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STATISTICAL DESIGN AND EVALUATION OF A SIMVASTATIN GASTRIC FLOATING TABLET

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ABSTRACT

The study is to design and statistical optimization of Simvastatin floating tablets using 3^2factorial design for the identification of best formula composition to overcome the first-pass effect and reduce the frequency of administration. The tablets were prepared by wet granulation method using HPMC, $NaHCO_3$, PVP K-30, Citric acid Talc and Magnesium stearate. Totally 4 batches were prepared using different drug to polymer ratio for preliminary trial. The prepared floating matrix tablets were evaluated for FT-IR, hardness, thickness, friability, weight variation, floating property and *In vitro* release study etc. the results of the study indicates all the prepared formulations had desired floating lag time and constantly floated on dissolution medium maintaining the matrix integrity. Best preliminary trial batch (B3) selected for optimization using 3^2factorial design. Independent variables were HPMC (X1) and PVP K-30 (X2). Hardness, Buoyancy, Total floating time and *in-vitro* release study for 12 h were considered for dependent variables. Batch f3 selected from the optimization batch through in-vitro characterization techniques. This means relaxation of polymer chains, water diffusion which influences the drug release mechanism. This dosage form reduces the frequency of administration, improved bioavailability and patient compliance. The optimized batch could useful for further large scale production.

KEYWORDS: Floating drug delivery system, Simvastatin, optimization, 3^2 factorial design

INTRODUCTION

Controlled drug delivery systems have been introduced to overwhelm the drawbacks of fluctuating drug levels associated with conventional dosage forms. Gastro retentive system can remain in the gastric rejoin for several hours and significantly prolong gastric residence

of the drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, improve solubility of drugs that are less soluble in a high pH environment. It has application also for local drug delivery to the stomach and proximal small intestine. Simvastatin is a derivative of lovastatin and potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (hydroxy methylglutaryl COA reductases), which is the rate-limiting enzyme in cholesterol biosynthesis. It is widely prescribed in the treatment of hypercholesterolemia. Being a BCS class II drug, It often shows a dissolution rate limited oral absorption and high variability in oral absorption and high variability in pharmacological effects. The drug undergoes extensive first pass excretion in the liver and hence, the availability of the drug to the general circulation is very low (5%). Therefore gastro retentive drug delivery system might be advantageous for Simvastatin. The main aim of the research work is to develop and optimize the oral floating tablets containing Simvastatin. The present study focused to formulate floating drug delivery system of simvastatin using HPMC, PVP sodium bicarbonate and citric acid to release the drug in controlled manner in upper gastro intestinal tract to minimizes the pre-systemic metabolism of drug.

The specific aim of study is to investigate the influence of PVP and HPMC on the Physico chemical properties of controlled release floating tablet containing Simvastatin using 3^2 factorial design in order to achieve a stomach specific delivery system and large scale production.

The optimized Simvastatin floating tablets could reduce the frequency of administration, cost effective, patient compliance and suitable for large scale production.

MATERIALS AND METHODS

Simvastatin (Fourrts India, Chennai), HPMC (HIMEDIA, Mumbai), PVP (HIMEDIA, Mumbai), Sodium bicarbonate (NICE chemicals, Kochi), Magnesium stearate (Loba Chemie, Mumbai), Talc (Prowess Lab Chemicals, Ottappalam). All the excipients were of USP/NF grades and all other chemicals used were of analytical grade.

Preparation of Simvastatin Floating tablet

The tablets of simvastatin were prepared by wet granulation method using PVP paste in the mixture of Drug, HPMC, PVP, sodium bicarbonate and citric acid. Here, Sodium bicarbonate and Citric acid were using as gas generating agents and PVP as binding agent.

Each formulation was composed of drug and excipients in various proportions as shown in table 1 for the formulation Simvastatin, HPMC, PVP K30, Sodium bicarbonate and citric acid were sifted through mesh (#10) and mixed well in a mortar. The paste of PVP in ethyl alcohol used as granulating agent. Then the mass again pass through mesh (#10) and dried in oven at 60^0c for 30 min. Magnesium stearate and talc were added as lubricant and compressed into tablet.[68]

Evaluation of Simvastatin Floating Tablet

Precompression Parameters like Angle of repose, Bulk and tap density, Hausners ratio Compressibility index were determined. Post compression parameters like Thickness Hardness Weight variation test, Friability test, Buoyancy study, *In-vitro* dissolution study, Drug content estimation, were performed.

Release kinetic study

In-vitro release kinetics was performed by plotting Cumulative percentage release of drug and time in Percentage drug release profile, zero-order plot, first-order plot, Higuchi Plot, and Korsemeyer peppa's plot separately and from that R^2, k, n values were calculated.

Statistical optimization: The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and choice of responses. Optimization has been done by using 3^2 full factorial design, where the amount of HPMC (X1) and the amount of PVP K30 (X2) were taken as independent variables.

RESULTS

Table. 1: Composition of Simvastatin floating tablet.

S. No	Ingredients (mg)	B_1	B_2	B_3	B_4
1	Simvastatin	10	10	10	10
2	HPMC	70	70	70	70
3	PVP	27	27	27	27
4	Sodium bicarbonate	60	65	70	75
5	Citric acid	45	40	35	30
6	Glucose	5	5	5	5
7	Magnesium stearate	3	3	3	3
8	Talc	30	25	35	30
9	Total weight	250	250	250	250

- All the quantities are in mg.

Table. 2: Summary Results of Preliminary Trail Batch.

Code	Average Weight of 20 tablets	Friability (%)	Drug content (%)	Hardness (Kg/cm^2)	Buoyancy (S)	Total Floating time(h)	*In-vitro* release at 12th Hour
B1	244.77	0.67	93.00	1.46	3	7	94.00
B2	255.14	0.83	91.34	3.13	8	8	90.19
B3	248.37	0.42	74.86	3.60	3	11	76.95
B4	246.86	0.55	93.71	2.23	2	8	92.12

Table. 3: *In-vitro* Release Kinetics of Preliminary Batch of Simvastatin Floating Tablets.

Code	Zero order plot		First order plot		Higuchi plot	Korsemeyer peppa's plot	
	R^2	k	R^2	k	R^2	R^2	n
B1	0.988	8.088	0.020	-0.019	0.975	0.993	1.114
B2	0.962	7.800	0.935	0.077	0.946	0.936	1.555
B3	0.975	5.929	0.914	-0.043	0.936	0.994	1.566
B4	0.980	7.560	0.900	-0.076	0.957	0.955	1.471

Experimental Design for Optimization

Table. 3: Independent and dependent Variables.

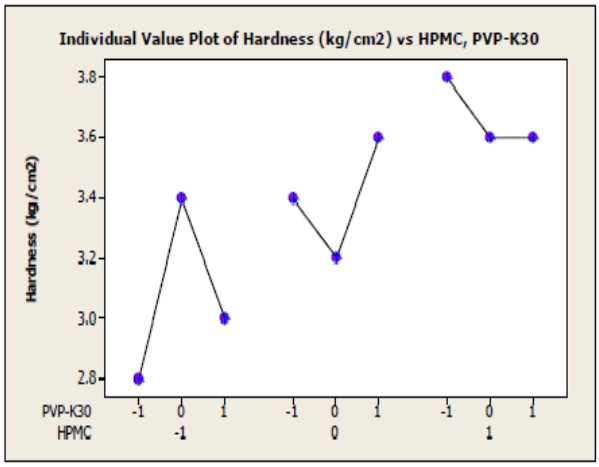
Test Run	HPMC (X_1)	PVP (X_2)
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Table. 4: Factorial design for preparation of 9 optimized batch.

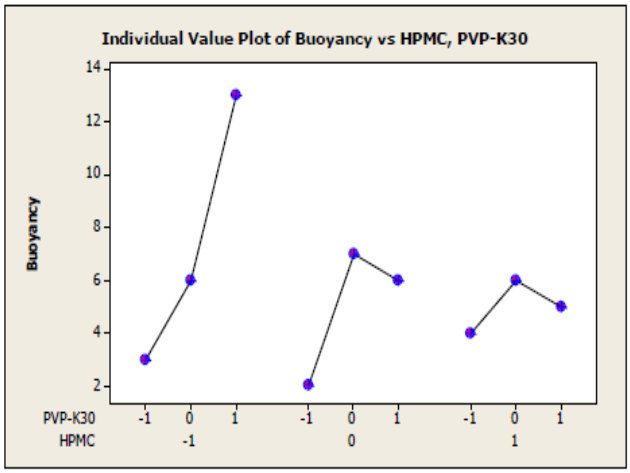
Independent variables (mg)	Dependent variables
HPMC (X1)	Hardness (Y1)
PVP K-30(X2)	Buoyancy (Y2)
	Total floating time (Y3)
	In-vitro release study (%) (Y4)

Table. 5: Evaluated Parameters of Floating Tablets for Factorial Design.

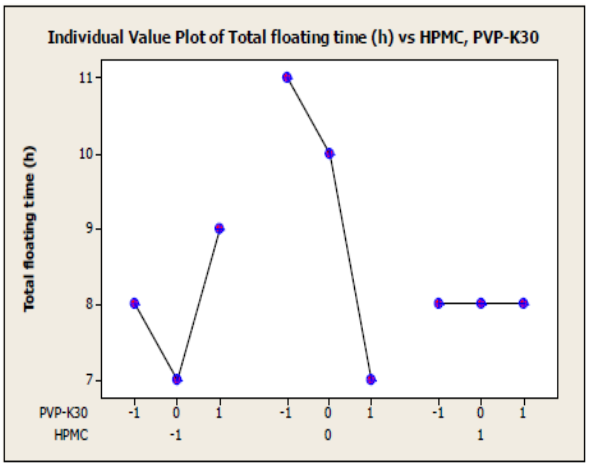
Code	Independent variables		Dependent variables			
	X1	X2	Y1 Kg/cm^2	Y2 (s)	Y3 (h)	Y4 (%)
F1	-1	-1	2.8±0.2	3±.0.5	8±1	92.19±0.37
F2	-1	0	3.4±0.4	6±0.5	7±0.5	86.41±0.46
F3	-1	+1	3.0±0.3	13±.0.5	9±1	78.81±0.57
F4	0	-1	3.4±0.1	2±.0.3	11±0.5	97.80±0.28
F5	0	0	3.2±0.1	7±.0.6	10±1	86.40±0.32
F6	0	+1	3.6±0.3	6±.0.5	7±0.5	90.22±0.23
F7	+1	-1	3.8±0.2	4±.0.1	8±0.4	94.00±0.74
F8	+1	0	3.6±0.1	6±.0.5	8±0.2	86.45±0.62
F9	+1	+1	3.6±0.1	5±.0.4	8±0.6	94.00±0.17



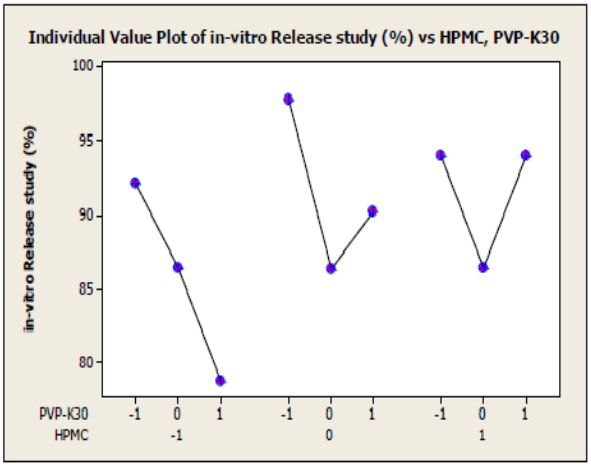
Effect of formulation variables on hardness (Factorial fit Y1 vs X1, X2)



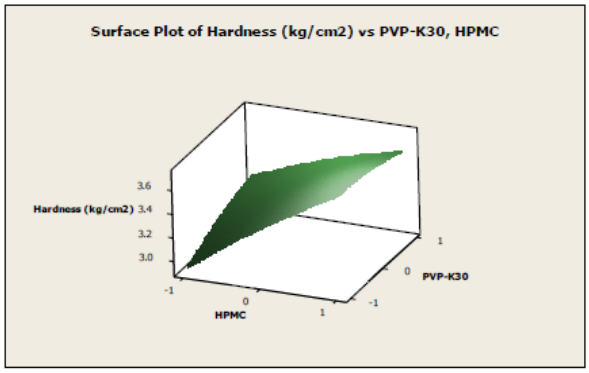
Effect of formulation variables on Buoyancy (Factorial fit Y2 vs X1,X2)

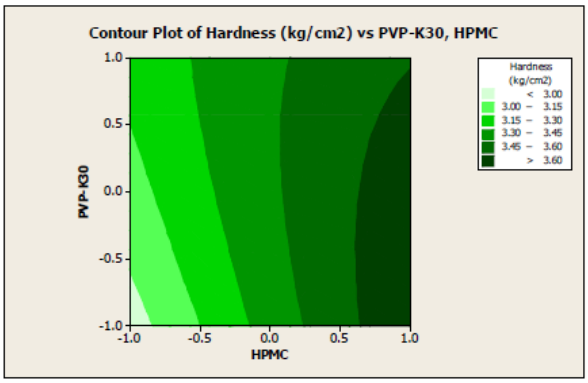


Effect of formulation variables on Total floating time(Factorial fit Y1 vs X1, X2)

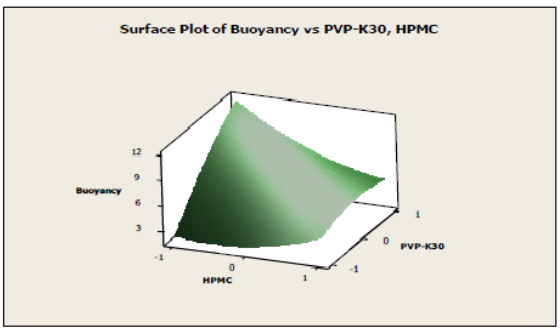


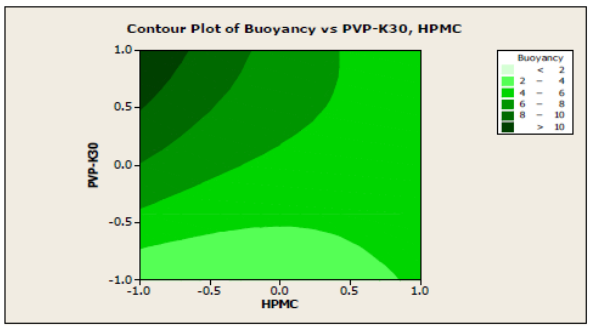
Effect of formulation variables on test Buoyancy test (Factorial fit Y2 vs X1,X2)



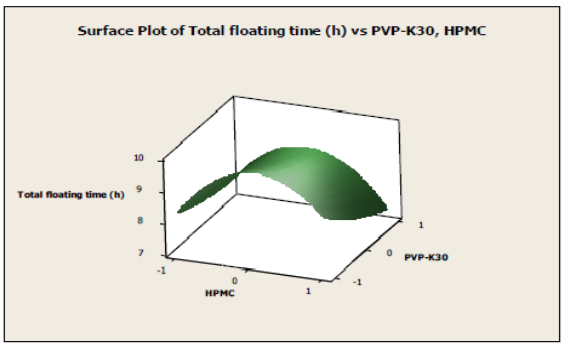


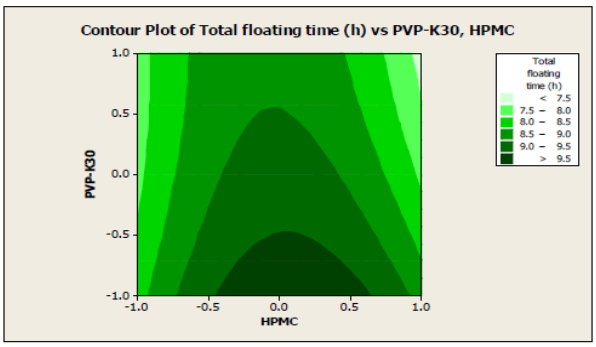
Effect of formulation variables on hardness test (Factorial fit Y1 vs X1, X2)



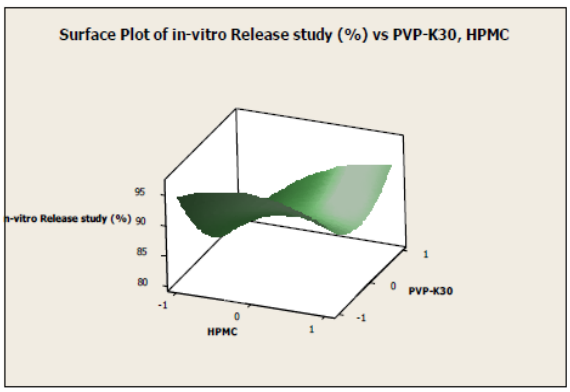


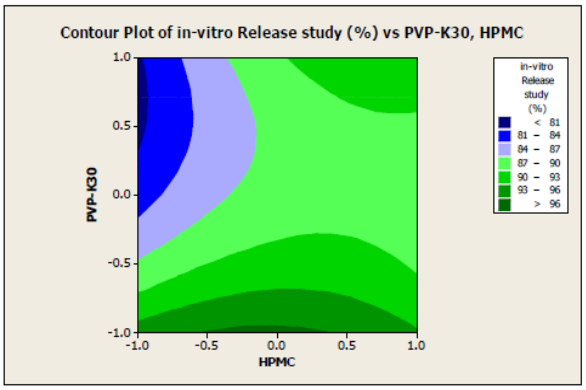
Effect of formulation variables on Buoyancy test (Factorial fit Y2 vs X1,X2)





Effect of formulation variables on Total floating time (Factorial fit Y2 vs X1,X2)





Effect of formulation variables on Total floating time (Factorial fit Y2 vs X1,X2)

Statistical optimized formula (Polynomial Equations for factorial fit)

Hardness (Y1) = 3.42+ 0.30 X1+0.003 X2-0.10 X1X2

Buoyancy (Y2) = 5.55- 1.16 X1+ 2.50 X2- 2.25 X1X2

Total Floating Time (Y3) = 9.22 + 0.00 X1-0.50 X2- 0.25 X1X2

In-vitro release (Y4) = 88.30+ 2.84 X1- 3.49 X2 + 3.34 X1X2

Table. 6: Summary results of regression analysis.

Coefficient	b_0	b_1	b_2	b_{12}	R^2
Y1	3.42	0.30	0.03	-0.10	0.40
Y2	5.55	-1.16	2.50	-2.25	0.12
Y3	9.22	0.00	-0.50	-0.25	0.84
Y4	88.30	2.84	-3.49	3.34	0.13

DISCUSSION

The main aim is the preparation of optimized Simvastatin floating tablets to target the upper GIT. The prepared tablets could reduce the frequency of administration, low cost, improved efficacy and suitability for large scale production. The Simvastatin floating tablets were prepared by HPMC, PVP K-30, Sodium bicarbonate, Citric acid, Talc and Magnesium stearate for preliminary trail. Before the development of formulation the drug and excipients compatibility study was performed using FT-IR technique. FT-IR spectrum ruled out drug and excipient interaction. The granules developed and characterized for Bulk density, Tapped density, Carr's index, Hausners ratio and Angle of repose. The prepared tablets were characterized for Weight variation, Content uniformity, Friability, Hardness, Buoyancy, Total floating time, *in-vitro* release. The granules were compressed using Rimek minipress. In the preliminary trail B3 formulation selected according to the best characterization for optimization. A 3^2 factorial design was design was designed for optimization of Simvastatin floating tablet. In this HPMC (X1), PVP K-30 (X2) was selected for optimization. Response variables were Hardness (Y1), Buoyancy (Y2), Total floating time (Y3), and *in-vitro* release study (Y4) .The results of the study indicate increased concentration of HPMC and decreased concentration of PVP K30 increase the hardness of tablet and the study indicate that increased concentration of HPMC decrease the buoyancy time floating of tablet. While increased concentration of PVP K30 alone increased the lag time to float. The combined effects of HPMC and PVP positively increase the buoyancy time. The medium amount of HPMC (0) with decreased amount of PVP K30 show an increase in total floating time of tablet. Increasing concentration of HPMC increase the drug release pattern. While increase amount of PVP K30 shows slowdown the release pattern. When considering combined effect

of HPMC and PVP positively increase release pattern. The results of the optimization technique revealed f4 formulation was considered as optimized formulation because of longer floating time, reduced buoyancy and maximum *in-vitro* release pattern. All the formulation follows the controlled release pattern.

CONCLUSION

In the current work optimization of matrix floating tablets incorporating Simvastatin is describe. The most successful batch (f4) contained Simvastatin (10mg), HPMC (75mg), PVP K30(22 mg), Sodium bicarbonate (70mg), Citric Acid (35mg), Glucose (5mg), Magnesium stearate (3mg) and Talc (20mg). This formulation took 2 seconds to buoyant and have appropriate hardness (3.4kgcm^2). This dosage form reduces the frequency of administration improved bioavailability and patient compliance. The optimized batch could useful for further large-scale population.

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