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FORMULATION AND EVALUATION OF PUSH-PULL OSMOTIC TABLET OF CYPROHEPTADINE HYDROCHLORIDE

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ABSTRACT

Cyproheptadine is serotonin antagonist and histamine H1 blocker used as antipruritic, anti-allergic, appetite stimulant and for post gastrectomy dumping syndrome. Push-pull osmotic tablet of Cyproheptadine hydrochloride was developed using Sodium chloride as a key ingredient which gives osmogent property, which provides driving force from push layer (lower layer) inside the core tablet and which leads to release of drug from drug layer. Hydroxy propyl methyl cellulose was used as a release retardant material in the present work. Different formulations were prepared by varying the concentrations using 3^2 factorial design. It was applied to see the effect of variables Sodium chloride and HPMC on the response percentage drug release as a dependent variable. These formulations were evaluated for, Hardness, Flow property, Thickness, Friability, Drug content and In-vitro drug release. Tablets were coated with a semipermeable membrane using 10% w/v cellulose acetate in acetone and PEG 400(5%) used as Plasticizer. Coated Push-pull osmotic tablets were drilled for delivery orifice using standard micro drill of diameter size 0.6 mm on drug layer coated surface. Drug release rate was increased as the increase in the concentration of sodium chloride and release rate decreased on increasing the concentration of HPMC. SEM Study was carried out for detection of diameter size of delivery orifices. The FTIR studies demonstrate that there was no interaction between polymer and drug. The optimized formulation was stable for 3 months of accelerated stability study.

KEYWORDS: Cyproheptadine, HPMC, Nacl, Push-pull Osmotic Tablet.

INTRODUCTION

Osmotic Drug Delivery System (ODDS) is a novel drug delivery system and it is most controlled drug delivery system in human body and could be a device or tablets. Osmosis is an elegance bio-phenomenon, which is exploited for the development of delivery systems with every desirable property of an ideal controlled drug delivery system. Push-pull osmotic drug delivery system is an orally control drug delivery system which is utilized for delivery of drug by controlled zero order release manner for long duration of action. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system.

Cyproheptadine hydrochloride is H_1 receptor antagonist, serotonin antagonist also having calcium channel blocking actions, used as the hydrochloride for symptomatic relief of allergic conditions including rhinitis, urticaria, angioedema, pruritic skin disorders other uses include management of migrane.

The PPOP, which was developed by Alza Corporation, consists of two compartments separated by an elastic diaphragm (optional). The upper compartment contains the drug and is connected to the outside environment via a small delivery orifice. A polymeric osmotic agent is present in the lower compartment and has no delivery orifice. The drug layer accounts for 60– 80% of the tablet weight, while the osmotic polymer layer accounts for 20–40%. When the device comes in contact with the aqueous environment, both the drug layer and the osmogent layer imbibe water. As the lower compartment is devoid of any orifice, it expands and pushes the diaphragm into the upper chamber, thereby delivering the drug via the delivery orifice. The osmotic agent in the non-drug layer simultaneously attract water into that compartment, causing it to expand volumetrically and the expansion of osmotic layer pushes the drug suspension out of the delivery orifice.

The aim of this study was to develop, Push-pull Osmotic Tablet of Cyproheptadine by using 3^2 full factorial design. Sodium chloride is a key ingredient which gives osmogent property which provides driving force inside the core tablet which leads to release of drug by pushing the drug layer and hydroxyl-propyl-methyl-cellulose used as a release retardant material. Core tablet was coated by cellulose acetate (10%) and PEG 400 (5%) used as a plasticizer. Tablets were drilled 0.7mm on drug layer side by mechanical driller.

MATERIAL AND METHODS

Cyproheptadine was obtained as a gift sample from Vamsi labs Ltd, Chincholi, Solapur. Cellulose acetate, Sodium chloride, HPMC, Lactose, Starch, PEG 400, Acetone was procured from Research – Lab Fine chem. Industry, Mumbai. All other chemicals used in study were of analytical grade.

Drug-Excipients Interactions

The physicochemical compatibilities of the drug and excipients were tested by FT-IR spectrometry. FT-IR spectra of the drug alone and drug-excipients physical mixtures.

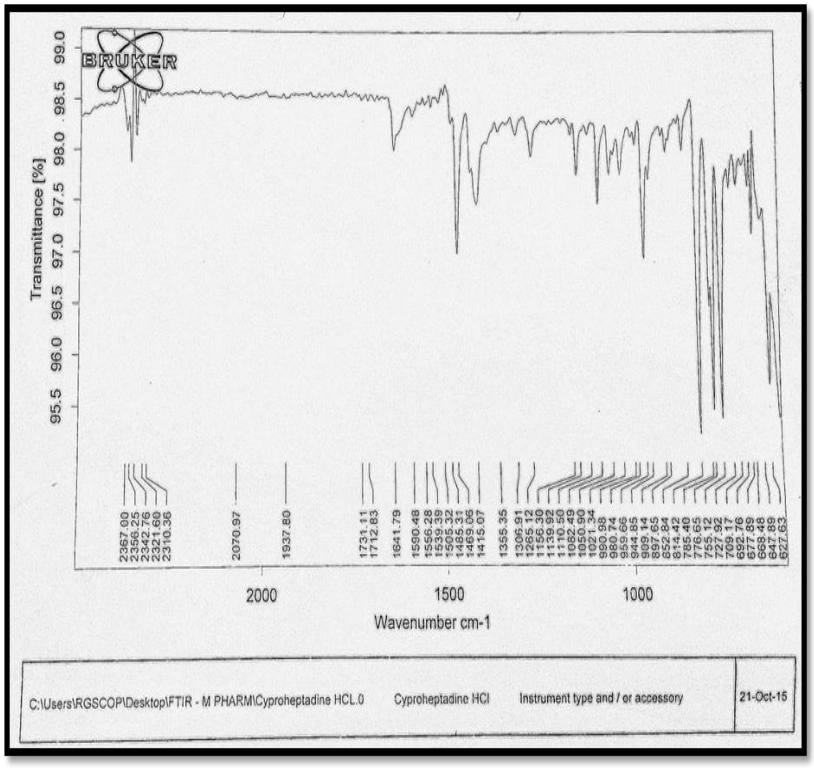

Figure 1: FT-IR Spectra of Pure Cyproheptadine Hydrochloride

The FTIR spectra of pure Cyproheptadine showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug.

Infra-red spectra of drug and polymer mixture showed matching peaks with the drug spectra. The characteristic peak of drug was also seen in the spectra of physical Mixture

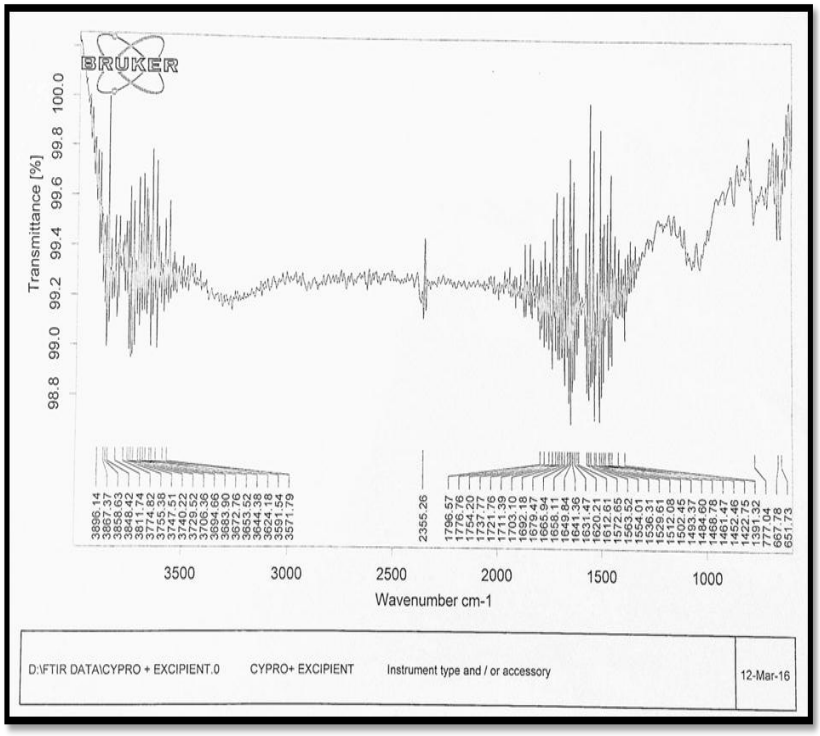

Figure 2: FT-IR Spectra of Physical Mixture

Factorial Design

The application of mathematical optimization in the pharmaceutical field was first reported by Fonner et al (1970), using the Lagrangian method as a constrained optimization technique. A factorial design is used to evaluate two or more factors simultaneously. The treatments are the combinations of levels of the factors. The advantages of factorial design over one factor at a time experiment are that they are more efficient and they allow interactions to be detected. Intervention studies with 2 or more categorical explanatory variables leading to a numerical outcome variable are called as "Factorial design". A factor is simply a categorical variable with 2 or more values referred to as levels. A study in which there are 2 factors with 3 levels is called as 3^2 Factorial designs. For present work 3^2 Factorial designs was selected.

In this design, 2s factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations as reflected.

Table 1: Composition of Push-pull Osmotic Pump Tablet as per Factorial Design (All values are expressed in mg)

Ingredients	Formulation code								
Quantity (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug Layer									
Drug	5.24	5.24	5.24	5.24	5.24	5.24	5.24	5.24	5.24

Nacl	2	2	2	2	2	2	2	2	2
HPMC	30	40	50	30	40	50	30	40	50
Talc	2	2	2	2	2	2	2	2	2
Mg Stearate	2	2	2	2	2	2	2	2	2
Lactose	103.7	93.7	83.7	103.7	93.7	83.7	103.7	93.7	83.7
Total Weight (D)	145	145	145	145	145	145	145	145	145
Push Layer									
Nacl	5	5	5	10	10	10	15	15	15
Mg.Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
HPMC	20	20	20	20	20	20	20	20	20
Lactose	76	76	76	71	71	71	66	66	66
Total Weight (mg)(P)	105	105	105	105	105	105	105	105	105
Total weight of tab	250	250	250	250	250	250	250	250	250

Method of preparation of Core tablet of Cyproheptadine

Wet granulation is the most famous, complex but reliable method of granulation. Most of the drugs can be granulated by this method. It includes the use of a solvent to form a wet mass of drug and excipients together followed by the drying and lubricating process, in this the drug and excipients are mixed together in a geometric progression pattern and the mixture is then wet massed with the addition of volatile solvent. This wet mass is then passed through the appropriate mesh size to obtain the granules which were evaluated and finally compressed to get tablets. Granules of both drug layer and osmotic layer were prepared separately.

All the ingredients except magnesium stearate were weighed and mixed properly for 15 minutes. Then the powder mixture was passed through sieve 22#. Starch was added into Distilled water into a beaker. This mixture of Starch and Distilled water was added into a drug mixture. This was kneaded to form a wet mass and the mass was passed through 22# to obtain granules. The granules were dried in hot air oven and finally after drying and magnesium stearate were added. These granules were punched in tablet compression machine using 8 mm punch.

Coating of Osmotic Tablet

The core tablets of Cyproheptadine were coated with 10% w/v Solution of Cellulose acetate in Acetone was used as a semipermeable membrane provider. PEG 400 5% v/v was used as plasticizer. The tablets were warmed to 40±2°c before applying coating solution .The composition of coating solution used for coating of core tablets is given in (Table 2). Dip coating technique was used for the coating of osmotic tablet. Coating was continued until

desired weight gain (10%) was obtained and tablets were dried at 50°C for 10 h, before further evaluation.

Table 2: Coating composition

Ingredients	Quantity for 100 ml
Cellulose Acetate	10%
Polyethylene glycol 400	5%
Acetone	100 ml

Drilling

For the coated tablets, small orifice was drilled through drug layer side of each coated tablet by standard mechanical drilling technique using 0.6 mm needle. Orifice size was 0.7 mm.

RESULTS

1.Evaluation of Powder Bulk

Many different types of angular properties have been employed to assess flow ability, of these; angle of repose is the most relevant. Repose angle of the powder was investigated. The value of Angle of repose (°θ) decreased after the addition of lubricant. Angle of repose (°θ) is an indicative parameter of powder flow ability from hopper to die cavity. The angles of repose of all the formulations were within the range of 40°–52° indicative of excellent and good flow ability. Bulk density may influence compressibility, tablet porosity, dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. The bulk density of powder was found to be between 0.36-0.38 gm/cm^3. The value indicates good packing capacity of granules. The tap density of the granules of factorial design batches were found in the range of 0.41-0.47gm/cm^3. The bulk density and tap density was used to calculate the percent compressibility of the powder.

The compressibility index of the Powder was observed in range of 11 to 23, indicating good compressibility of the granules. The values of the Hausner's ratio were found to be in the range of 1.12 to 1.30 indicating good and fair flow ability. Data is summarized in table 3.

Table 3: Evaluation of Powder

Code	Angle of repose(θ) Mean ± S.D	Bulk density (gm/cm^3) Mean± S.D	Tapped density (gm/cm^3) Mean± S.D	Compressibility index (%) Mean± S.D	Hausner's ratio Mean± S.D
F1	42.03 ± 0.04	0.3809±0.0040	0.47± 0.0068	19.25±2.224	1.23±0.033
F2	40.55 ± 0.52	0.3766±0.0034	0.42± 0.0043	11.72±1.502	1.12±0.019
F3	45.37 ± 0.88	0.3786±0.0034	0.44± 0.0274	14.58 ±1.214	1.17±0.084

F4	48.90 ± 0.71	0.3650±0.0032	0.41± 0.0040	11.26±0.836	1.12±0.010
F5	47.68 ± 1.06	0.3669±0.0032	0.42± 0.0043	13.87 ±1.443	1.16±0.019
F6	52.74 ± 0.37	0.3640±0.0081	0.44± 0.0046	17.58 ±2.415	1.21±0.359
F7	48.55 ± 0.69	0.3612±0.0031	0.47±0.0084	23.16 ±1.971	1.30±0.033
F8	46.39 ± 1.39	0.3726±0.0033	0.45± 0.0049	17.20± 1.433	1.20±0.020
F9	46.77 ± 1.17	0.3786±0.0034	0.44± 0.0046	15.82± 1.380	1.18±0.019

2.Evaluation of Tablets:

A) Pre coating evaluation

All formulated coated osmotic tablet batches were evaluated for weight variation, hardness, thickness, friability and drug content. Weight variation, hardness, thickness, friability and drug content of uncoated tablet were found within the range.

All formulated osmotic core tablet batches were shiny white with smooth surface, with good texture. The Average weight of the tablets was found to be 250 mg. Thickness of the tablet was found to be 3.4 mm, Hardness of the tablet was found 4.18-4.29 kg/cm^2, Friability of the tablets was found to be 0.11-0.68% and Drug content of the tablet was found to be 97-99%. Due to constant tablet press setting across all batches irrespective of weight variation. This ensured good mechanical strength (Table 4).

Table 4: Pre coating evaluation parameters of osmotic tablet

Formulation Code	Average Weight(mg) Mean ± S.D	Hardness (kg/cm$^{2)}$ Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean±S.D	Drug content (%) Mean± S.D
F1	250.2±2.5298	4.19±0.21082	3.425±0.0085	0.24±0.003	98.08
F2	250.1±1.6633	4.25±0.24152	3.433±0.00919	0.11±0.002	97.66
F3	250.1±2.3309	4.18±0.24152	3.432±0.00994	0.30±0.002	97.90
F4	250.5±1.90029	4.22±0.21082	3.436±0.00843	0.68±0.001	98.29
F5	251.9±2.3309	4.25±0.24152	3.442±0.00919	0.23±0.004	97.47
F6	251.3±2.2632	4.22±0.31623	3.444±0.00994	0.28±0.002	97.38
F7	249.4±3.0983	4.26±0.3496	3.440±0.01792	0.22±0.003	98.43
F8	248.4±3.06232	4.29±0.39441	3.441±0.00422	0.20±0.002	97.80
F9	251.3±1.82878	4.23±0.2582	3.437±0.00919	0.60±0.001	98.18

B) Post coating evaluation

All formulated coated osmotic tablet batches were evaluated for Weight variation, thickness and Film thickness. After coating of the tablets average weight of tablets was found to be 256.2 mg, thickness of coated tablet was found to be 3.78-3.80 mm and thickness of film was found to be 0.36 mm. Due to uniform coating weight variation and thickness of coated tablet was found within the range. Evaluated data is shown in (Table 5).

Table 5: Post coating evaluation parameters of osmotic tablet

Formulation code.	Average Weight (mg) Mean	Thickness of coated tablet Mean	Thickness of film(mm) Mean
F1	254.4	3.805	0.358
F2	255.4	3.803	0.365
F3	256.1	3.796	0.356
F4	255.2	3.788	0.352
F5	253.7	3.799	0.357
F6	256.4	3.801	0.362
F7	255.8	3.789	0.355
F8	256.6	3.785	0.344
F9	256.7	3.785	0.350

From above evaluated data of coated osmotic tablet it was confirmed that weight variation and thickness of film was found within the range.

C) Diameter of delivery orifice

Evaluation of diameter size of delivery orifice were measured by Scanning Electron Microscope and was found to be 700um data give in fig 3.

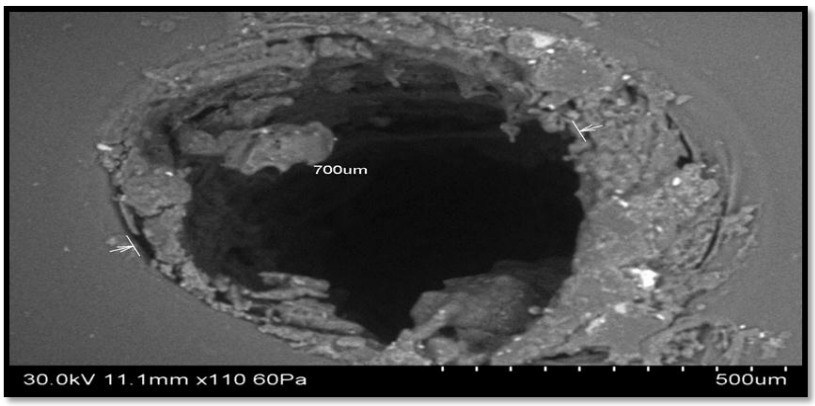

Figure 3: Scanning Electron Microscopy (SEM) of delivery orifice

***3.In Vitro* Dissolution study of Formulations (F1-F9)**

Osmotic tablets were subjected to *In-vitro* drug release studies in simulated gastric and intestinal fluid. Dissolution study was performed in 0.1 N Hcl for 2 hrs and for remaining 22 hrs. In Phosphate buffer pH 6.8, obtained result summarized in (Table No. 6).

Table 6: Cumulative Drug Release of Formulations (F1-F9)

Time (hr)	Cumulative Drug Release (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	2.12	1.62	1.57	1.06	2.47	1.77	2.22	2.07	1.16

2	4.57	4.12	5.07	4.72	4.47	4.17	4.72	4.37	5.32
3	7.07	9.53	9.78	9.98	9.68	9.08	9.93	8.68	10.83
4	11.48	11.53	11.18	14.48	13.08	12.08	13.23	13.93	14.99
5	14.53	14.89	14.58	19.54	18.19	18.69	18.79	18.09	20.09
6	19.34	17.19	16.54	24.30	22.70	22.20	23.15	24.50	24.75
7	23.90	22.00	20.99	31.01	25.60	25.35	28.81	30.21	32.11
8	26.95	24.90	24.60	34.42	29.51	28.41	33.91	34.62	35.52
10	37.62	30.61	29.51	44.08	39.37	38.32	46.53	45.73	44.98
12	47.08	39.22	37.07	59.85	49.49	48.04	58.10	59.45	60.96
16	56.40	50.29	48.34	68.17	58.15	57.60	72.52	71.97	70.52
24	75.63	72.17	70.42	86.85	83.99	80.49	93.66	90.95	88.20

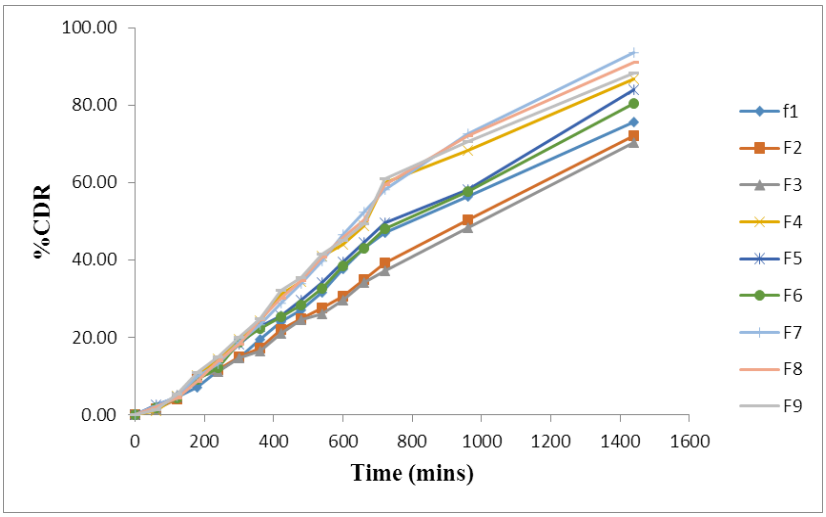

Figure 4: Dissolution Profile of Formulation Batches (F1-F9) (Time Vs %CDR)

4.Optimization

Statistics are apply to the results obtained from General Factorial Design in which Two independent Variables varied namely Sodium chloride (Nacl) (X1) and HPMC (X2) and their effect is recorded on dependent Variable namely % drug release (Y1).

Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings. Drug release was directly proportional to the level of osmotic agent. The values of X_1 and X_2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of both the variables on the selected responses. Decreasing the concentration of the Sodium chloride (Nacl) resulted in the decrease in the release. Variable caused significant change in the responses. From this data optimum concentration of Nacl and HPMC was found.

A) Drug release

Table 7: ANOVA for % drug release (Y1)

Source	Sum of Squares	Degree of Freedom	Mean Square	F value	P-value	Inference
Model	552.60	5	110.52	391.38	0.0002	Significant
A-Nacl	496.68	1	496.68	1758.87	<0.0001	
B-HPMC	48.34	1	48.34	171.17	0.0010	

Standard deviation = 0.53
R-Squared = 0.9985

The Model F-value of 391.81 implies the model is significant. There is only a 0.02% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > P" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms.

The Variance Inflation Factor (VIF) measured how much the variance of that model coefficient was inflated by the lack of orthogonality in the design and was calculated for % drug release. It was found to be near one indicating good estimation of the coefficient. Similarly R1-squared was near to zero which led to good model. The values of Prob > F were less than 0.05, which indicated model terms were significant.

The quadratic model obtained from the regression analysis used to build a 3-D graph's in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots.

The response surface plot was generated using Design Expert 8.0.4 software presented in (Figure 5). To observe the effects of independent variables on the response studied % drug release. From response surface 3 level factorial design was chosen using quadratic design mode.

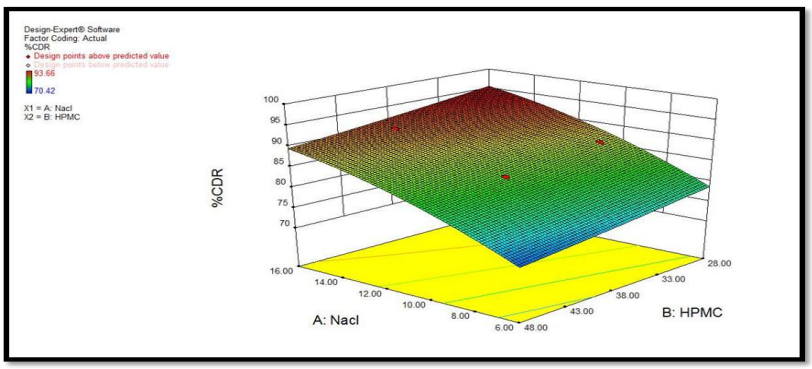

Figure 5: Surface Response plot showing effect of Sodium chloride and HPMC on release

B) Contour plot

The contour plot showing effect of Sodium chloride and HPMC on release is shown in (Figure 6).

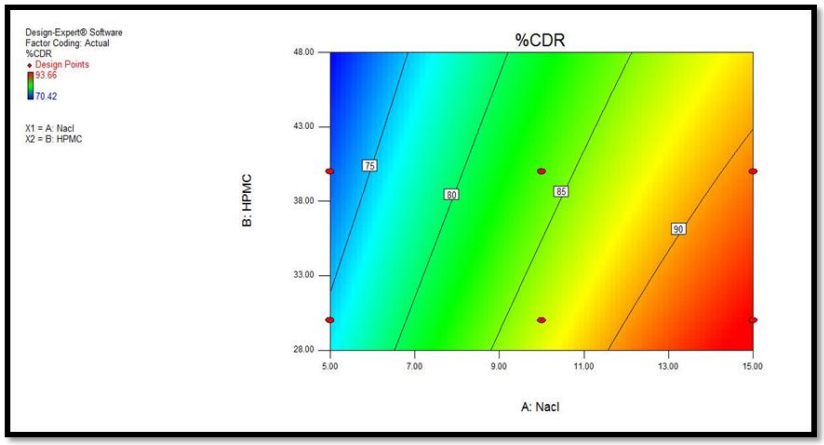

Figure 6: Contour plot showing effect of Sodium chloride and HPMC on drug release.

C) Design summary and Response summary

Design summary is shown in (Table 8)

Table 8: Design Summary

Factor	Name	Unit	Type	Minimum	Maximum	-1 Actual	+1 Actual	Mean
A	Nacl	Mg	Numeric	5.00	15.00	05	15	10
B	HPMC	Mg	Numeric	30	50	30	50	40

D) Perturbation plot

The perturbation plot is shown in (Figure 7)

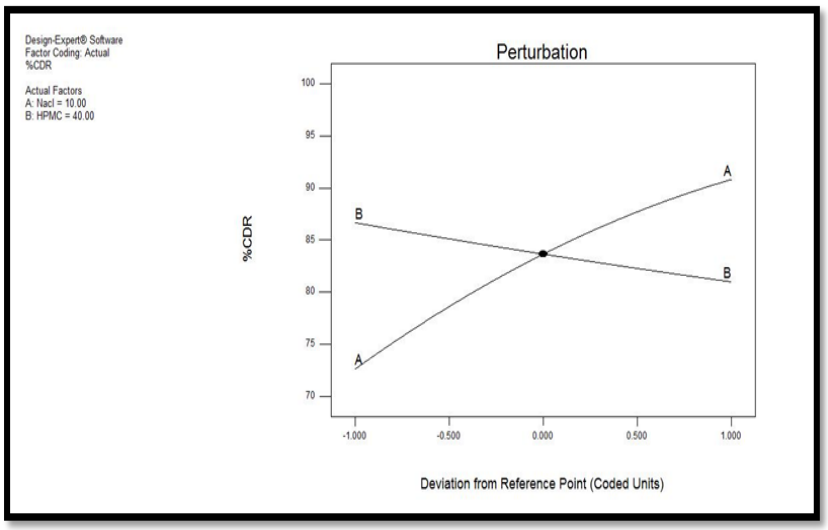

Figure 7: Perturbation

5.Dissolution Kinetics

In present study dissolution was analyzed by PCP Disso Version 3software to study the dissolution kinetics is given in (table 9).

Table 9: Kinetic treatment of prepared Cyproheptadine Hydrochloride osmotic tablet formulations

Formulation code	Coefficient of determination (R^2)				
	Zero order	First order	Higuchi square root	Hixon crowell	Korsemeyer plot
F1	0.9888	0.9763	0.8932	0.9882	0.9949
F2	0.9982	0.9706	0.8931	0.9872	0.9927
F3	0.9988	0.9711	0.8936	0.9872	0.9914
F4	0.9820	0.9666	0.9045	0.9868	0.9799
F5	0.9943	0.9549	0.8996	0.9824	0.9941
F6	0.9933	0.9671	0.9004	0.9873	0.9916
F7	0.9884	0.9245	0.8908	0.9708	0.9941
F8	0.9855	0.9467	0.8949	0.9793	0.9919
F9	0.9817	0.9641	0.9065	0.9864	0.9797

Different kinetic treatments (zero order, first order, Higuchi's square root equation and Korsmeyer treatment) were applied to interpret the release of Cyproheptadine hydrochloride from different matrices The best formulation i.e. Optimized formulation **F7** follow Zero order kinetics $\mathbf{r^2 = 0.9884}$ and $\mathbf{n < 0.5}$ for all batches. So the drug release is of fickian release.

6.Stability Studies

Table 10: Characteristics of optimized formulation F7 after 3 months storage

Parameter	Initial sample of optimized formulation	After storage at 25±2°c / 60% RH, For 3 month
	F7	F7
Hardness	4.26 kg/cm^2	4.21 kg/cm^2
Drug content	97.85 %	97.45 %
% Drug Released (After 3 mth)	93.66 %	93.04 %

Table 11: In vitro drug release study of formulation F7 stored at 25°c / 60% RH for 3 months

Time (Hrs.)	Cumulative Drug Release (%) F7 Batch	Cumulative Drug Release (%) F7 Batch
	Before 3 month	After 3 month
0	0.00	0.00
1	2.22	2.01
2	4.72	4.02
3	9.93	9.12

4	13.23	12.54
5	18.79	17.08
6	23.15	22.65
7	28.81	27.02
8	33.91	31.55
9	39.67	38.22
10	46.53	45.45
11	52.34	51.89
12	58.1	57.31
16	72.52	71.02
24	93.66	93.04

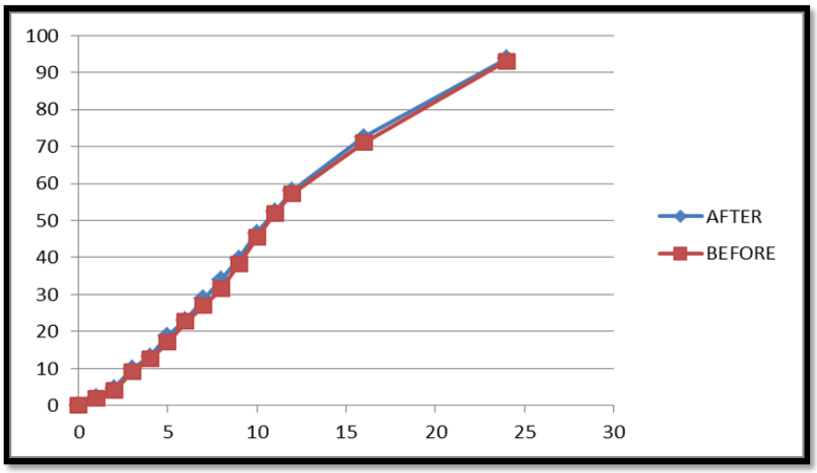

Figure 8: Dissolution profile of optimize F7 formulation before and after 3 months

The selected formulation were wrapped in aluminum foil and stored at 25±2ºc temperature for 3 months. After 3 months the formulation F7 were evaluated for the hardness, drug content and in vitro % drug release. It was observed that there was no significant variation in the physical appearance, average weight, hardness and loss of drying after placing the tablets at various temperature and humidity conditions for a period of 3 months. Also the cumulative % drug release data showed that each of the formulation released a drug amount, within the limits laid down as per the ICH guidelines for stability studies.

CONCLUSION

The results of experimental studies of Cyproheptadine osmotic tablets proved that the granules of Cyproheptadine showed good flow properties, tablet evaluation tests are within the acceptable limits, IR spectral analysis proved that there was no drug-excipients interaction, the kinetic studies revealed that optimized formulation followed zero order drug release kinetics and stability studies revealed that all the formulations were found to be stable after storing at temperature of $45^{o} \pm 2^{o}$, 75% ± 5% relative humidity for 3 months. Thus the

results of the above study clearly indicated that Developed osmotically controlled release tablet of Cyproheptadine provide release of drug at a predetermined rate and for a predetermined time.

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