formulated with different Polymers by using solvent evaporation technique. A series of 8 formulations was prepared based on 2^3 Design of experiments. The formulated microspheres were evaluated flow characteristics, Practical yield (up to 80 %) and Encapsulation efficiency (up to 94%). Scanning electron Microscopy confirmed their porous and spherical structure and the particles were of the Size range of (65-525 µm). The release of drug at 1 hour and 8 hours' time points were taken as the measurable parameters for running the DOE experiments. According to design space Hollow Microspheres formulated with Drug in the range of 50 to 70 mg/unit, Ethyl cellulose 7 cps in the range of 145 to 150 mg/unit and HPMC 5 cps in the range of 0.4 to 2 mg/unit were observed to have the best floating characteristics and *in vitro* dissolution profile as per the preset target product profile. Stability studies showed no significant change in the drug content in the formulations at 3 months accelerated condition. In this study concluded that a micro particulate floating dosage form of an anti-infective drug can be successfully designed to give controlled release and improved oral bioavailability.

KEYWORDS

Gastro retentive system, Ciprofloxacin Hcl, Ethyl Cellulose 7 cps, HPMC 5cps, Hollow microspheres.

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INTRODUCTION

Oral Controlled Drug Delivery System[1, 2]

Oral controlled release dosage forms (CRDF) have been extensively used to improve therapy of many important medications. The design of oral controlled drug delivery systems (CDDS) should primarily be

aimed at achieving more predictable and increased process is precluded by several physiological difficulties, such as inability to restrain and locate the CDDS within desired regions of gastrointestinal tract (GIT) due to the variable gastric emptying and motility. The variability may lead to unpredictable time for peak plasma levels and bioavailability. Therefore, the CRDF approaches has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the GIT, i.e. stomach and small intestine, which is due to relatively short transit time of the dosage form in these anatomical segments. Thus within a short period (less than 6 hours), the CRDF of such drugs leave the upper part of GIT and reaches to the non-absorbing distal segment, eventually resulting in a short absorption phase accompanied with lesser bioavailability.

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 forms (GRDF). GRDF are the drug delivery systems 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 application 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.

Advantages of FDDS[3, 4, 5]

It is advantageous for drugs absorbed through the stomach. For e.g. Riboflavin, Ferrous salts, antacids. It is not restricted to medicaments, which are absorbed from stomach, since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine. It is advantageous for drugs meant for local action in the stomach for e.g. antacids, antiulcer drugs. The dissolved drug gets available for absorption in the small intestine after emptying of the stomach bioavailability of drugs. However, the developmental contents. It is therefore expected that a drug will be fully absorbed from the floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine. It releases drug slowly and for prolonged period of time and hence reduces dosing frequency, it reduces fluctuations in circulating blood level of drug as shown by the conventional dosage form. It shows more uniform levels of drug in plasma. As it prolongs drug release it helps to avoid night time dosing. It reduces GIT irritation and other dose related side effects. It increases patient compliance as the dosing frequency is reduced.

MATERIAL AND METHOD

Material

Ciprofloxacin Hcl was received as gift samples from EMCO Industries, Hyderabad, India. Ethyl Cellulose 7cps and HPMC 5cps was a Gift sample from DOW Chemicals, U.S. Dichloromethane (DCM), Isopropyl alcohol (IPA), Tween 80, Hydrochloric Acid G.R and Sulphuric Acid G.R was a Gift sample from S.D Fine Chemicals, Mumbai. All other chemicals and ingredients were used for study are of Analytical grade.

Method

Preparation of hollow microspheres (micro balloons)

Ciprofloxacin Hcl hollow microspheres (micro balloons) were prepared by the solvent evaporation technique. Ciprofloxacin Hcl, Ethyl cellulose 7cps, HPMC 5cps were dissolved in solvent mixture of IPA and DCM acidulated with 0.5ml Conc. Sulphuric acid. The solution was filled into a syringe fitted with 22 gauge needle. It was dropped at a rate of 50 drops/minute into a beaker containing 500 ml water with 2.5 ml Tween 80 as the continuous phase. The continuous phase was stirred using 3 blade Remi stirrers at 500 rpm. After complete addition of the drug-polymer solution, the mixture was allowed to stirrer for 2 hours. The hollow microspheres (micro balloons) on the top of the continuous phase were harvested and dried at 40^0C for 1 hour in a hot air oven. The hollow microspheres (micro balloons)

were stored in air tight containers till taken for further evaluation. The dried hollow microspheres (micro balloons) were weighed and yield was determined.

Characterization of Ciprofloxacin Hcl Hollow Microspheres (Micro Balloons)

Particle size[6]

Determination of average particle size of Ciprofloxacin Hcl hollow microspheres (micro balloons) was carried out by optical microscopy in which stage micrometer was employed. A minute quantity of hollow microspheres (micro balloons) was suspended in liquid paraffin and spread on a clean glass slide and average size of 100 hollow microspheres (micro balloons) was determined in each batch.

Surface morphology[7]

Scanning electron microscopy has been used to determine particle distribution, surface topography, and texture and to examine the morphology. SEM studies were carried out by using JEOL JSMT-330A scanning electron microscope (Japan). The samples of SEM were prepared by lightly sprinkling the hollow microspheres (micro balloons) powder on a double adhesive tape, which was stuck on an aluminum stub. The stubs were then coated with gold to thickness of about 300A using a sputter coater. The photomicrographs were taken with the help of SEM analyzer.

Percentage yield

The percentage yield of the prepared hollow microspheres (micro balloons) was determined by using the formula.

% yield = Actual weight of product / Total weight of excipients and drug X 100

Drug entrapment efficiency[8]

The hollow microspheres (micro balloons) sample was powdered using mortar and pestle. An accurately weighed sample of 20mg of hollow microspheres (micro balloons) was dispersed in 47.5 ml of 0.1N Hcl and 2.5ml of methanol and sonicated for 30 minutes at a temperature of 37.5^0C. The resultant solution was filtered, and the filtrate was suitably diluted with 0.1N Hcl. Absorbance was measured at 278nm by using

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

Estimation of drug content

Drug content in the hollow microspheres (micro balloons) was calculated by UV spectrophotometric method. A sample of hollow microspheres (micro balloons) equivalent to 100 mg was dissolved in 25 ml Methanol and the volume was adjusted up to 100 ml 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 278 nm after suitable dilution.

***In vitro* Buoyancy Studies**

The duration of floatation for all the batches of hollow microspheres (micro balloons) was evaluated as follows: Quantity of hollow microspheres (micro balloons) equivalent to 100 mg of Ciprofloxacin Hcl was accurately weighed out for each batch. This amount was added to a 500 ml glass beaker containing 250 ml 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 hollow microspheres (micro balloons) was observed at 2, 4, 8 and 12 hours interval and the visual observations were noted.

***In vitro* dissolution**[9, 10]

Dissolution is the main evaluation study conducted for the estimation of the drug release from the dosage form. USP-TYPE II apparatus was selected for the study. Formulations with entrapment efficiency more than 65% were selected for the study. The hollow microspheres (microballoons) equivalent to 100mg of drug were weighed accurately and filled in the capsule Shells. 0.1N Hcl for 8 hours. Type of apparatus USP II and RPM is 50, Temperature 37 ± 0.5^0C.

MECHANISM OF DRUG RELEASE[11]

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as

- Cumulative percentage drug released Vs Time (*In vitro* drug release plots)
- Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
- Log cumulative percentage drug remaining Vs Time (First order plots)
- Log percentage drug released Vs Log time (Peppas plots)

Method for Stability Testing

The hollow microspheres (micro balloons) were filled at level equivalent to 100 mg drug content in size '1' hard gelatin capsules shells, packed in 90 cc HDPE container and subjected to accelerated stability studies at 40^0C/75% RH stability conditions. Samples were withdrawn at 1M, 2M and 3M intervals and evaluated for assay and *in vitro* dissolution testing.

RESULTS AND DISCUSSIONS

Characterization of Hollow Microspheres (Micro Balloons)

Particle size analysis

In order to understand the mechanism of drug release from the hollow microspheres (micro balloons), the *in vitro* drug release data of the optimized formulations were fitted to Korsmeyer-Peppas release model and interpretation of release exponent values enlightens in understanding the release mechanism from the dosage form. The release exponents thus obtained were from 0.874, 0.996 and 0.927. Based on these values we can say that formulations exhibited super case II transport. All the optimized formulations showed higher R^2 values for first order plot indicating that the drug release followed first order kinetics and also the drug release from hollow microspheres (micro balloons) were by both diffusion and erosion.

Table No.1: Full factorial DOE of Ciprofloxacin Hcl hollow microspheres (micro balloons)

Formulation	Ciprofloxacin Hcl	Ethyl cellulose 7cps	HPMC 5cps
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, H-high

Table No.2: Experimental Design of Formulation- DOE (mg/unit)

S.No	Ingredients	LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
		F1	F2	F3	F4	F5	F6	F7	F8
1	Ciprofloxacin Hcl	50	50	50	50	200	200	200	200
2	Ethyl cellulose 7cps	50	50	200	200	50	50	200	200
3	HPMC 5cps	0.4	4	0.4	4	0.4	4	0.4	4

Ciprofloxacin Hcl- L-50mg, H-200mg, Ethyl cellulose 7cps- L-50mg, H- 200mg,
HPMC 5cp - L- 0.4mg, H- 4mg.

Table No.3: Mean Particle size of the hollow microsphere (microballoons) of the Formulations

S.No	Formulation	Mean Particle Size (D90) (µM)
1	LLL	355.86
2	LLH	344.86
3	HLL	278.98
4	LHH	330.77
5	HLL	357.29
6	HLH	288.86
7	HHL	386.55
8	HHH	289.26

Table No.4: Percentage Yield of Formulations

S.No	Formulation	Percentage Yield(%w/w)
1	F1	54.82
2	F2	59.45
3	F3	77.92
4	F4	80.23
5	F5	46.87
6	F6	48.57
7	F7	65.97
8	F8	68.97

Table No.5: Entrapment efficiencies of the Formulations

Formulation	Entrapment efficiency	Assay
F1	67.39	33.567
F2	70.58	34.734
F3	94.00	18.799
F4	84.61	17.768
F5	74.97	63.873
F6	72.41	57.567
F7	89.27	44.592
F8	91.70	45.578

Table No.6: *In vitro* buoyancy studies

S.No	Formulation No	Time (Hours)				
		0	2	4	8	12
1	F1	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface
2	F2	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface
3	F3	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping
4	F4	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping
5	F5	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface	The clumps of ethyl cellulose are formed on the surface	The clumps of ethyl cellulose are formed on the surface
6	F6	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface	The clumps of ethyl cellulose are formed on the surface	The clumps of ethyl cellulose are formed on the surface
7	F7	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed on the surface
8	F8	Floating without clumping	Floating without clumping	Floating without clumping	Floating without clumping	The clumps of ethyl cellulose are formed

Table No.7: Dissolution profiles for Ciprofloxacin Hcl hollow microspheres (micro balloons)

Time (hrs)	Cumulative Percent Drug Release For Ciprofloxacin Hcl Hollow Microspheres (Micro balloons)							
	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	6.35	9.23	1.87	3.23	35.87	44.32	4.32	7.54
1	11.87	18.45	3.69	7.89	72.61	89.45	7.29	15.88
2	24.79	42.67	10.44	18.44	88.45	90.76	18.35	33.49
4	45.32	75.34	35.68	43.87	90.26	98.12	38.44	67.7
8	85.29	94.35	65.43	72.64	98.23	98.5	82.48	90.58

Table No.8: Release rate of Ciprofloxacin Hcl from formulations (F1 to F8)

Formulation	R^2				Peppas N
	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

Table No.9: Composition of Optimised Formulation

S.No	Formulation No	Formulation Ingredients	Mg/unit
1	Foptima 1	Ciprofloxacin Hcl	50
		Ethyl cellulose 7cps	145
		HPMC 5cps	0.4
2	Foptima 2	Ciprofloxacin Hcl	60
		Ethyl cellulose 7cps	147
		HPMC 5cps	1.0
3	Foptima 3	Ciprofloxacin HCl	70
		Ethyl cellulose 7cps	150
		HPMC 5cps	2
4	-	Tween 80 (ml)	-
5	-	IPA (ml)	-
6	-	DCM (ml)	-
7	-	Water (ml)	-

Table No.10: Characterization of optimized formulations

Charcterstics	F-optima-1	F-optima-2	F-optima-3
YIELD(%w/w/	74.82	79.45	77.92
ASSAY(mg cipro/100mg)	25.357	24.734	28.799
ENTRAPMENT EFFICIENCY	87.39	88.58	78.00
AVG.PARTICLESIZE DISTRIBUTION (D90, MICRONS)	355.86	344.25	278.98

Table No.11: Dissolution profile for optimized forumulation of Ciprofloxacin Hcl hollow microspheres (microballoons)

Time	F optima 1	F optima 2	F optima 3
0	0	0	0
0.5	6.35	9.23	7.54
1	11.87	18.45	15.88
2	24.79	28.67	33.49
4	65.32	75.34	67.7
8	85.29	94.35	90.58

Table No.12: Release rate of Ciprofloxacin Hcl from optimized formulations

Formulation	R^2				Peppas N
	Zero	First	Higuchi	Peppas	
F-optima 1	0.9377	0.9843	0.9195	0.9797	0.996
F-optima 2	0.9241	0.9846	0.9281	0.9746	0.874
F-optima 3	0.9420	0.9946	0.9491	0.9803	0.927

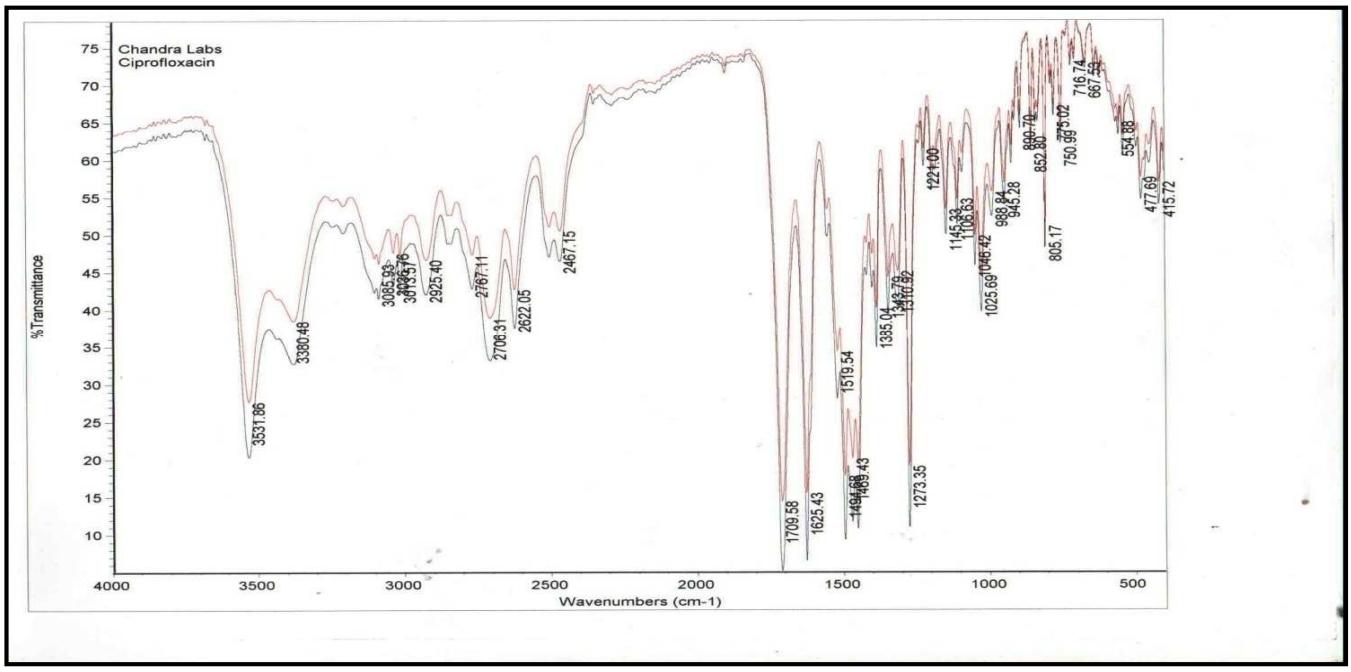

Figure No.1: Fourier Transform Infrared spectroscopy of Ciprofloxacin Hcl

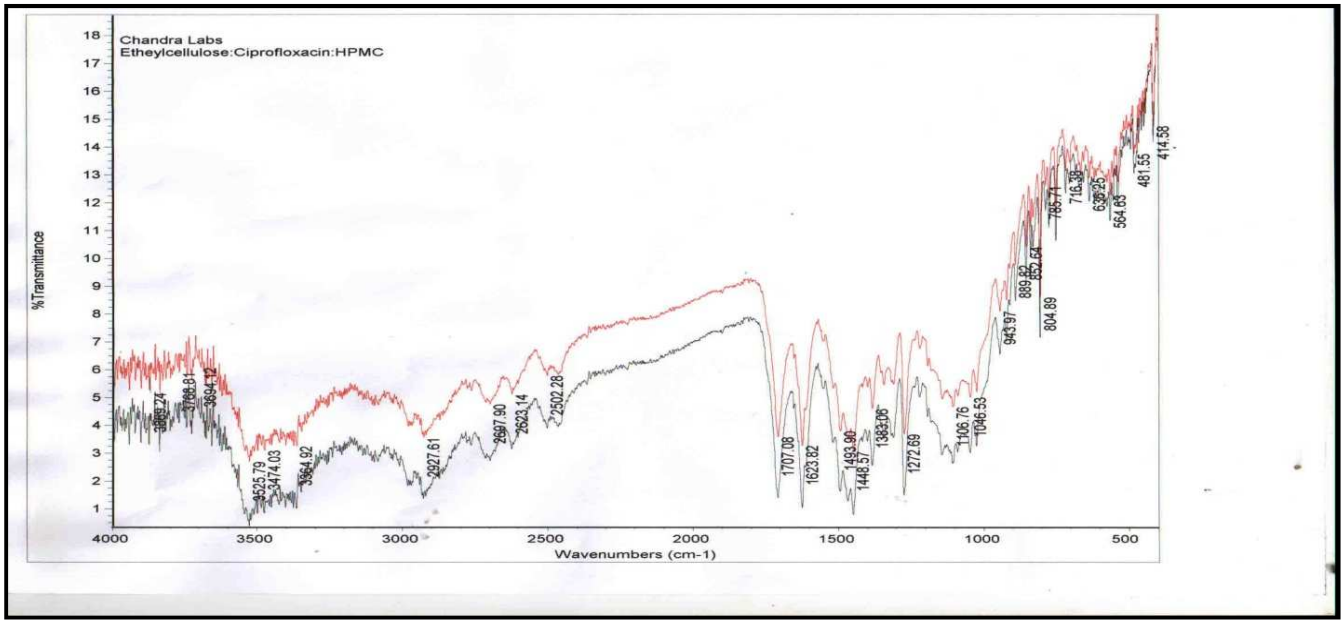

Figure No.2: Fourier Transform Infrared spectroscopy of Formulation-F1

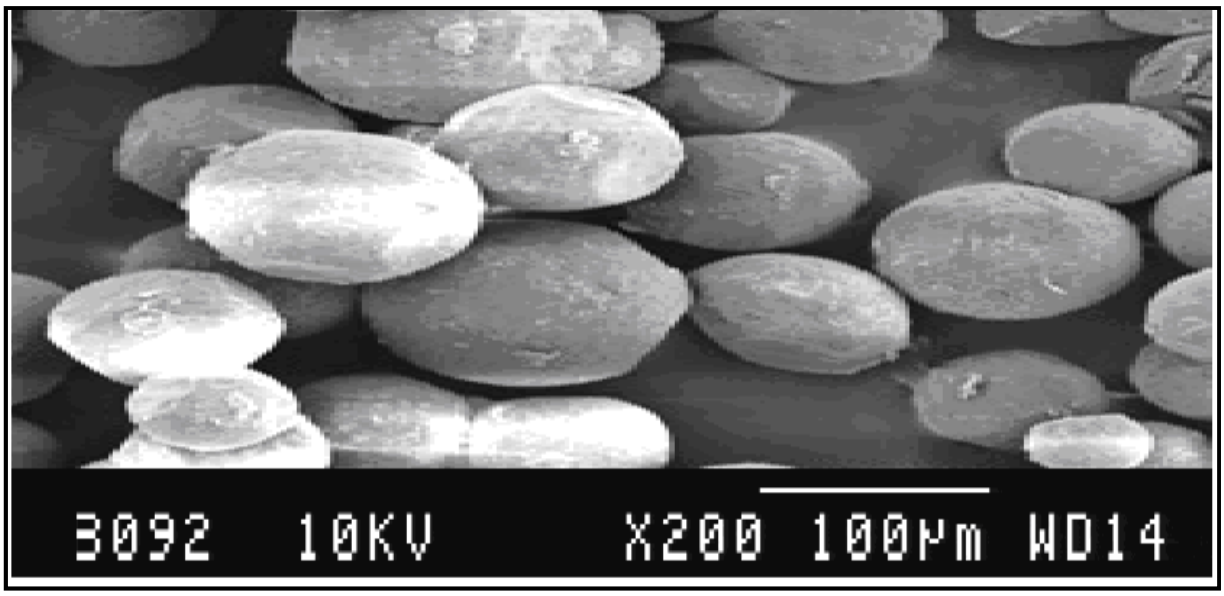

Figure No.3: Scanning Electron Microscopy of Formulation-F1

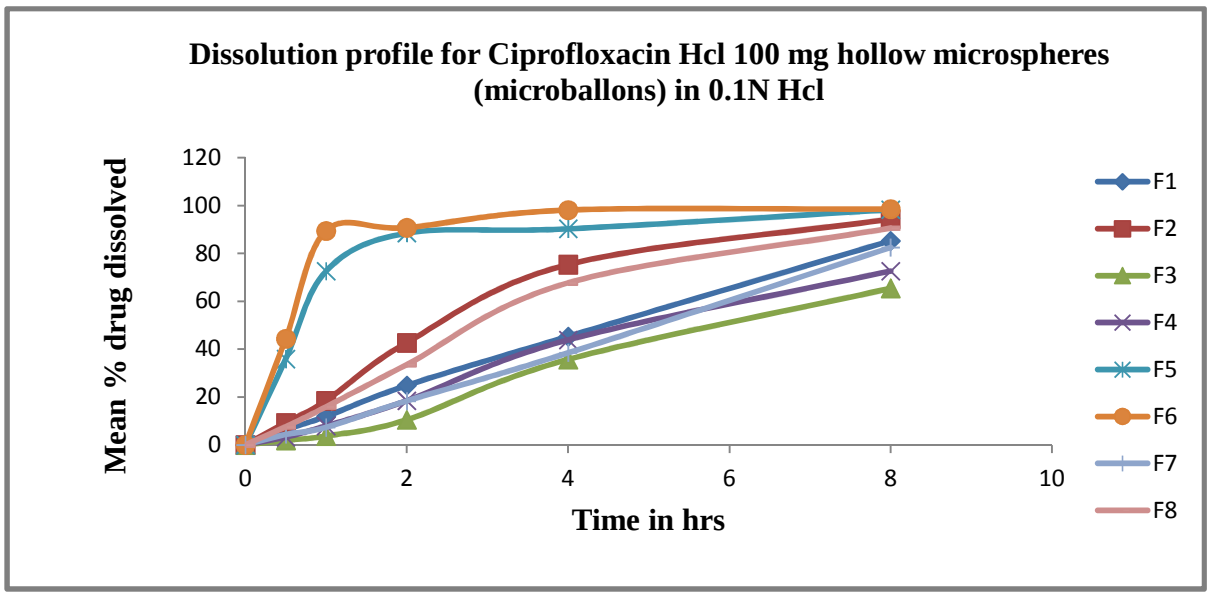

Figure No.4: Comparative release profile of formulated for Ciprofloxacin Hcl 100 Mg Hollow Microspheres

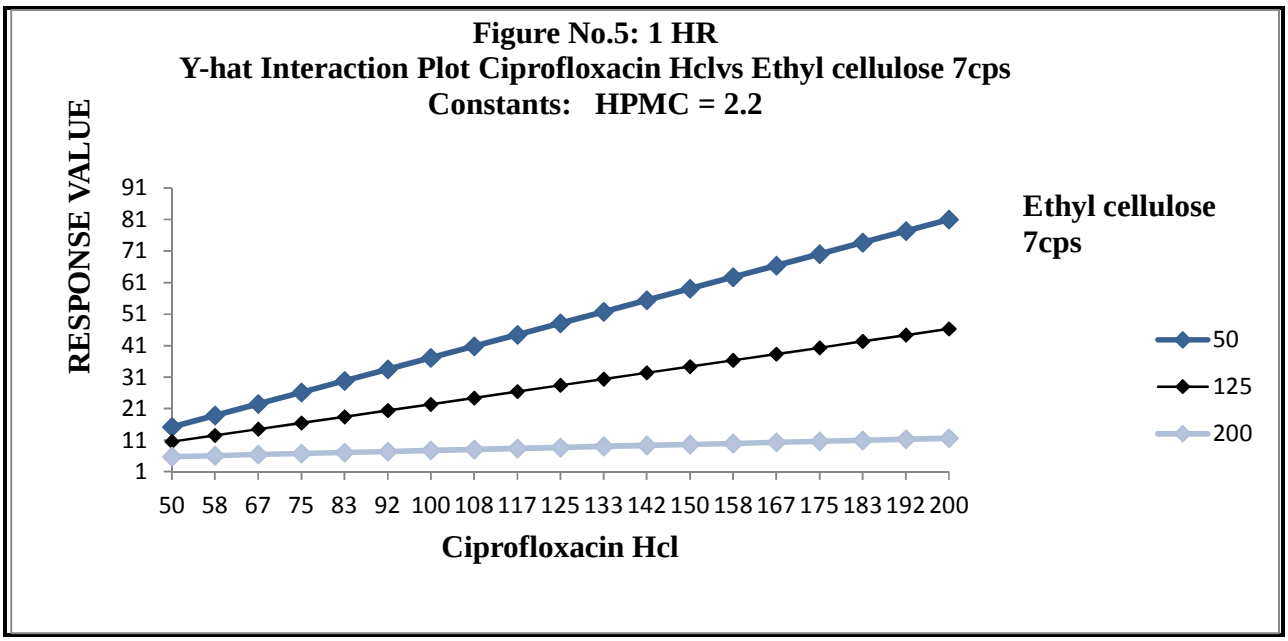

Figure No.5: Y-hat Interaction Plot Ciprofloxacin Hcl vs Ethyl cellulose 7cps

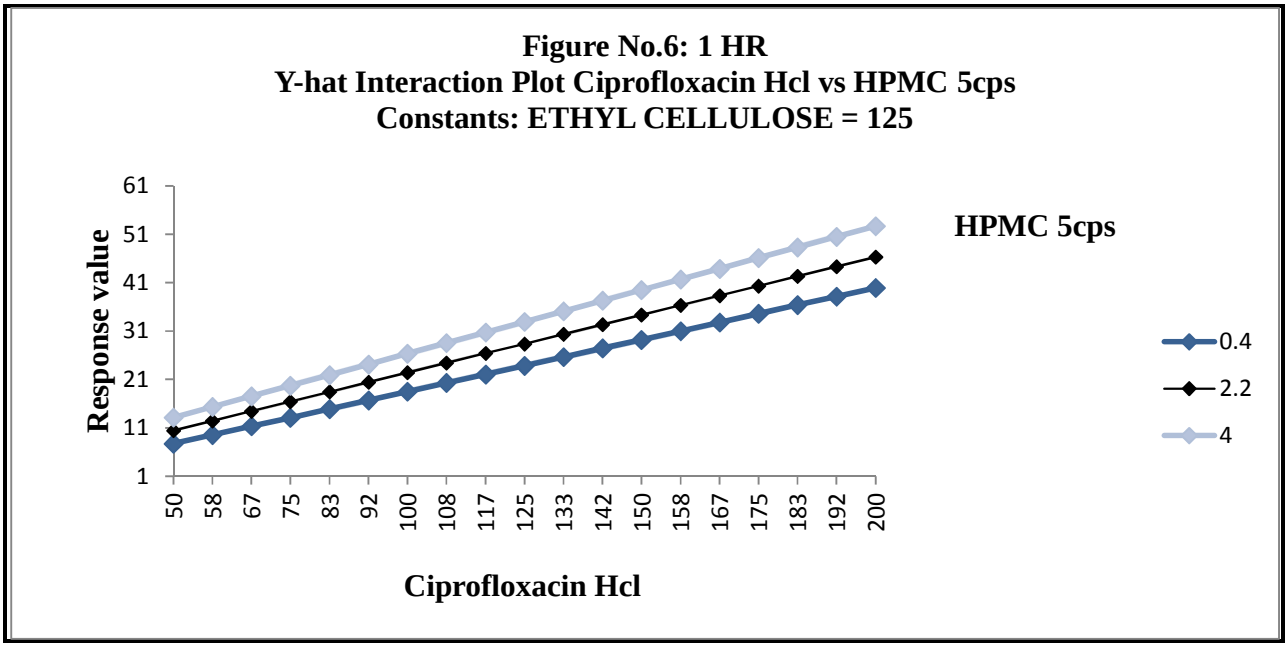

Figure No.6: Y-hat Interaction Plot Ciprofloxacin Hcl vs HPMC 5cps

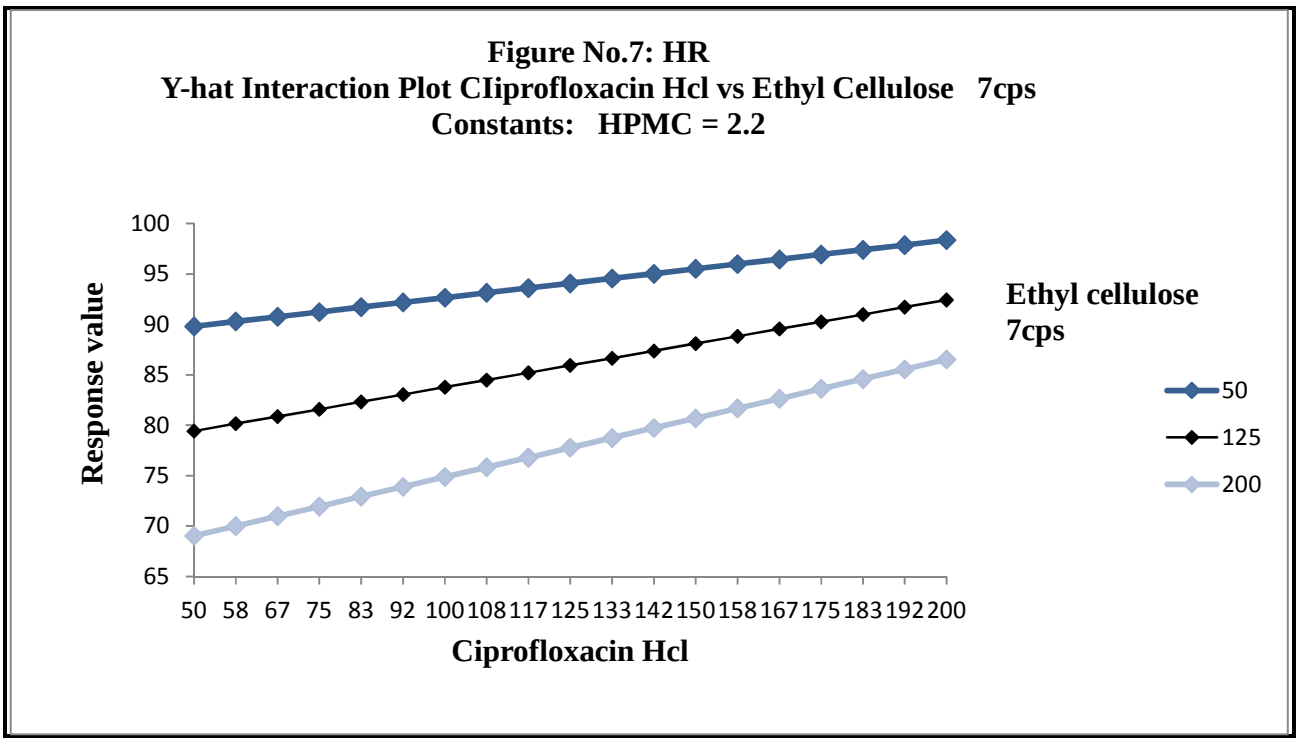

Figure No.7: Y-hat Interaction Plot Ciprofloxacin Hcl vs Ethyl Cellulose 7cps

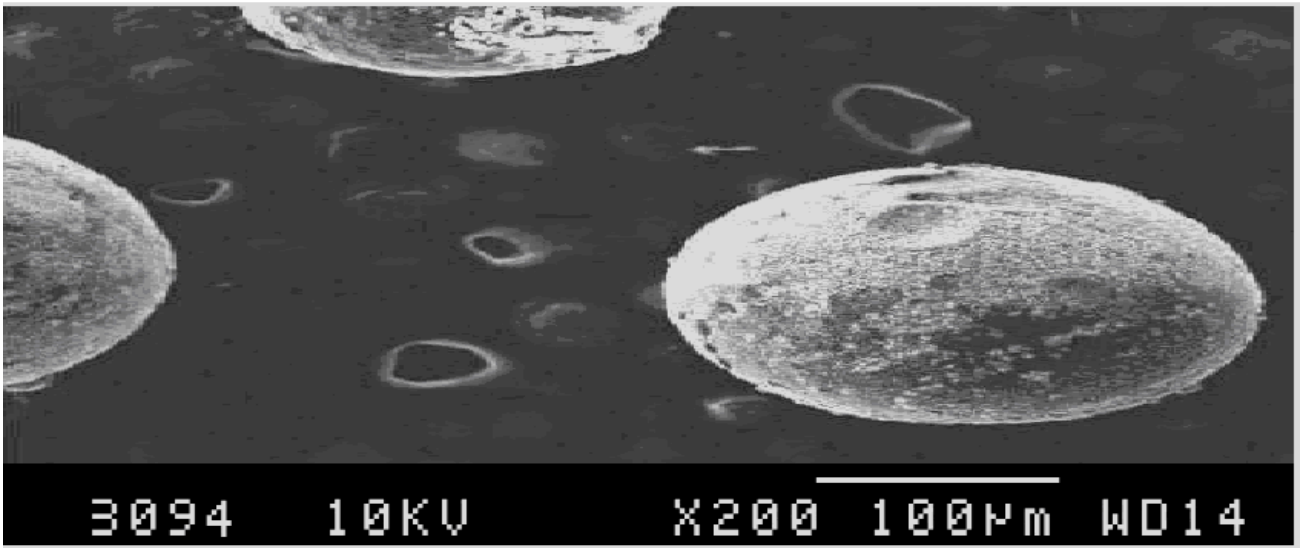

Figure No.8: Scanning Electron Microscopy of Foptima1

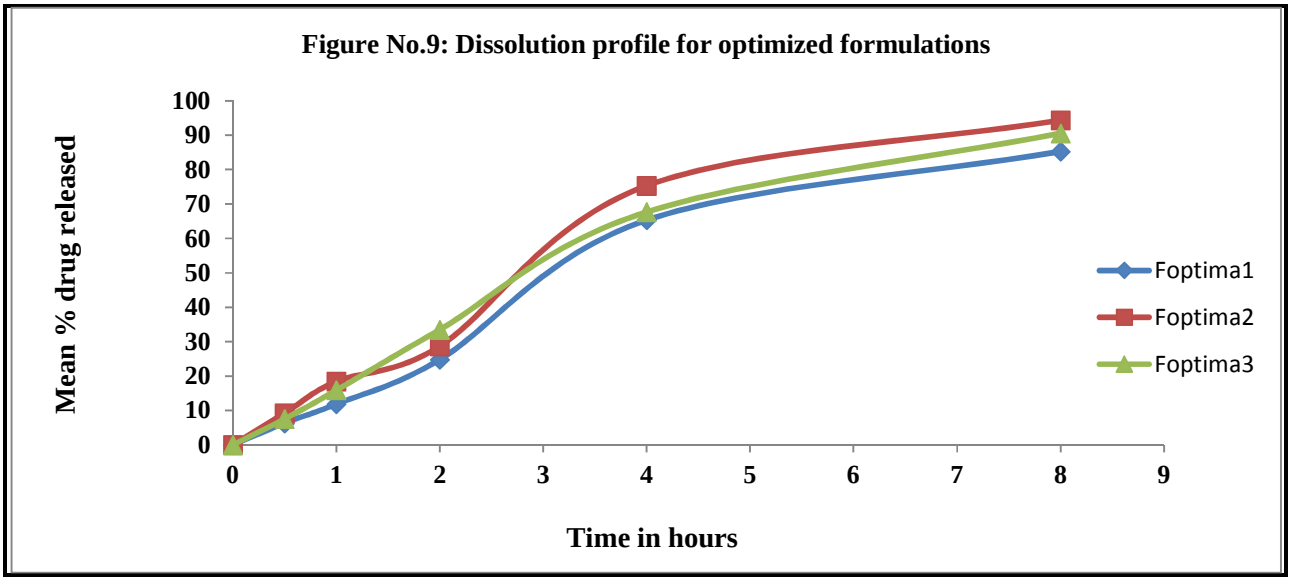

Figure No.9: Dissolution profile for optimized formulations

CONCLUSION

The hydro dynamically balanced modified release dosage form of Ciprofloxacin Hcl was targeted to be developed using a unique micro balloons platform. Micro balloons were formulated using Ethyl cellulose 7 cps as the controlled release polymer, HPMC 5 cps as the pore former and DCM and IPA as solvents for the drug and polymers. Water with 1% Tween 80 was used as the continuous phase. The formulation was optimized by using statistically designed 2^3 Design of experiments. The particle size, particle yield, drug content, entrapment efficiency, buoyancy studies and *in vitro* dissolution profile were the measurable parameters. The formulation showed that the particle size distribution, batch yield, drug content, entrapment efficiency, buoyancy studies were not the dependent variable. There were no significant differences in any of the above parameters in all the 8 experimental runs. However, in case of the *in-vitro* dissolution studies, the rate and extent of the release profile was strongly dependent on the drug and polymer ratio as well as on the pore forming concentration. A design space was defined within which an optimum formulation could be successfully achieved with the in vitro release profile matching to the Target product profile.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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