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Research Article

FORMULATION AND EVALUATION OF HYDRODYNAMICALLY BALANCED SYSTEM FOR VERAPAMIL HYDROCHLORIDE- GASTRO RETENTIVE APPROACH

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ABSTRACT

Objective: The aim of present investigation was to develop HBS system (sustained release) for Verapamil HCl used for the treatment of hypertension. The drug delivery system was designed to retain the system in stomach so that increase in absorption of drug and decrease in dosing interval.

Methodology: Single unit capsules were filled with weighed mixture of Verapamil HCl and polymers such as HPMC K15M, sodium alginate and magnesium stearate.

Results: The release profile and retention of capsule depending upon the amount of HPMC K15M and sodium alginate concentration. Optimization was done using 3^2 factorial design considering two independent factors at three levels. Data was evaluated statistically by Stat Ease Design Expert 8.0.1 software. The optimized batch F9 gave drug release at 12 h 65.27±0.35 and at 24 h 92.39±0.21 which consisted of 35% HPMC K15M and 30% Sodium alginate.

Conclusion: The Hydrodynamically balanced system of Verapamil HCl was achieved which can increase the gastric residence time as well as bioavailability and thereby showing increased therapeutic efficacy.

Keyword: Hydrodynamically balanced system, HPMC K15M, Sodium alginate, 3^2 factorial design.

INTRODUCTION

Until now numerous oral controlled drug delivery systems have been developed to prolong drug release. The crucial point in this respect is that the drug has to be absorbed well throughout the whole gastrointestinal tract. For drugs with a narrow absorption window in the GIT or acting locally in the stomach, the challenging task is not only to prolong drug release but the retention of the dosage form in the upper gastrointestinal tract. Such dosage form having density less than that of the gastric fluid floats on the gastric juice for an extended period of time while slowly releasing the drug. [1]

In gastro retentive delivery system there is two approaches one is effervescent drug delivery system and another one is non effervescent delivery system i.e. hydrodynamically balanced system. The most commonly used excipients in non effervescent FDDS are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene.[2] One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier. [3,4] The need for gastro retentive dosage forms (GRDFs) has led to extensive efforts in both academics and industry towards the development of such drug delivery systems.

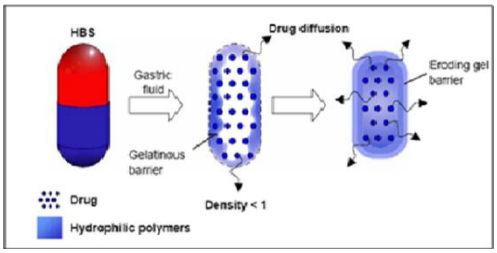

Fig. 1: Hydrodynamically balanced system

Verapamil is an inhibitor of calcium ion influx (slow calcium channel blocker or calcium entry blocker) and causes dose-dependent inhibition of the transmembrane influx of calcium ions into muscle cell via the 'L' channel it is stable in acidic pH, has a narrow therapeutic absorption window in the GI tract. [5,6] So verapamil hydrochloride meeting the criteria for selection as the drug candidate to be formulated as a hydrodynamically balanced system. The objective of present study was to formulate floating capsules of Verapamil HCl to deliver the drug continuously with set limits of dissolution profile and minimum floating time of 24 h.

MATERIALS AND METHODS

Materials

Verapamil HCl was obtained as a gift sample from Nicholas Piramal, Mumbai (India.) Sodium alginate was obtained from kamman Corporation as gift samples. HPMC K15M was obtained from Colorcon Asia Pvt. Ltd. (Goa) as a gift sample.

Methods

Preformulation study

1. Fourier Transform Infrared (FTIR) Spectroscopy

Fourier Transform Infrared (FTIR) spectroscopy was conducted. The procedure consisted of, placing a drug sample in FTIR cuvette. The drug sample was placed in the light path and scanned over the range of 4000-400 cm^{-1} on Shimadzu FTIR Prestige-21. The obtained spectrum was recorded. [7,8]

2. Drug-excipient compatibility study

The compatibility of drug and excipients was studied by DSC with their physical mixture in ratio 1:1. The mixtures were prepared by triturating the drug with excipients and the mixtures were stored for 24 hours at room temperature. The mixtures were then filled in aluminum cup and the DSC thermogram was obtained.

3. Drug solubility study

The solubility of the drug was determined in different pH ranges from pH 1.2 to 7.4. Various pH solutions were prepared by adjusting the pH of the deionised water by 1N HCl or 1N NaOH. In 2ml of different pH

solution excess quantity of drug was added and dissolved to obtain saturated solution of drug. The solution was shaken intermittently to assist the attainment of equilibrium with undissolved particles. The solution was filtered after 24 h, diluted with 0.1N HCl solution and analyzed by UV spectrophotometer at 278 nm. [9,10]

Formulation study

1. Characterization of Blend of factorial batches

The powder blend were evaluated for parameter like bulk density, tapped density, angle of repose, compressibility and Hausner ratio. [11,12]

2. Formulation of HBS system

Single unit capsules were formulated with the help of low density floating polymers which upon administration would attain a density of less than that of gastric fluids and therefore would float. HPMCK15M and sodium alginate were used as hydrophilic swellable polymer or release retardant polymer and magnesium stearate as lubricating agent.

Verapamil HCl (180 mg) was weighed accurately and mixed with different ratios of the polymer in mortar pestle for 10 min to achieve a homogenous blend. Magnesium stearate was added to the blend and mixed for additional 3 min. factorial design batches were formulated according to formulae given in Table 1. The final blend was filled into hard gelatin capsules (size00) manually using slight compression. For each formulation, a total of 50 capsules were prepared for evaluation.

3. Factorial Design

A factorial design is used to evaluate two or more factors simultaneously. The treatments are combinations of levels of the factors. The advantages of factorial designs over one-factor-at-a-time experiments 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 Factorial Designs. A factor is simply a categorical variable with two or more values, referred to as levels. A study in which there are 2 factors with 3 levels is called a 3^2 factorial design. For the present work 3^2 factorial designs was selected. The two independent variables selected were HPMC K15M (X_1) and sodium alginate (X_2). And the nine formulations formulated as per the experimental design.

Table 1: Formulation of Factorial Batches

Ingredients (mg)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Verapamil HCl	180	180	180	180	180	180	180	180	180
HPMC K15M (X_1)	100	100	100	120	120	120	140	140	140
Sodium alginate(X_2)	80	100	120	80	100	120	80	100	120
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total weight	365	385	405	385	405	425	405	425	445

Evaluation of capsules

The capsules were evaluated for various parameters as follows and observations recorded in Table 6. [13,14]

Appearance

The general appearance of the capsules includes the morphological characteristics like size, Shape, colour, etc.

Weight variation

To study weight variation, an intact capsule was weighed. Capsule was opened without losing any part of shell and the content was removed as completely as possible. The shell was weighed. The weight of the content was the difference between the weighing. The procedure was repeated for further 19 capsules. [15]

***In vitro* buoyancy study**

All formulations were subjected to buoyancy test. It was done by using USP type-2 apparatus at 50rpm maintained at 37±5°C. The capsules were immersed in 900ml jar containing 0.1 N HCl as dissolution medium. The time for which the capsule remained buoyant was observed and was taken as floating time [16, 20]

Dissolution Studies

The release rate of Verapamil HCl from floating capsules was determined using USP dissolution test apparatus Type II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCl at 50 rpm. The temperature of the medium was maintained at 37 ± 0.5ºC and the study was carried out for 24 hrs. Aliquot of 5 ml were withdrawn at an interval of 30 min, 1hr, 2hr, 3 hr, 4hr, 6 hr, 8hr, 10hr, 12hr, and 24hr respectively. The withdrawn samples were replaced with fresh dissolution medium. The volume made up to 10 ml with 0.1N HCL. The samples were analyzed at 278 nm. [17]

Drug content

Weigh and powder capsule. Weigh accurately a quantity of the powder containing 0.1g of Verapamil hydrochloride, shake with 150ml of 0.1M hydrochloric acid for 10minutes, add sufficient 0.1M hydrochloric acid to produce 200ml and filter. Dilute 10ml of the filtrate to 100ml with water and measure the absorbance of the resulting solution at the maximum at about 278nm. Calculate the content of C27H38N2O4, HCl taking 118 as the specific absorbance at 278nm.

Kinetics of Drug Release

The dissolution profile of all the formulations were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model. The observations were summarized in the Table. 8.

In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of n i.e. release exponent was calculated. The n value is used to interpret the release mechanism [18]

Analysis of Data by Design Expert Software

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively as shown Table.2. The statistical treatment and interpretation of data was done by Stat Ease Design Expert 8.0.1 software. The data were also subjected to 3-D response surface methodology to study the interaction of independent variables.

Table 2: Amount of Variable in 3^2 Factorial Design Batches

Coded Values	Actual Values (%)	
	X_1	X_2
-1	25	20
0	30	25
+1	35	30

To study the effect of independent variables HPMC K15M (X_1) and sodium alginate (X_2) on dependent variables Q_{12}(%Drug release at 12 hr) and Q_{24} (% Drug Release at 24hr). A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses. [19]

$$Y=b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+B_{11}X_1^2+b_{22}X_2^2$$

Where, Y is the dependent variable

Optimization

Optimization was performed using Design Expert 8.0.7.1 software to obtain optimized batch.

RESULT AND DISCUSSION

A. Preformulation study

1. Fourier Transform Infrared (FTIR) spectroscopy

The IR spectrum of Verapamil HCl was recorded, and it was in accordance with the reported peaks. It is shown in Figure. 2. The structural assignments for the characteristics absorption bands are listed in Table. 4.

2. Drug-Excipient Compatibility Study

DSC thermogram of Verapamil HCl showed endothermic peak of fusion, having peak maximum of 148.00^{0}C. This was in accordance with the reported (140-144^{0}C). DSC thermogram was shown in Figure. 3. The possible interaction between the drug and the polymers was studied by differential scanning calorimeter (DSC). There was no considerable change in DSC endothermic values, comparing pure Verapamil hydrochloride and with the excipients (HPMC K15M, sodium alginate, and magnesium stearate) which indicated the absence of any interaction between drug and excipient used in the preparation. Peak value was obtained at 154.39^{0}C which is very much nearer to pure drug. DSC thermogram is shown in Figure 4.

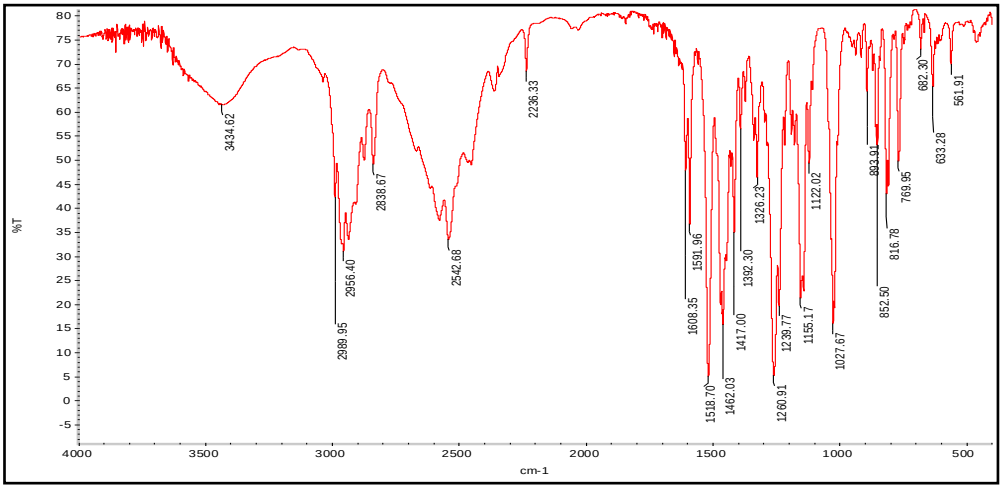

Fig. 2: FTIR of Verapamil HCl

Table 3: IR Ranges for Different Functional Groups in Verapamil Hcl

S. No.	Energy (wave numbers cm^{-1})		Assignment
	Reported	Sample	
1	3030-2860	2989.95	C-H stretching of methyl and methylene gr.
2	2840	2838.67	C-H stretching of methoxy gr.
3	2800-2300	2542.68	N-H stretching of protonated Amine
4	2236	2236.33	C=N gr. Alkyl nitrile
5	1607, 1591 & 1518	1608.35, 1591.96 & 1518.70	Streching of benzene ring
6	1262	1260.91	C=O stretching

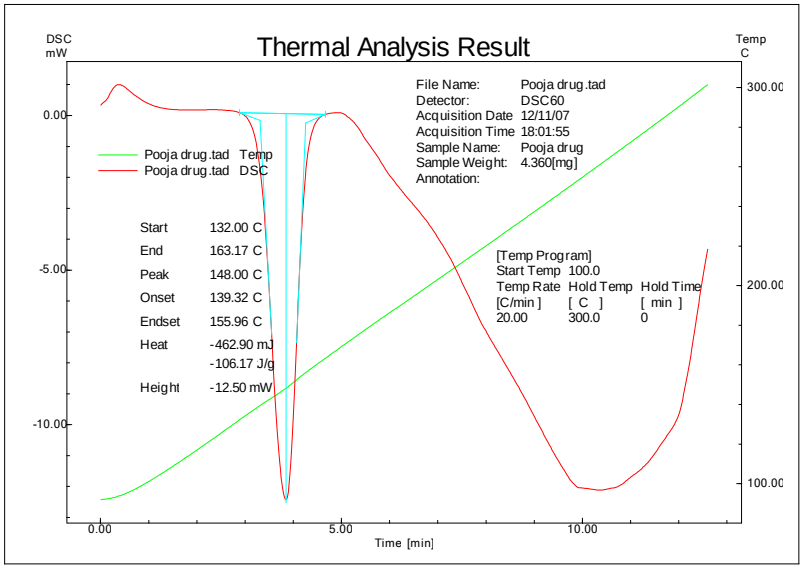

Fig. 3: DSC Thermogram of Verapamil Hcl

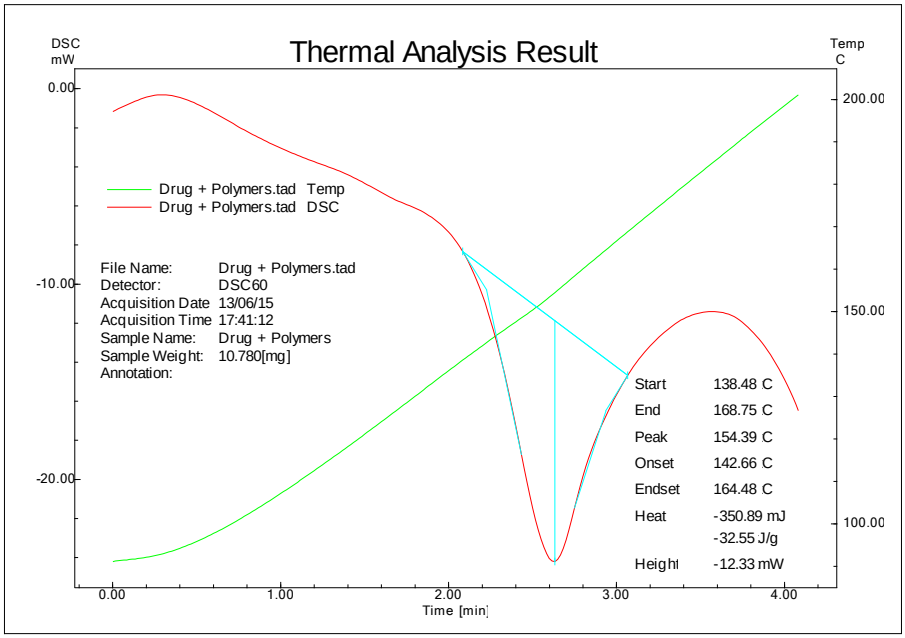

Fig. 4: DSC Thermogram of Verapamil Hcl+ Polymers.

3. Drug Solubility Study

The solubility study of Verapamil HCl in different pH solution was carried out. Verapamil HCl is having pH dependent solubility. At lower pH, the solubility was high and as the pH was raised from pH 1.2 to 7.4 solubility decreases. At pH 7.4 it has very less solubility. The results were shown in Table 5.

Table 4: Drug solubility study

S. No.	Solution pH	Solubility (mg/ml)
1	Deionised water, adjusted to pH 1.2	224.42
2	Deionised water, adjusted to pH 4.5	145.26
3	Deionised water, adjusted to pH 6.8	6.88
4	Deionised water, adjusted to pH 7.4	0.536

B. Formulation study

1. Characterization of blend of factorial

Table 5: Characterization of blend of factorial

S. No.	Angle of repose(⁰)	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner ratio	Flowability
1	26.85±0.01	0.2561±0.19	0.32±0.06	15.48±0.49	1.13±1.10	Good
2	27.5±0.05	0.264±0.07	0.334±0.08	13.54±0.53	1.15±1.05	Good
3	27.3±0.07	0.2758±0.08	0.3052±0.09	15.42±0.89	1.18±1.07	Good
4	28.29±0.09	0.2456±0.05	0.2789±0.21	12.76±1.10	1.17±0.97	Good
5	25.65±0.01	0.2864±0.011	0.315±0.01	14.94±0.48	1.15±0.83	Good
6	27.35±0.03	0.2589±0.10	0.2959±0.09	13.26±0.67	1.14±1.12	Good
7	26.45±0.06	0.2678±0.08	0.3098±0.17	15.52±0.94	1.17±1.06	Good
8	28.54±0.04	0.2875±0.09	0.2845±0.19	15.24±0.54	1.18±0.95	Good
9	27.84±0.05	0.2749±0.01	0.2937±0.13	14.61±0.12	1.12±0.76	Good

Appearance

All the capsules of the factorial design batches were transparent with capsule size 00.

Weight variation

According to I.P. for capsules weighing 300mg or more, not more than two capsules differ from the average weight by 7.5% deviation. The percent deviation in weight variation from average value for all formulation of factorial design batches were within limit.

2. *In vitro* buoyancy study

The preliminary studies revealed that polymer HPMCK15M below 20% was not able to float for a period of 24 h and possessed poor capsule integrity. Thus, polymer HPMC K15M was used above 20% and sodium alginate was incorporated for capsule integrity for further studies.

The factorial design batches were then formulated and in vitro buoyancy was studied. As the amount of HPMC K15M increased, total floating time also increased as observed in the formulations F1-F3 (25%), F4-F6 (30%), F7-F9 (35%) respectively. This may be accounted to increased gel strength of the matrices. The mechanism involved in buoyancy of the HBS capsule, is the rapid dissolution of capsule shell in the gastric fluid, with subsequent hydration and swelling of the surface polymer producing a floating mass.

Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy.

3. *In vitro* drug release study

Preliminary studies showed that HPMC K15M alone not able to sustain release for 24 h and this may due the fact that HPMC upon contact with water forms a hydrogel layer which act as gel boundary for the delivery system, but it fail to retard the release of drug through the matrix because of the high solubility of drug into the stomach pH. The incorporation of sodium alginate not only retard the drug release but also prolonged the drug release for 24 h. from batches F1 to F9 HPMCK15M and sodium alginate concentration increased, so drug release decreased. The drug release of F1-F9 batches was found to be 100.02%-92.93%. The 3^2 factorial designed batches were formulated and in vitro drug release was studied.

4. Kinetics of Drug Release

In present study the dissolution were analyzed by PCP Disso Version 2.08 software to study the kinetics of drug release mechanism. The results showed that most of the factorial design batches followed Peppas model. The R^2 value of Peppas model was found close to one as shown in Table.8.

Table 6: Evaluation of factorial batches

Formulation	Appearance	Weight variation	In vitro buoyancy	Drug content (%)	% Drug release
F1	Transparent, size00	364.24±0.05	24	99.60±0.17	100.02±0.63
F2	Transparent, size00	382.59±0.04	24	98.60±0.46	98.26±0.15
F3	Transparent, size00	403.92±0.13	24	99.73±0.89	97.18±1.52
F4	Transparent, size00	384.61±0.17	24	100.10±0.37	97.65±0.51
F5	Transparent, size00	403.84±0.61	24	103.54±0.24	94.62±0.71
F6	Transparent, size00	424.10±0.08	24	101.80±0.84	95.77±0.67
F7	Transparent, size00	404.15±0.09	24	99.90±0.93	95.79±0.97
F8	Transparent, size00	423.84±0.05	24	98.23±0.67	92.73±0.54
F9	Transparent, size00	444.24±0.03	24	98.40±0.51	92.39±0.21

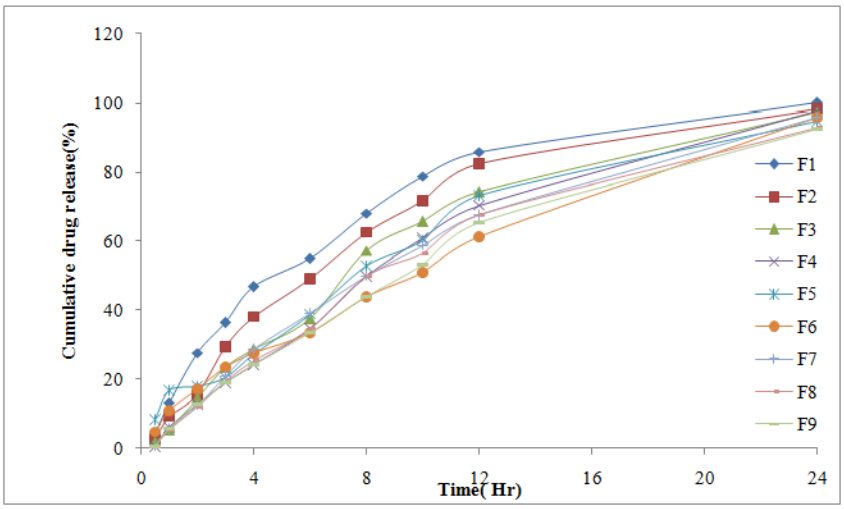

Fig. 5: Percent Cumulative drug release of batches F1 to F9

Table 7: Kinetics of drug release

Formulation code	R^2						
	Zero order	1st order	Matrix	Peppas	Hixon crowell	n	k
F1	0.7746	0.7748	**0.9937**	0.9928	0.7747	0.5130	0.0213
F2	0.7903	0.7905	**0.9915**	0.9901	0.7904	0.5334	0.0194
F3	0.8054	0.8056	0.9925	**0.9940**	0.8056	0.5251	0.0188
F4	0.8490	0.8491	0.9943	**0.9964**	0.8491	0.5405	0.0176
F5	0.8653	0.8654	0.9925	**0.9954**	0.8654	0.5984	0.0151
F6	0.8907	0.8908	0.9892	**0.9971**	0.8908	0.5875	0.0147
F7	0.8933	0.8934	0.9907	**0.9977**	0.8934	0.5850	0.0145
F8	0.9334	0.9335	0.9803	**0.9974**	0.9335	0.5767	0.0133
F9	0.9273	0.9274	0.9841	**0.9987**	0.9274	0.5936	0.0129

Korsmeyer et al. (1983) developed a simple, semi-emperical model, relating exponentially the drug release to the elapsed time (t):

$$F_t = at^n$$

Where, a is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism, and the function of t is M_t / M_∞ (fractional release of drug).

Peppas (1985) used this n value in order to characterise different release mechanisms, concluding for values for a slab, of n=0.5 for Fick diffusion and higher values of n, between 0.5 and 1.0, or n=1.0, for mass transfer following a non-Fickian model (Table 8).

In present study the n values were found to be between 0.5-1, indicating non-Fickian diffusion or anomalous transport. The n (0.5<n<1) value also revealed the drug release mechanism via diffusion coupled with erosion.

5. Statistical analysis by design expert software

The Q_{12} and Q_{24} for the nine batches (F1-F9) that the Q_{12} and Q_{24} values strongly dependent on the selected variables. The fitted regression equation relating the response $Q_{12}$and Q_{24} was shown in the equations. The equation conveyed the basis to study of the effect of variables. The regression coefficient values re the estimates of the model fitting. The r^2 was high indicating the adequate fitting of the quadratic model.

Effect of formulation variables on amount of drug release at 12 h (Q_{12}) and 24h (Q_{24}).

Final equation in terms of coded factor

Q_{12} =+70.51-7.01 *A- 3.87*B+2.3 *A*B+5.66*A^2-3.55*B^2

Q_{24} =+95.17-2.43* A- 1.35* B-0.14 * A * B+0.051* A^2+1.26* B^2

The quadratic model for the amount of release at 12 and 24 h was found to be significant. An increase in drug to polymer ratio caused decrease in the amount of drug release at 24 h and this may be due to hindrance caused by swollen hydrogel network to the drug diffusion through polymer matrix.

The relationship between the variables was further elucidated using response surface plot. If X_1 and X_2 is kept at lower level then there is increased in drug release, and if they kept at high level then there is decrease in drug release so as the polymer concentration increase from (F1-F9), the drug release is decreases. The Q_{12} and Q_{24} for the nine batches (F1-F9) showed a wide variation (i.e.61.14-85.82% and 89.42-99.83%, respectively).

6. ANOVA Study

The coefficients of X1 and X2 were found to be significant at p <0.05, hence confirmed the significant effect of both the variables on the selected responses. Increasing the concentration of the HPMC K15M and sodium alginate resulted in the decrease in the release of Verapamil hydrochloride. Overall both the variables caused significant change in the responses.

The model F value calculated was 19.04 and 19.41 for Q12 and Q24, respectively which implied the models were significant. The values of Prob>F were less than 0.05, which indicated model terms were significant. In all cases A, B, AB, A2 and B2 were significant model terms. However, both the variables favour the preparation of sustained release floating capsules of Verapamil hydrochloride.

7. Response surface analysis

The response surface plot were generated using Design Expert 8.0.7.1 Stat ease USA software presented in figure 6 and 7 to observe the effects of independent variables on the response studied such as Q12 and Q24, respectively. Graphical presentation of the data helped to show the relationship between the response and the independent variables. The information given by graph was similar to that of mathematical equations obtained from statistical analysis. The response surface plots showed that various combinations of independent variables X1 and X2 may satisfy any specific requirement (i.e. maximum drug release with floating upto24hrs) while taking into consideration of various factors involved in dosage form.

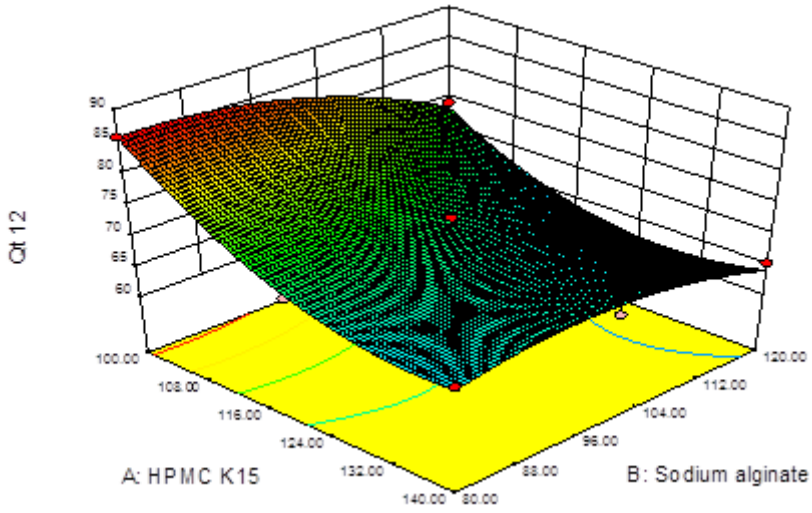

Fig. 6: 3D Response Surface Plot for Q12

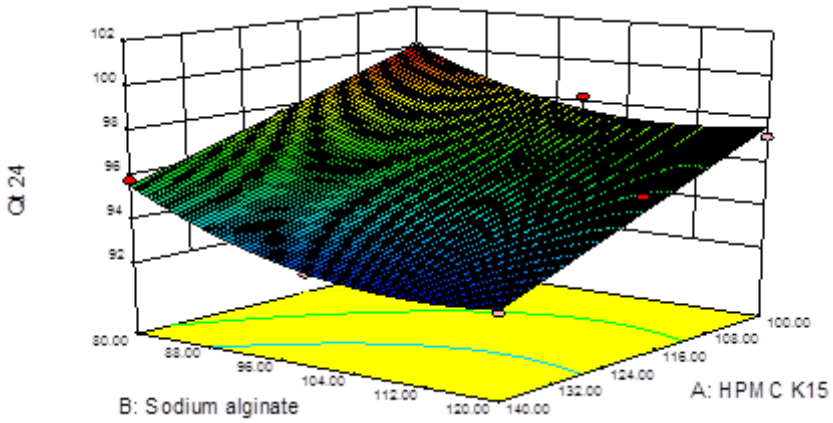

Fig. 7: 3D Response Surface Plot for Q24 (HBS)

Optimization

Optimization was performed using design expert 8.0.7.1 software. Numerical optimization and graphical optimization methods were used for optimization of formulation.

- **Numerical optimization** – Goals were set for response (i.e. drug release) then software generated optimal solutions. It gave two solutions. As shown in diagram below,

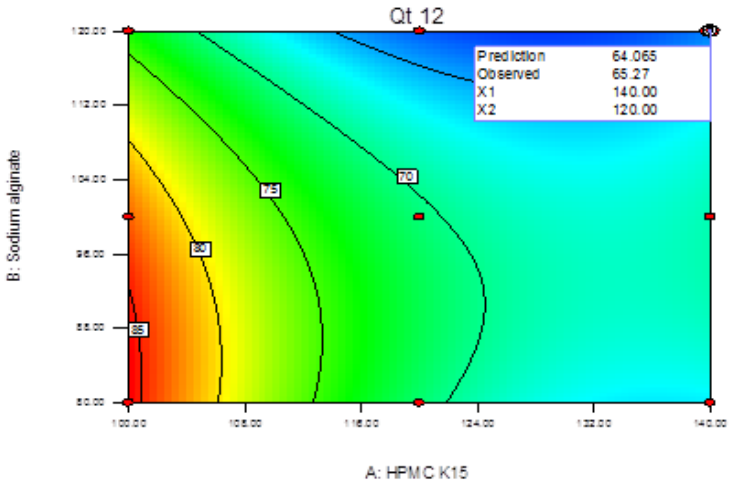

Fig. 8: Optimization for drug release at 12hrs

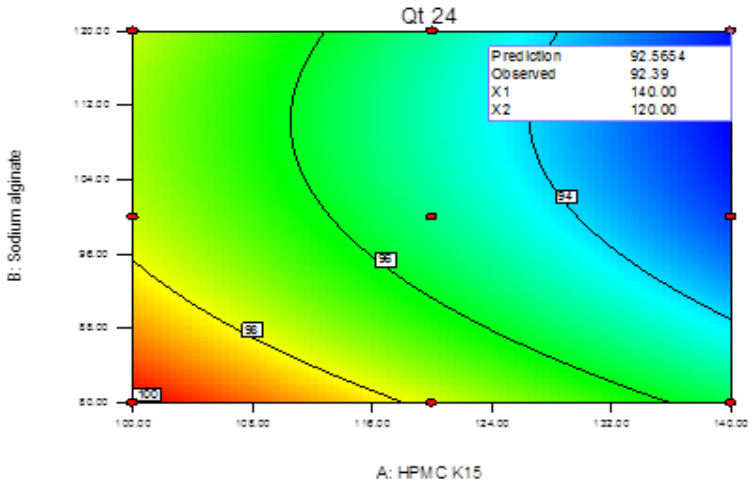

Fig. 9: Optimization for drug release at 12hrs

Optimization for drug release at 24hrs

- **Graphical optimization** –after setting minimum or maximum limits for each response software created an overlay graph highlighting the area of operability. As shown below.

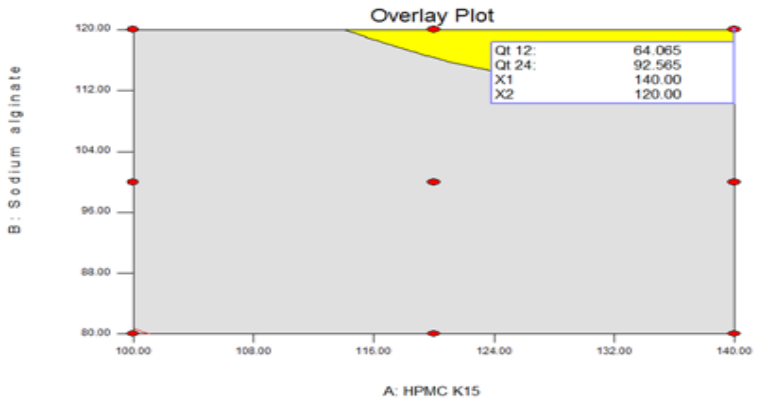

Fig. 10: Graphical optimization overlay plot

From the optimization methods used batch F9 was found to be in desirability range. The composition of that batch was 140 mg HPMC and 120 mg Sodium alginate. So batch F9 was selected as optimized batch.

CONCLUSION

The Hydrodynamically balanced system of Verapamil HCl was achieved which can increase the gastric residence time as well as bioavailability and thereby showing increased therapeutic efficacy. Formulations F9 showed sustained release and good retention for 24 hr. A 3^2 full factorial design was performed to study the effect of formulation variables on in vitro floating time and the release properties by applying a computer optimization technique. The mechanism of the drug release from the optimized formulation was confirmed as non-fickian diffusion or anomalous transport. The statistical approach for formulation optimization is a useful tool, particularly in simultaneously evaluating several variables. The observed responses were in close agreement with the predicted values of the optimized formulations, demonstrating the feasibility of the optimization procedure in developing hydrodynamically balanced system of Verapamil HCl.

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