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Research Article

Innovation and optimization of Rizatriptan Benzoate Oromucosal Tablets by Using Design of Experiment (DoE)

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Abstract

The present study deals with the formulation and study of oromucosal tablets of Rizatriptan Benzoate (RB) using different bioahdesive polymer. Nine formulations were prepared by using direct compression method. Hydroxypropyl methyl cellulose (HPMC K4M), Gum acacia and Sodium Alginate were used as buccal mucoadhesive polymer. Ethyl cellulose (EC) used as an impermeable backing layer. FTIR Studies showed no interaction with drug, polymer and excipients. 3^2 full factorial design was used to optimize the effect of independent variable such as concentration of HPMC K4M (X1) and concentration of Sodium Alginate (X2) on dependent variables such as % drug release (Y1), Mucoadhesive strength (Y2), Swelling Index (Y3). The prepared buccal mucoadhesive tablets were evaluated for weight variation, Hardness, Surface pH and drug content, content uniformity, swelling index, In-vitro drug release study and mucoadhesive strength. In-vitro drug release study showed sustained drug released for 9 hours. The In-vitro release kinetics reveals that formulation DE5 follows Higuchi model for drug release.

Keywords: Buccal Mucoadhesion, HPMC K4M, Sodium alginate, Design of experiments.

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INTRODUCTION:

In immediate release dosage form repetition of dosing frequency is most prominent cause of patient incompliance. Few drawbacks associated with IR dosage form like maintenance of dose, difficult to achieve steady state level.[1] considering drawbacks of IR dosage form sustained release dosage form come into demand. Few drug candidatures were not suitable for drug deliver through oral route, due to its nature of first pass hepatic metabolism and enzymatic degradation in GIT.[2, 3, 4] Some class of drugs like peptides and proteins were prohibited for oral administration.[4, 5] Drug degradation in GIT circumvented by administering drug through buccal route [5, 6]

Buccal mucoadhesive drug delivery system (BMDDS) or oromucosal tablets was considered favorable site for by pass hepatic metabolism, avoidance of enzymatic degradation and avoidance of presystematic elimination in GIT [4,7]. Buccal mucosa surrounded with rich blood supply and it has relatively permeable. In buccal mucosa drug directly reaches into systematic circulation through jugular vein.[7, 8, 9] Buccal drug delivery system should provide good bioadhesion, Ability of bioadhesive polymer to retain at the mucous layer and prolong the drug release in sustained manner.[10]

Migraine is associated with series of head pain that is often throbbing and it may be severe. In migraine attacks symptoms are nausea, vomiting, patient having more sensitive to light, sound, or movement. Migraine is a disease condition in which headache is a common symptom. Headache is due to dilation of blood vessels. Triptan class of drugs used for the treatment of migraine. Triptan class of drug based on principal of dilated blood vessel by narrowing in to its normal size.[1, 10] 5 Hydroxy Tryptamine (5-HT) is drug of choice and it initiate the vasoconstrictor phase of migraine and involved in neurogenic inflammation of the affected blood vessels. Migraine is the third most common neurovascular disorder in the world with an estimated global prevalence of 14.7% [11] Chronic migraine affects around 1-2% of the world population.[12] Triptans class of drugs and 5-HT1B and 5-HT1D receptor agonists, are contemplate to be the first line therapy in the treatment of migraine attack.

Triptan class of drugs (Sumatriptan) prone for first pass hepatic metabolism and after oral administer low bioavailability due to first pass hepatic metabolism. Triptan class of drugs prefers for subcutaneous injection and considered good candidature for buccal drug delivery[13]

Rizatriptan also shows effect of first pass hepatic metabolism[14]

Though there is advance and novel drug delivery system introduced and they are quite effective. Till most of the pharma industries involved in the development of buccal mucoadhesive drug delivery system. There are some

commercial products available in market in the form of tablets, oral liquid, oral paste, oral mucosal gel, and lozenge.

Now a day's concept of Quality by Design (QbD) was useful and popular among pharmaceutical industry and academic researcher, Quality is important parameter and it should build from initial stage of development, continous improvement and throuout the product lifecycle management. Safety and efficacy are key point should consider during stages of product development. Elements of QbD plays the important role in development of Quality products. Quality target product profile (QTPP), Critical Quality Attribute (CQA), Critical Process Parameters (CPP), Critical Material Attribute (CMA), Risk Assessment, Design Space. Control Strategy and Life cycle management these are elements of quality by design. As per regulatory requirement and ICH (Q82) Pharmaceutical development enhances implementation of QbD. QbD approach used during product development. Design of experiment (DOE) used for implementation of QbD.[15, 16]

MATERIALS AND METHODS:

Mannitol was used of Innophos, Microcrystalline Cellulose (MICCEL 102) was used from Ankit Pulp and Boards, HPMC K4M was used from Ashland, Gum acacia was used from supplier Kanthilal Brothers, Sodium alginate was collected from supplier loba chem. Colloidal silicon Dioxide was from Evonik Degussa, Magnesium stearate was from Vasa Pharmachem and Ethyl cellulose was from Ashland. The entire chemicals were of analytical grade and double distilled water was used throughout the experiment.

Compatibility Studies:

Compatibility studies were performed by using Fourier transforms infrared spectrometer. Infrared spectra of pure drug and drug with polymer were recorded by potassium bromide method using Fourier transform infrared spectrometer (FT-IR). The powder sample was uniformly mixed with dry powder of potassium bromide. This mixture sample was compressed into transparent disc under high pressure by using special dies. This disc was placed in IR spectrometer and spectrums were recorded. The scanning was done from the range 400–4000 cm_1.

Evaluation of Rizatriptan Benzoate API:

Rizatriptan Benzoate API evaluated by using physical test like description, bulk density, tapped density, Hausner ratio. Outcome of physical evaluation represented in table no. 1

Table 1: Physical Evaluation of API

Sr. No.	Physical Test	Results
1	Description	White to off white crystalline powder
2	Bulk Density(g/ml)	0.30 g/ml
3	Tapped Density(g/ml)	0.52 g/ml
4	Hausner Ratio	1.73 (Very Poor flow)
5	Compressibility Index (%)	42.30% (Very Poor flow)

Preparation of Rizatriptan Oromucosal Tablets

Rizatriptan Benzoate (RB) oromucosal tablets were prepared by direct compression Method.

HPMC K4M, Gum Acacia and Sodium Alginate were used as mucoadhesive polymer. RB available in market with 5mg and 10 mg strength. For research work 10 mg strength was selected. Rizatriptan Benzoate Salt form 14.530 mg equivalent to 10 mg of Rizatriptan. Steps involved in the manufacturing of weighing and sifting, dry mixing, blending, lubrication and Compression.

Oromucosal tablets fabricated by using polymer, combination of polymer in the ratio of 1:1, 1:2, 1:3 Formulation details mentioned in table no.2 All the excipients were sifted through a mesh 40#, lubricant was sifted through mesh 60#. All the excipients were uniformly mixed in polybag for 10 minutes. Lubricant was added and final blend was mixed for 3 minutes in polybag. Tablet was compressed on 200 mg tablet weight. For evaluation of lubricated blend different test were performed like Bulk density, Tapped density, Angle of repose, Compressibility Index and Hausner ratio. Compressed tablets were evaluated by using hardness test, thickness, diameter, friability and weight variation.

Table 2: Formula composition

Ingredients (mg/tablet)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rizatriptan Benzoate	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53
HPMC K4M	25	---	---	25	25	25	25	25	25
Sodium Alginate	---	25	---	25	50	75	---		---
Gum acacia	---	---	25	---	---	---	25	50	75
Mannitol	118.97	118.97	118.97	93.97	68.97	43.97	93.97	68.97	51.26
Microcrystalline Cellulose (MICCEL 102)	10	10	10	10	10	10	10	10	10
Magnesium stearate	1	1	1	1	1	1	1	1	1
Colloidal silicon Dioxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethyl cellulose	30	30	30	30	30	30	30	30	30
Total weight	200	200	200	200	200	200	200	200	200

Evaluation of chemical test of compressed tablets of Rizatriptan Benzoate:

a. Determination of Drug Content [5, 6, 7, 18, 19, 20]

Manufactured oromucosal tablet were evaluated for drug content. 10 tablets sample were crushed by using mortar pestle and make fine powder. 200 mg of fine powder (equivalent to 10 mg of Rizatriptan Benzoate) transferred in to 50 ml of volumetric flask. Flask containing 30 ml of methanol was stirred regularly for 30 minutes.

b. Surface pH Study [2, 5, 7, 18, 20, 21]

To evaluate the irritation effect of mucosa. pH of the prepared buccal mucoadhesive tablets. Buccal mucoadhesive tablets were poured in beaker containing 10 ml of distilled water. After 9 hours electrode was kept into the beaker for pH measurement.

c. Swelling Index (SI) [2, 5, 7, 18, 20, 21]

Swelling index test was evaluating swelling behavior of fabricated mucoadhesive buccal tablets. (W1) indicate initial weight of tablets. (W2) indicate final weight of tablet after completion of experiment. Buccal mucoadhesive tablet was kept in petridish containing 5 ml of phosphate buffers pH 6.8. After 9 hours tablet removed and excess amount removed by filter paper.

$$\text{Swelling Index} = \frac{W2 - W1}{W2} \times 100$$

Where, W1 - initial weight of the tablet,

W2 - weight of the tablet after swelling.

d. Ex vivo mucoadhesive Strength [2, 5, 4, 6, 7, 17, 19, 20, 21]

Ex vivo mucoadhesion strength was performed by using sheep buccal mucosa. Fresh mucosal membrane collected and utilized for testing of mucoadhesive strength. Physical balance was utilized with slight modification. Left side of pan removed. Cleaned and washed mucosa. Used for experimental study. Already removed left side of pan of balance tight with thick thread of sufficient length was hanged. End side of thread of a glass stopper with steady surface was tied. Buccal mucosa was tied by using thread over the base an inverted position to the 50 ml glass beaker. 50 ml glass beaker was placed in a 500 ml beaker. pH 6.8 phosphate buffer filled in 500 ml glass beaker in such a way that buffer reaches the surface of mucosal membrane and buccal mucosa keeps it moist for longer time. Buccal tablet was then adhered to glass stopper from one side of membrane. Weight was placed at one side of the pan mostly on right side of the pan. Weight of 5 g was removed from the right side of the pan. Sequentiality increase weight on the pan until tablet was separated from mucosal membrane.

e. *In-vitro* Drug Release Study [5,6,7,17,19]

I*n-vitro* release of Rizatriptan Benzoate Oromucosal tablets was estimated by using dissolution apparatus according to USP Type II apparatus i.e. Paddle. Bath temperature maintained 37±0.5°C. Speed of paddle was 50 rpm Volume of dissolution medium was 900 ml.

pH 6.8 phosphate buffer was used for dissolution study. The impermeable layer of the tablet was stick to glass slide and glass slide kept at the bottom of the dissolution bowl. 5 ml samples were withdrawn frequent time interval time and same amount of fresh dissolution media was added. Invitro drug release was estimated after 1, 2, 3, 4, 5, 6, 7, 8, 9 hours. Withdrawn samples were filtered by using filter paper. UV-spectrophotometer was used for determination of In vitro drug release at 227 nm.

f. Drug release kinetics [5,2,6,7, 25, 26]

The data obtained from all the formulations were fitted into various mathematical models including zero order, first order, Higuchi, Hixon Crowell and korsmeyer –Peppas release models.

g. Residence (mucoadhesion) time [20, 21]

USP disintegration apparatus test was used with modification. Sheep buccal mucosa was isolated from connective tissue. Sheep mucosal membrane was clean and washed twice with required amount of distilled water and then followed by phosphate buffer. 3 to 4 cm long mucosal membrane was separated and the glued to the surface of a glass slide. Impermeable layer of the tablet was wetted with few drops of phosphate buffer pH 6.8. Mucoadhesive buccal tablet was stick to the mucosal membrane .The glass slide was kept in such a way that modified disintegration apparatus was allowed to up and down direction. Mucoadhesive tablet was kept in such a position that tablet was completely immersed in the 6.8 phosphate buffer. The beaker was filled with 800 mL of 6.8 phosphate buffer and was kept at 37 ± 1 °C. The time required for detachment of the tablet from the buccal mucosa. Observed time was recorded as the mucoadhesion time.

h. In vitro buccal permeability studies [5,6,7,20,21]

Permeability is important parameter in the absorption of oral route of drug administration.

Franz diffusion apparatus was used for experimentation of In-vitro buccal permeation study. Collected sheep buccal mucosa stored in phosphate buffer pH 6.8. Separated buccal mucosa clamped in between donor and receptor compartment of diffusion cell. 2 ml of phosphate buffer filled in donar compartment. The receptor compartment was filled with adequate quantity of pH 6.8 phosphate buffer. Continuous stirring and movement of magnetic bead at constant and slow speed used for maintaining hydrodynamics in the compartment. One ml of sample was withdrawn at regular intervals of time and analyzed by using UV spectrophotometer.

i. Optimization of formulation by using 3^2 full factorial designs [15, 19, 22, 23, 24]

Optimization is the important aspect during formulation development product. 3^2 full factorial design implemented for evaluation of two or more factors simultaneously. Study in which two 2 factors and three levels are involved in the experimental design and it called 3^2 full factorial designs. In the present work, 3^2 full factorial designs selected and 2 factors (X1: Amount of HPMC 4M, X2: Amount of Sodium Alginate were evaluated at three possible levels. (Y1:% Drug release, Y2: Swelling Index, Y3: Mucoadhesive strength) Total 9 formulations were prepared. Details of factorial design mentioned in table no. 3 & 4.

Table 3: 3^2 full factorial design.

Batch No.	X1- Amount of HPMC HPMC K4M	X2 -Amount Sodium Alginate
D1	-1	-1
D2	-1	0
D3	-1	+1
D4	0	-1
D5	0	0
D6	0	+1
D7	+1	-1
D8	+1	0
D9	+1	+1

Transaction of coded level in actual limit

Independent Variable	Real value		
	Low (-)	Medium (0)	High (+)
Amount of HPMC K4M(mg)	20	25	30
Amount of Sodium Alginate (mg)	70	75	80

A. Independent variable:
X1: Amount of HPMC K4M (in mg.) X2: Amount of Sodium Alginate (in mg.)

B. Dependent variable:
Y1: Mucoadhesive strength (g) Y2: In vitro drug release (%) Y3: Swelling Index (%)

Table 4: Optimization/DOE trials

Ingredients (mg/tablet)	Formulation code								
	DE1	DE2	DE3	DE4	DE5	DE6	DE7	DE8	DE9
Rizatriptan Benzoate	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53	14.53
HPMC K4M	20	20	20	25	25	25	30	30	30
Sodium Alginate	70	75	80	70	75	80	70	75	80
Mannitol	53.97	48.97	43.97	48.97	43.97	38.97	43.97	38.97	33.97
Microcrystalline Cellulose	10	10	10	10	10	10	10	10	10
Magnesium stearate	1	1	1	1	1	1	1	1	1
Colloidal silicon Dioxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethyl cellulose	30	30	30	30	30	30	30	30	30
Total weight	200	200	200	200	200	200	200	200	200

j. Stability study: Optimized batch (DE5) was loaded on accelerated stability condition (40^0 C/75% RH). After 1 month stability samples were withdraw and will be analyzed for description, drug content and Invitro drug release.

RESULT AND DICUSSION:

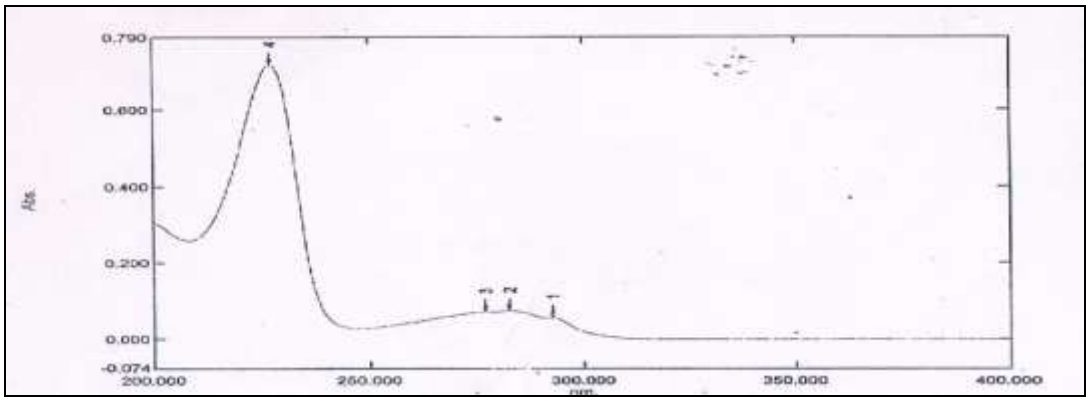
1. Standard calibration curve of RB in 6.8 phosphates Buffer:

Standard stock solution: By dissolving 10 mg of RB in 6.8 Phosphate buffer, sonicate for 10 minute (100 mcg/ml) Aliquots of 0.2,0.4,0.6,0.8,1.0,1.2 ml portion of the standard solution, transfer to a series of calibrated 10 ml volumetric flask and volume was adjusted with 6.8 phosphate buffer to get concentration of 2-12 mcg/ml. of Rizatriptan Benzoate.

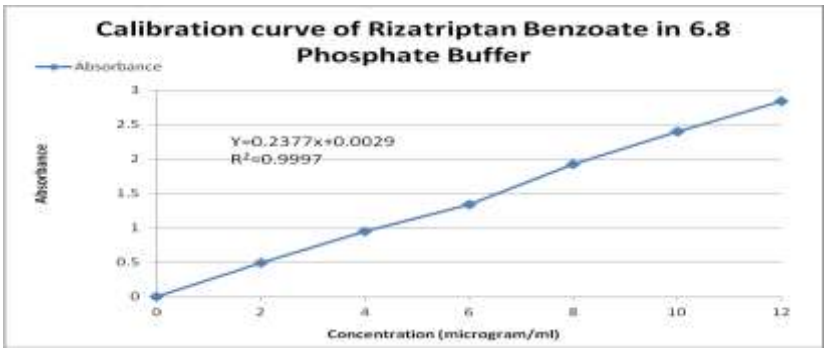
2. Determination of RB in 6.8 Phosphate Buffer:

Prepared solution was scanned in the range of 200-400 nm against blank 6.8 phosphate buffer. The absorption maximum of solution was found 227 nm.

3. Preparation of calibration curve: Aliquots of 0.1 to 1 ml portion of the standard solution transfer to a series of calibrated 10 ml volumetric flask and volume was adjusted. Calibration curve plotted as graph 1 a and lambda max determined at peak 4 (227 nm) for 6.8 pH phosphate buffer in graph 1b. Details of estimation of lambda max mentioned as table no.5



Graph 1 a: Lambda max for Rizatriptan Benzoate in 6.8 pH phosphate buffer.



Graph No.1 b: Calibration curve of Rizatriptan Benzoate in 6.8 pH phosphate buffer at 227 nm.

Table No.5: Lambda max of Rizatriptan Benzoate in 6.8 pH Phosphate Buffer

Concentration (mcg/ml)	Mean absorbance at (227 nm)±SD
0	0
2	0.489±0.003
4	0.954±0.002
6	1.339±0.003
8	1.921±0.006
10	2.399±0.005
12	2.841±0.004

b. Compatibility Studies

Based on the outcome of the FTIR study results, Drug was found compatible with selected combinations of polymer and excipients used in the formulations. The IR Spectrum of Rizatriptan Benzoate (API) absorption peak at 2988.34, 1567.39, 1375.77, 1136.88 and 1065.92. It is confirm that all the characteristics peaks that were present in the spectra of pure drugs replicate in the spectra of optimized formulation of Rizatriptan Benzoate Oromucosal Tablets i.e. 2956.57, 1570.95, 1397.51, 1130.89, and 1062.64. However, additional peaks were observed in optimized formulation which could be due to presence of polymer and excipients. FTIR spectra of Rizatriptan Benzoate API and FTIR spectra of Rizatriptan Benzoate Oromucosal Tablets mentioned as graph 2&3 respectively

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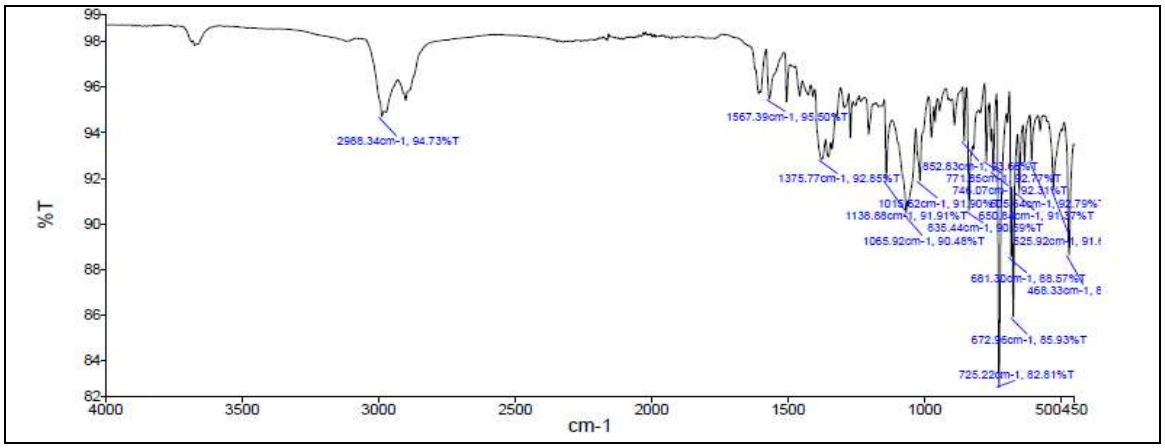
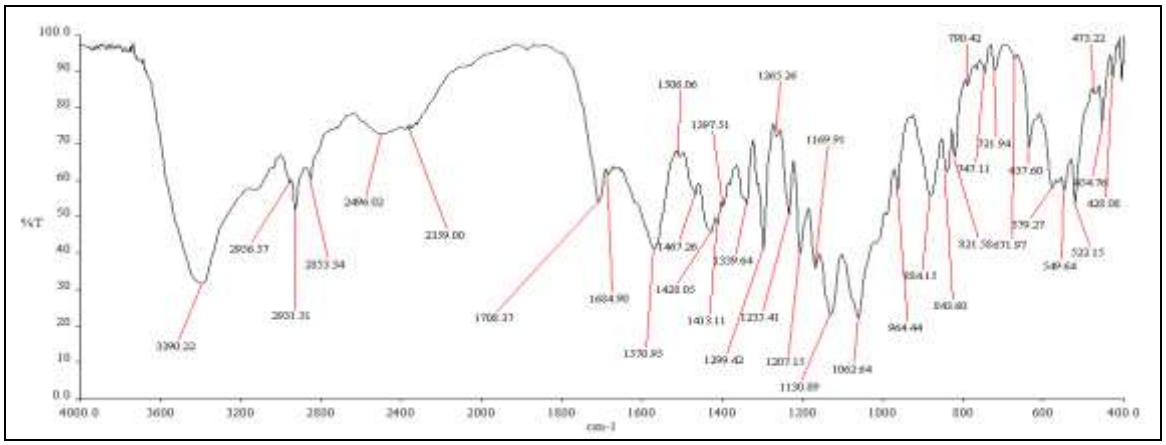


Graph 2: FTIR Spectra of Rizatriptan Benzoate



Graph 3: FTIR Spectra of Rizatriptan Benzoate Oromucosal Tablets

c. Precompression Evaluation

Bulk density of prepared batches was varying from 0.56 g/ml to 0.58g/ml. Tapped density of prepared batches was varying from 0.73 to 0.77 g/ml. Angle of repose of prepared batches was varying from 27.57^0 to $30.01^{0.}$ Based on values of Angle of repose it was denoted that blend having excellent flow property. Result of test of compressibility index was varying from 20.54 % to 25.97% and it was indicate that blend having passable flow. Hausner ratio varies in the range 1.25-1.35 and it was indicate that blend having passable flow. Details of pre compression parameters were mentioned in table 9. \

Table 9: Evaluation of Precompression Parameters of Blend

Formulation Code	Bulk Density (D_B)±SD	Tapped Density(D_T)±SD	Carr's Index (%CI)±SD	Hauser Ratio (HR)±SD	Angle of Repose (⌀)±SD
F1	0.56	0.73	23.28	1.30	27.57
F2	0.56	0.72	22.22	1.28	28.57
F3	0.58	0.73	20.54	1.28	29.52
F4	0.58	0.75	22.66	1.29	30.01
F5	0.57	0.77	25.97	1.35	28.10
F6	0.58	0.75	22.66	1.29	30.05
F7	0.59	0.76	22.36	1.28	26.50
F8	**0.58**	**0.73**	**20.54**	**1.25**	**29.45**
F9	0.58	0.74	21.62	1.27	27.80

d. Post Compression Parameters

The measured hardness of tablets of each batch ranged between 4.1 Kg/cm^2 to 4.7 Kg/cm^2

Tablets mean thickness were almost uniform in all the formulations and were found to be in the range of 3.00 mm to 3.20 mm. All the batches complies weight variation test as per pharmacopoeia specification. Percentage friability of all batches complies within 1 %. The percentage of drug content was in the range of 98.2% to 100.7% and found to be within acceptable limits. The values of post compression parameters were shown in table 10.

Table 10: Evaluation of Post compression parameters of Rizatriptan Benzoate Oromucosal Tablets.

Formulation Code	Hardness (kg/cm^2) ±SD	Thickness (mm)±SD	Individual Weight (m g) ±SD	Friability (%)±SD	Drug Content (%)±SD
F1	4.7 ± 0.69	3.10 ± 0.08	209.06 ± 0.19	0.10 ± 0.03	99.9 ± 0.16
F2	4.5 ± 0.90	3.12 ± 0.04	210.03 ± 0.17	0.15 ± 0.02	100.4 ± 0.13
F3	4.3 ± 0.76	3.20 ± 0.07	207.05 ± 0.25	0.23 ± 0.04	99.5 ± 0.21
F4	4.0 ± 0.80	3.13 ± 0.05	211.02 ± 0.18	0.08 ± 0.05	100.7± 0.15
F5	4.3 ± 0.78	3 .15 ± 0.09	206.07 ± 0.20	0.17 ± 0.03	98.9 ± 0.11
F6	4.2 ± 0.69	3.13 ± 0.02	205.09 ± 0.27	0.14 ± 0.09	98.2 ± 0.16
F7	4.2 ± 0.72	3.11 ± 0.09	209.03 ± 0.17	0.18 ± 0.06	99.3 ± 0.19
F8	**4.4 ± 0.63**	**3.15 ± 0.04**	**210.06 ± 0.25**	**0.20 ± 0.05**	**99.3 ± 0.17**
F9	4.1 ± 0.56	3.13 ± 0.06	208.04 ± 0.20	0.17 ± 0.08	99.1 ± 0.20

e. Surface pH study: Surface pH of all the formulation s F1 to F9 was evaluated and was varying in the range of 6.61 to 6.80.

f. Swelling Index (SI)

Due to hydrophilic nature of polymer, polymer gradually absorb water and swelling of tablet increased with increase in time. Higher the amount of water intake faster the rate and higher the extent of swelling. For formulation F1contain HPMC K4M the swelling index was 133.32, formulation F2 (Sodium Alginate) the swelling index was 143.51, formulation F3 (Gum acacia) the swelling index was 154.47, for formulation F4-F6 (HPMC K4M and Sodium CMC) the swelling index was vary in between 141.35-161.52. Formulation F7-F9 contains (HPMC K4M and Gum acacia) the swelling index was 160.34-175.45. The highest swelling index was observed 175.45 for formulations F9 which contains (HPMC K4M-15000 and Gum Acacia) in the ratio of 1:3. The swelling index values were shown in table no. 11,

Figure 8 a: Initial

Figure 8 b: After 1 Hour

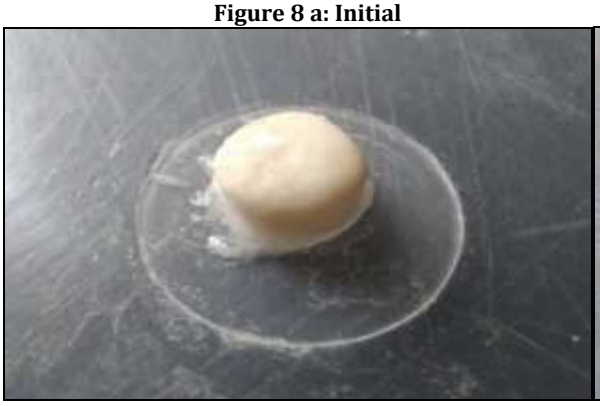


Figure 8 c: After 2 Hour

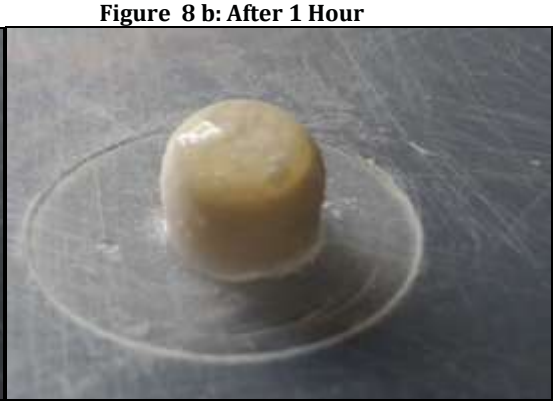


Figure 8 d: After 4 Hour

Figure 8 e: After 8 Hour

Figure 8 f: After 9 Hour

Figure 8 g: After more than 9 Hour

Table 11: Evaluation Parameters of Rizatriptan Benzoate Oromucosal Tablets.

Formulation code	Mucoadhesive strength(g)	% Swelling Index (9 Hour)	Surface pH ± SD	Residence Time (Mucoadhesion) (Hour)
F1	32.77 ± 0.18	133.32 ± 2.26	6.61 ± 0.30	7hours
F2	36.52 ± 0.34	143.51 ± 3.21	6.76 ± 0.27	7 hours
F3	39.57 ± 0.57	154.47 ± 2.52	6.70 ± 0.26	7 hours
F4	36.32 ± 0.42	141.35 ± 3.17	6.78 ± 0.37	> 9 hours
F5	40.32 ± 0.27	153.20 ± 1.60	6.79 ± 0.35	> 9 hours
F6	43.15 ± 0.62	161.52 ± 2.25	6.70 ± 0.30	> 9 hours
F7	39.62 ± 0.26	160.34 ± 2.14	6.80 ± 0.40	> 9 hours
F8	**44.45 ± 0.44**	**164.26 ± 3.12**	**6.79 ± 0.25**	**> 9 hours**
F9	45.37 ± 0.53	175.45 ± 2.26	6.70 ± 0.27	> 9 hours

g. Mucoadhesive Strength

Mucoadhesive strength for tablet formulation F1 contain HPMC K4M was 32.77 g, formulation F2 (polymer Sodium Alginate) was 36.52 g, formulation F3 (polymer Gum acacia) was 39.57 g for formulation F4-F6 contain (HPMC 4M: and Sodium Alginate) was 36.32-43.15 g, and for formulation F7-F9 contain (HPMC K4M: and Gum acacia) was 39.62-45.37 g.

The highest mucoadhesive strength was 40.32g for formulations F9 which contains (HPMC K4M: Sodium Alginate) in the ratio of 1:3.The results are illustrated in table no.11

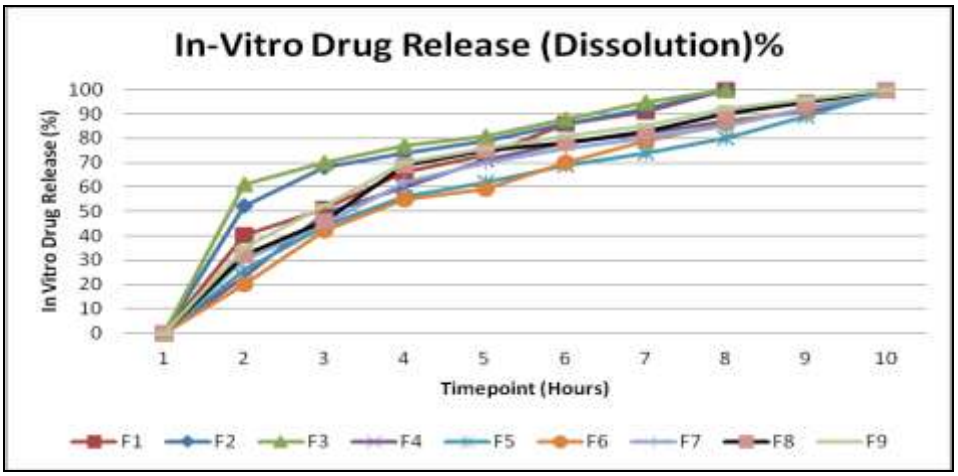
h. *In-vitro* Release Studies

The formulation F1, F2, F3 does not have the desired extended drug release up to 9 hours. The *in-vitro* cumulative drug release profile of formulations F1 containing HPMC K4M showed 100.0 % in 7 hours, cumulative drug release profile of formulations F2 containing (Sodium Alginate) showed 100.0% in 7 hours and cumulative drug release profile of formulations F3 containing (Gum acacia) showed 100.0 % in 7 hours.

The *in-vitro* cumulative drug release profile of formulations F4, F5, F6 containing HPMC K4M and Sodium Alginate in the range of (1:1, 1:2 and 1:3) was showed 99.0, 99.0, and 100.0 respectively in 9 hours.

The *invitro* cumulative drug release profile of formulations F7, F8,F9 containing HPMC K4M and Gum Acacia in the range of (1:1, 1:2 and 1:3) was showed 99.0,100.0,100.0 respectively in 9 hours. Details were mentioned in graph 9.

F5 has desired extended drug release profiling at the end of 9 hours hence it was selected as the optimumized formulation.

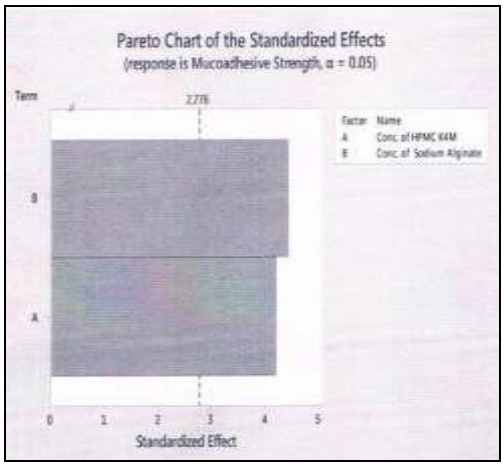


Graph 9: In-vitro Drug Release of Rizatriptan Benzoate Oromucosal Tablets

i. Optimization of formulation by using 3^2 factorial design:

Optimization of formulation done by statistical analysis software Minitab 17.1 utilized for Design of experiment (DoE).

I) Impact of variable: Pareto chart was type of bar chart. Chart shows frequency count from highest and lowest. Pareto chart and normal probability plot determine the impact of formulation process variables on CQA'S. i.e. % drug release, swelling index and mucoadhesive strength presented in figure no. 1a & 2a, 1b &2b, 1c & 2c. Figure shows the absolute values of the standardized effect from the largest effect to smallest effect. Reference line indicates effects are statistically significant. Pareto charts provide information about areas on which priories for earlier action to be taken for process improvement [27]



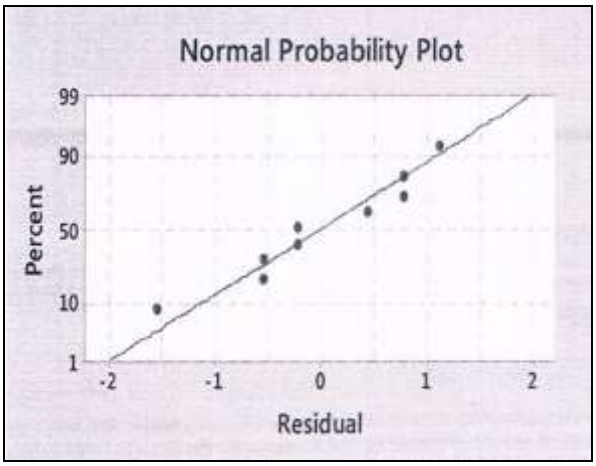
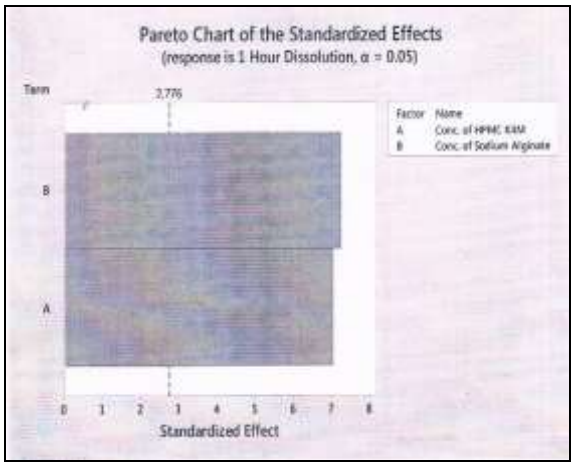


Figure No. 1a: Impact of formulation variables on mucoadhesive strength

Figure No. 2a: Normal probability plot for mucoadhesive strength.



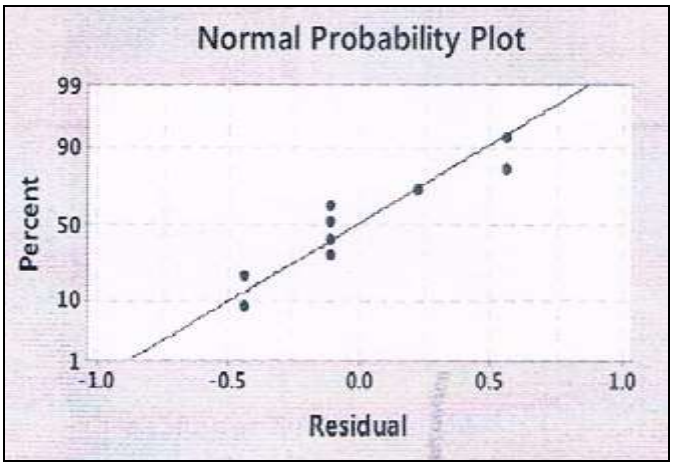
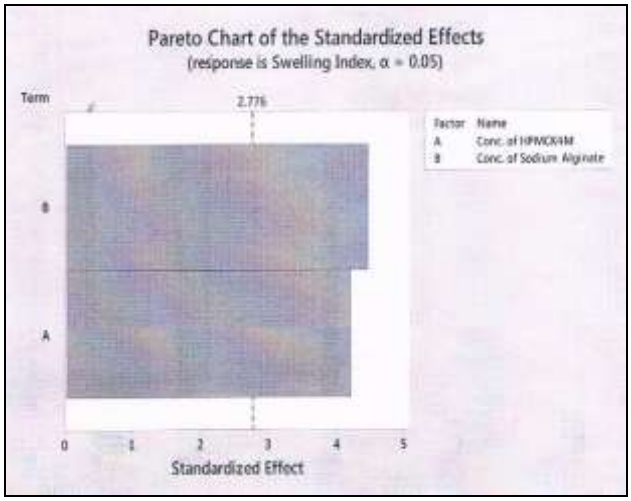


Figure No. 1b: Impact of formulation variables on 1 hour dissolution

Figure No. 2b: Normal probability plot for 1 hour dissolution



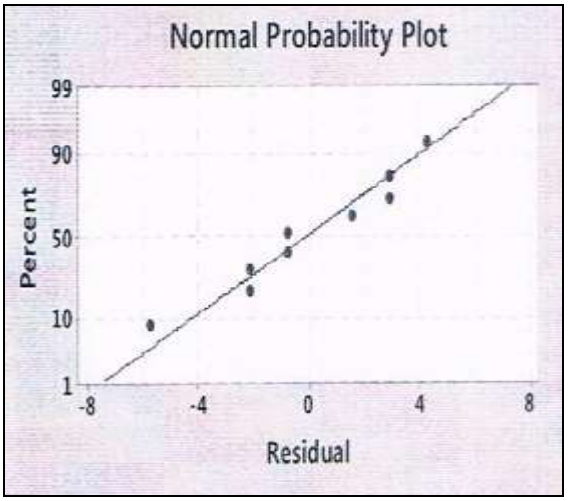


Figure No. 1c. Impact of formulation variables on swelling index

Figure No. 2c. Normal probability plot for swelling index

II) Main Effect Plot: The main effect plot showing impact of formulation variables within studied range on mucoadhesive strength, dissolution and swelling index are presented in figure no. 3a, 3b, 3c respectively. The lines were horizontal and parallel to the X axis, there was no main effect present and response mean was same across all factor level. If steeper the slope of the lines then greater the magnitude of main effect. [27]

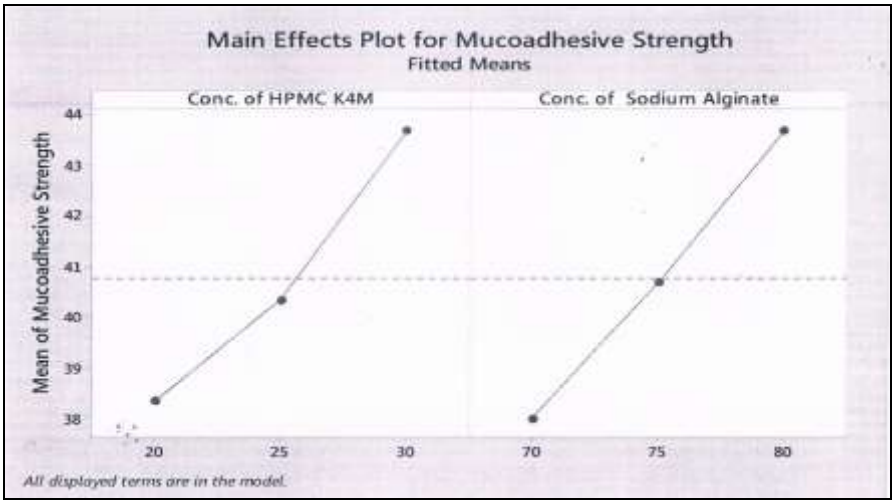


Figure No. 3a: Main effect plot for mucoadesive strength

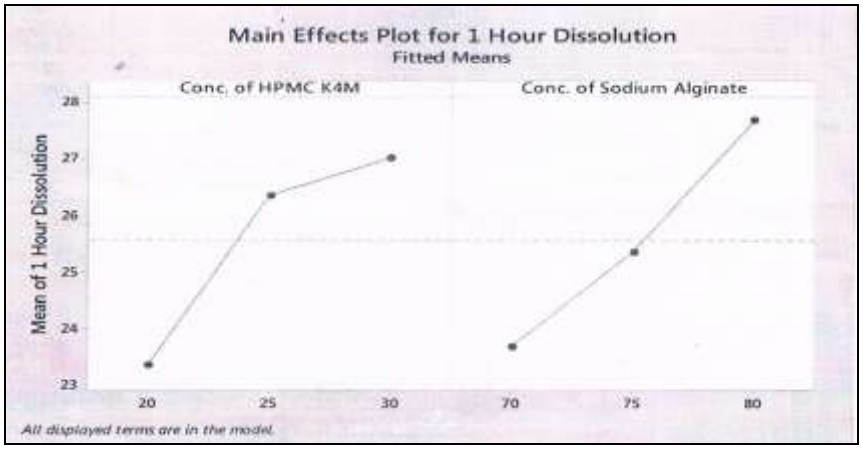


Figure No. 3b: Main effect plot for 1 Hour Dissolution

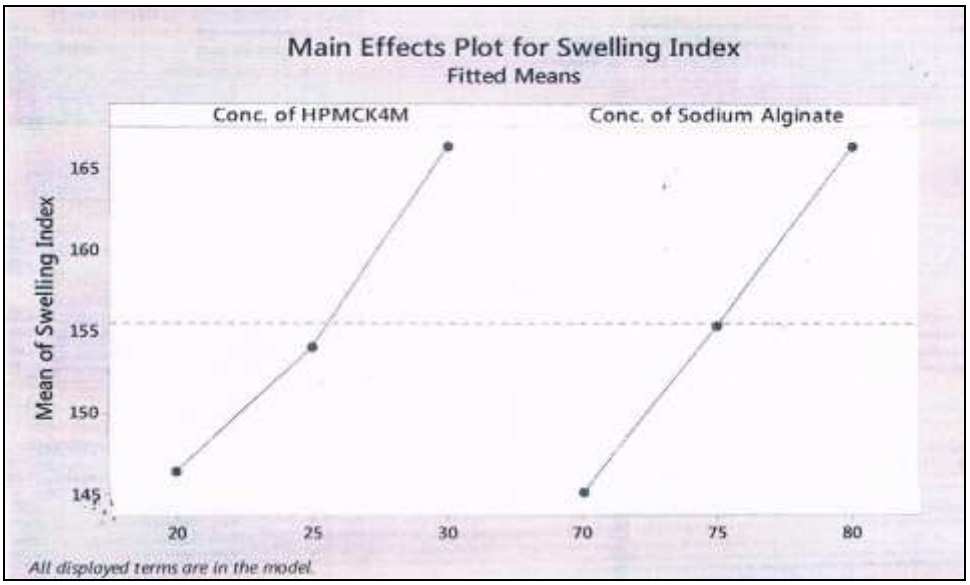


Figure No. 3c: Main effect plot for swelling index

III) Interaction of variables: The impact of interaction of formulation variables within studied range on mucoadhesive strength, % drug release and swelling index presented in figure No. 4 a, 4b, 4c respectively. In interaction plot indicated by parallel lines then there was no interaction observed. [27]

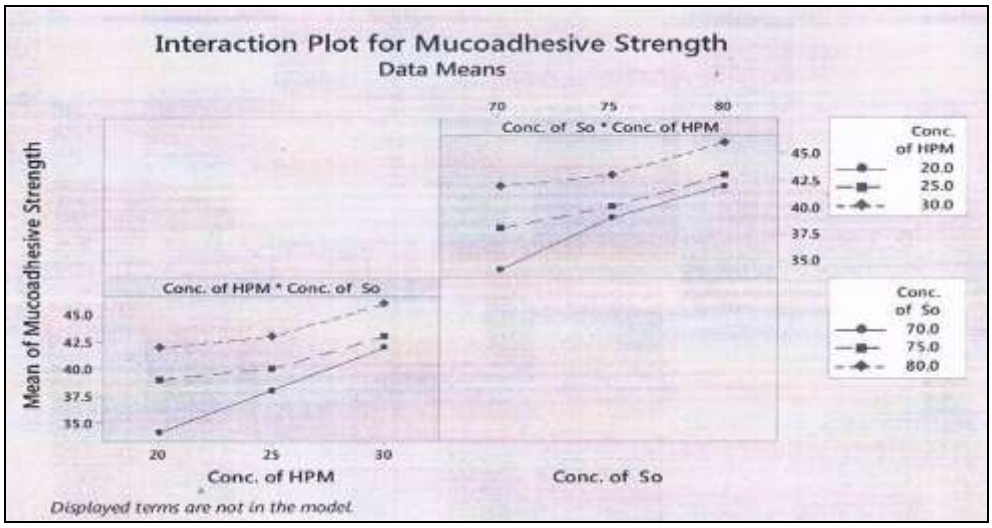


Figure No. 4a: Interaction Plot for Mucoadhesive strength

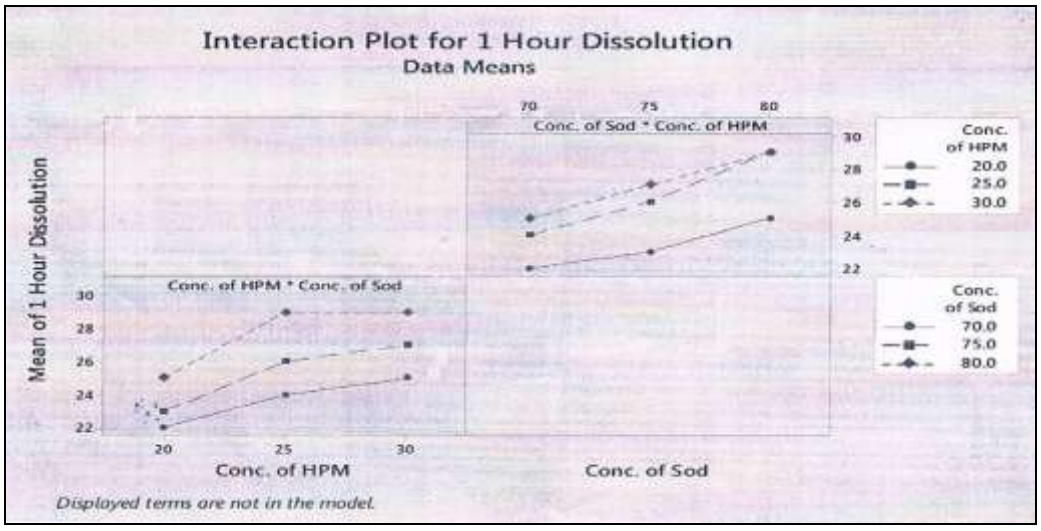


Figure No. 4b: Interaction Plot for 1 Hour Dissolution

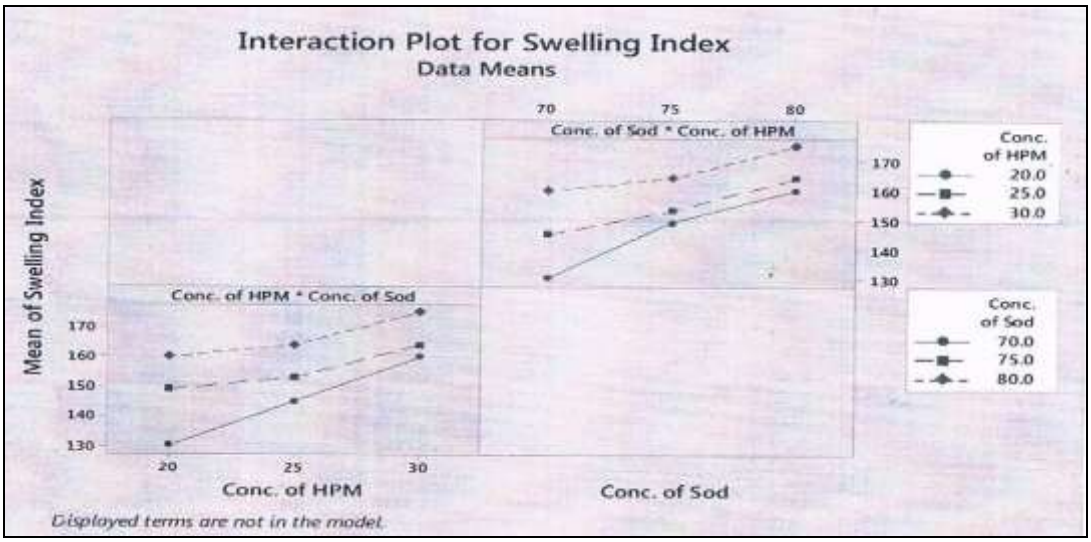


Figure No. 4c: Interaction Plot for Swelling Index

IV) Correlation of variables and response: 3D Surface plot and contour plot showing correlation between formulation variables of mucoadhesive strength, % drug release and swelling index presented in figure no. 5a, 5b and 5c respectively. 3D surface plot was three dimensional structure used for determination of correlation of response variable with two predicated variables. Predicator observed on X and Y axis and response on Z axis. [27]

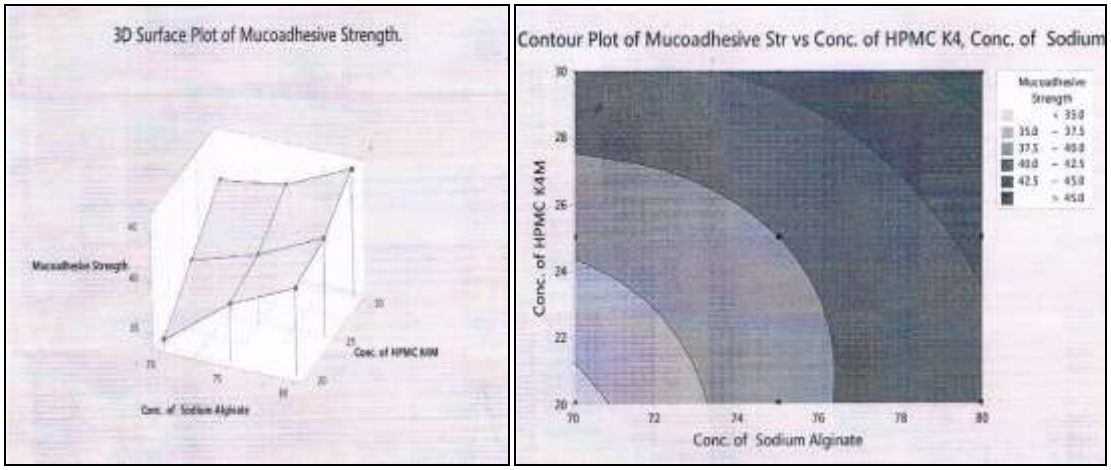


Figure No. 5a: Contour Plot and 3D Surface Plot for Mucoadhesive Strength

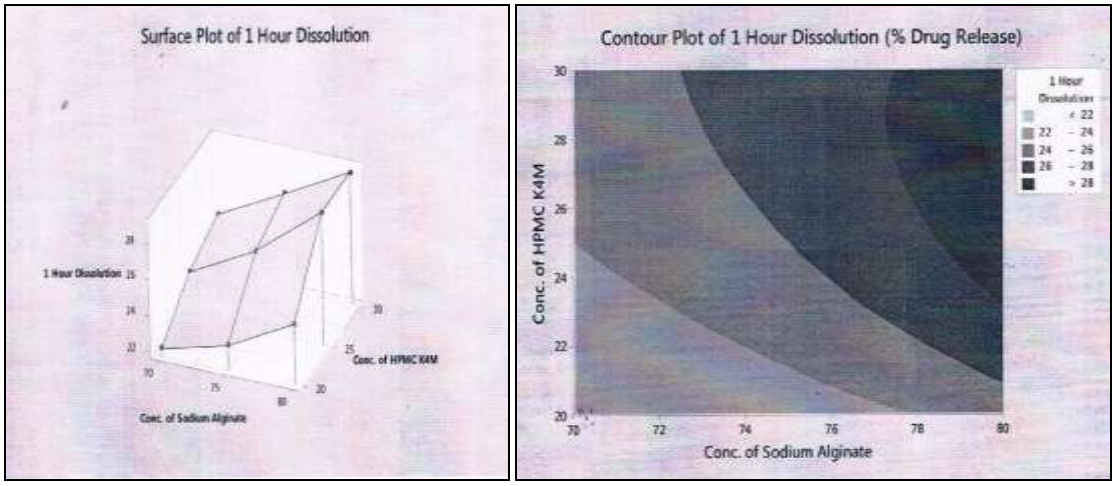


Figure No. 5b: Contour Plot and 3D Surface Plot for % Drug Release (Dissolution)

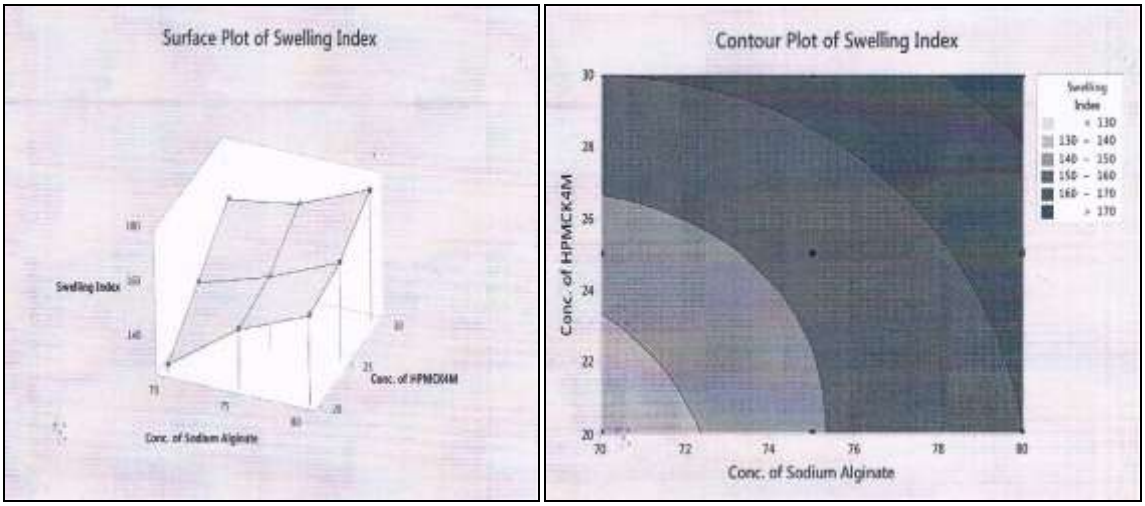


Figure No. 5c: Contour Plot and 3D Surface Plot for Swelling Index.

V) Formulation design space: The overlaid contour plots showing formulation design space were derived from varying level of critical material variables and its impact on mucoadhesive strength, % drug release (1 hour dissolution and swelling index were depicted in figure no. 6

VI) Statistical evaluation by using ANOVA table:

Statistical evaluation done for mucoadhesive strength, % Drug Release (In vitro drug release) and Swelling Index. IF P value was more than 0.05, it reveals that the model was not significant and vice versa. Statistical evaluation and regression equation and coefficient mentioned in table no. 6 a and 6 b

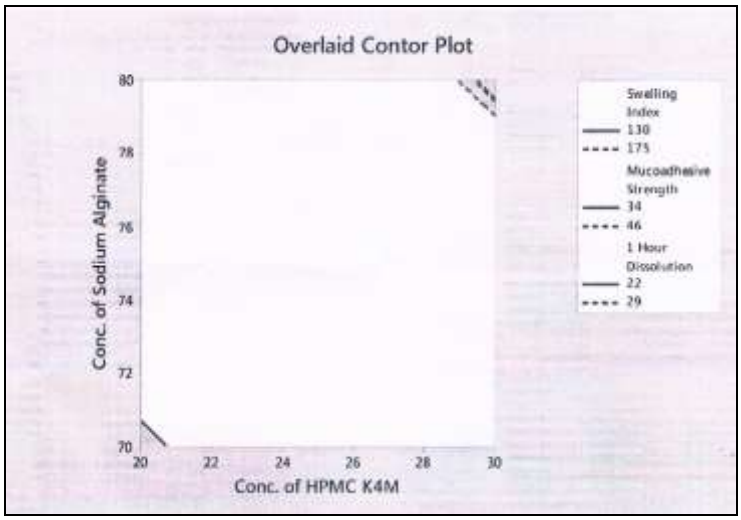


Figure No. 6: Overlaid Contour Plot for Mucoadhesive strength, % Drug Release (1 Hour Dissolution) and swelling index

Table No. 6 a Statistical evaluation by using ANOVA table

Response	Mucoadgesive Strength					% Drug Release (1 Hour Dissolution)					Swelling Index				
Analysis of Variance															
Source	Sum of square (Adj SS)	df	Mean Square (Adj MS)	F-value	P-value	Sum of square (Adj SS)	df	Mean Square (Adj MS)	F-value	P-value	Sum of square (Adj SS)	df	Mean Square (Adj MS)	F-value	P-value
Model Linear	91.778	4	22.9444	15.88	0.010	47.111	4	11.7778	42.40	0.002	1293.78	4	323.44	16.08	0.010
HPMC K4M	43.556	2	21.778	15.08	0.014	22.889	2	11.4444	41.20	0.002	610.89	2	305.44	15.19	0.014
Sodium Alginate	48.222	2	24.111	16.69	0.011	24.222	2	12.111	43.60	0.002	682.89	2	341.44	16.98	0.011
Error	5.778	4	1.444			1.111	4	1.111			80.44	4	20.11		
Total	97.556	8				48.222	8				1374.22	8			
Model Summary															
S	1.20185					0.527046					4.48454				
R-sq	94.08%					97.70%					94.15%				
R-sq (Adj)	88.15%					95.39%					88.29%				
R-sq (pred)	70.02%					88.34%					70.37%				

Table No.6 b Statistical evaluation by using ANOVA table

Coefficients						
Term	Coef	P-value	Coef	P-value	Coef	P-value
Constant	40.778	0.000	25.556	0.000	155.56	0.000
HPMC K4M						
20	-2.444	0.567	-2.222	0.248	-9.22	0.012
35	-0.444	0.567	0.778	0.248	-1.56	0.503
Sodium Alginate						
70	-2.778	0.567	-1.889	0.002	-10.56	0.008
75	-0.111	0.567	-0.222	0.422	-0.22	0.921
Regression equation	40.778-2.444 of HPMC K4M_20 -0.444 of HPMC K4M__25 +2.889 of HPMC K4M_30 -2.778 of Sodium Alginate_70-0.111 of Sodium Alginate +2.111_75 of Sodium Alginate _80		25.556-2.222 of HPMC K4M_20 +0.778 of HPMC K4M__25 +1.444 of HPMC K4M_30 -1.889 of Sodium Alginate_70-0.222 of Sodium Alginate _75+2.111 of Sodium Alginate _80		155.56-9.22 of HPMC K4M_20 +1.56 of HPMC K4M__25 +10.78 of HPMC K4M_30 -10.56 of Sodium Alginate_70-0.22 of Sodium Alginate _75+10.78 of Sodium Alginate _80	

Response optimization plot and desirability: Multiple response optimization used for estimation numerical technique of desirability function. Desirability functions obtained by using maximize, minimize and target optimization of the output responses. In our experiment for desirability function we utilize target optimization. The'd' indicate individual desirability. It evaluates how the settings optimize the single response. Composite desirability (D) has range 0 to 1 and value close to 1 indicate that the settings achieve favourable results for all responses as a whole, Details mentioned in figure 7a,7b, 7c. Details of response optimization and desirability mentioned in table no.7 and Analytical result of DoE trials mentioned in table no. 12

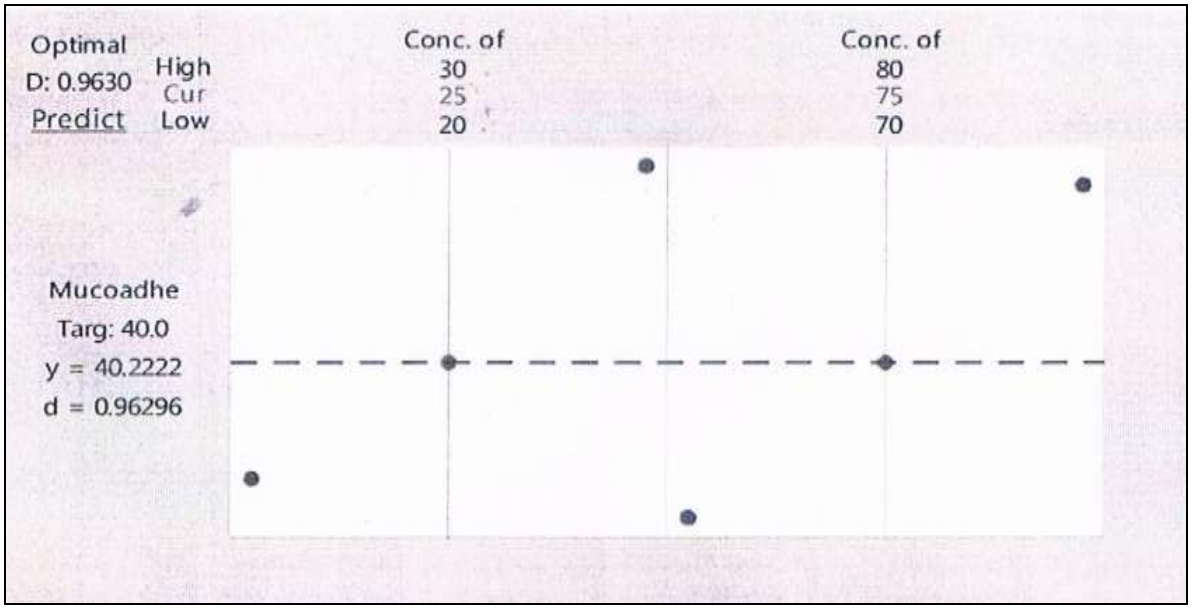


Figure No.7 a: Response optimization plot and desirability mucoadhesive strength

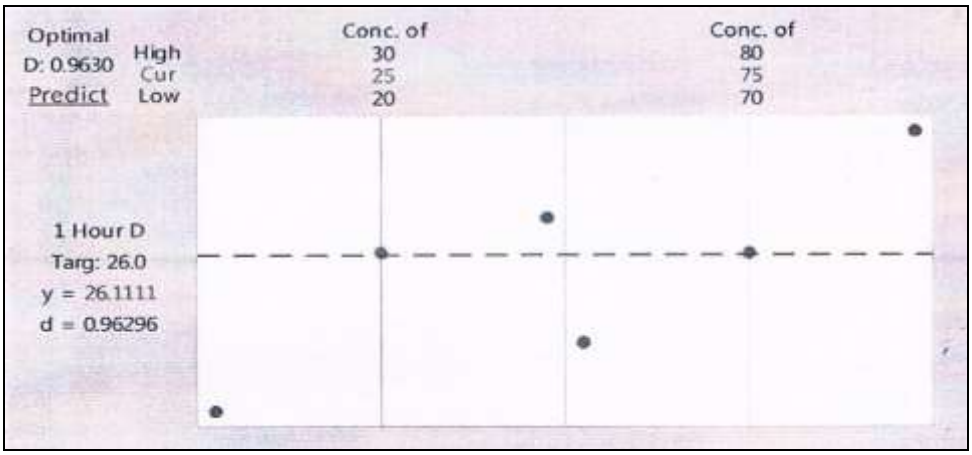


Figure No.7 b: Response optimization plot and desirability value for 1 hour dissolution

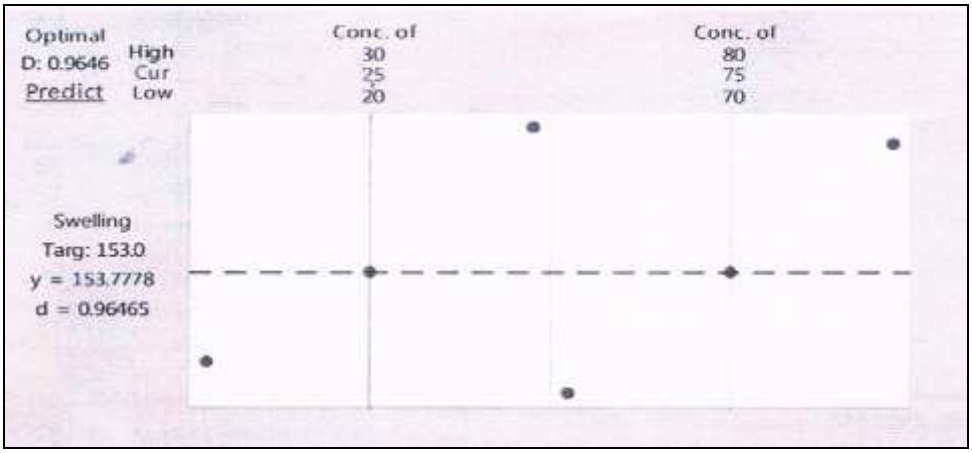


Figure No.7 c: Response optimization plot and desirability value for Swelling Index

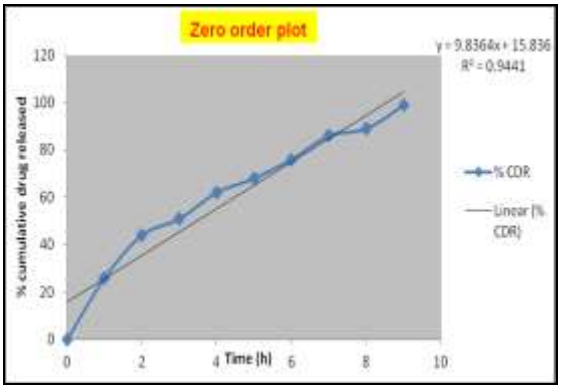
Table No.7: Details of response optimization and desirability

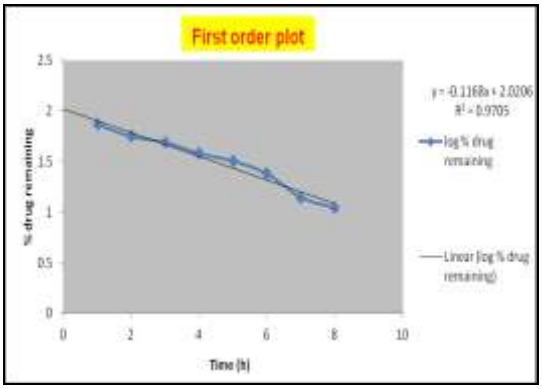
CQA	Conc. of HPMC K4M	Conc. of Sodium Alginate	Mucoadhesive Strength Fit	Mucoadhesive Strength Practical value	Composite Desirability(D)
Mucoadhesive Strength	25	75	40.2222	40.0000	0.96296
%Drug Release (1 hour)	25	75	26.11111	26.000	0.96296
Swelling Index	25	75	153.7778	153..000	0.96465

Table No.:12 Analytical result of DoE trials.

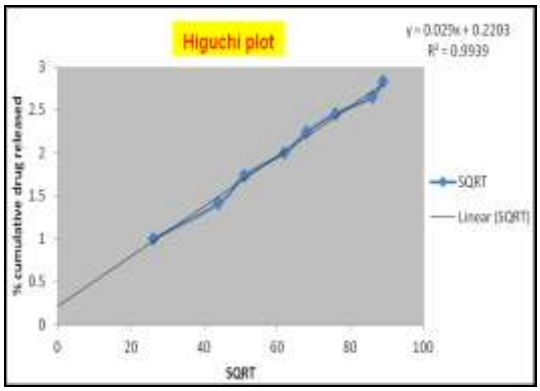
Formulation code		**DE1**	**DE2**	**DE3**	**DE4**	**DE5**	**DE6**	**DE7**	**DE8**	**DE9**
In vitro drug release (%)	0	0	0	0	0	**0**	0	0	0	0
	1 Hour	22	23	25	24	**26**	29	25	27	29
	2 Hour	49	58	60	39	**44**	45	40	35	39
	4 Hour	70	80	82	59	**62**	70	66	56	59
	8 Hour	89	99	97	85	**89**	87	82	90	85
	9 Hour	95	100	100	95	**99**	94	95	94	95
Mucoadhesive strength (g)		34.00± 0.11	39.00± 0.13	42.00± 0.11	38.00± 0.12	**40.00± 0.14**	43.00± 0.15	42.00± 0.12	43.00± 0.10	46.00± 0.16
% Swelling Index		130.00 ±1.27	149.00 ±1.32	160.00 ±1.29	145.00 ±1.21	**153.00 ±1.52**	164.00 ±1.30	160.00 ±1.22	164.00 ±1.24	175.00 ±1.27

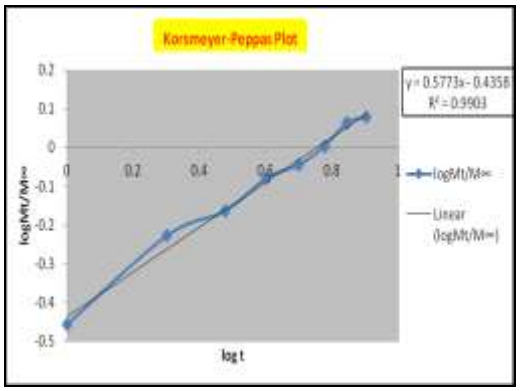
j. Drug release kinetics: The result of dissolution data were fitted in to mathematical model of the optimized formulation (F8) kinetic equations to assess the release mechanism. R^2 values of optimized formulation were found 0.9939. It was indicating that the drug release followed higuchi mechanism. The kinetics plot of optimized formulation for zero order, first order, Higuchi peppas and Hixson Crowell models were represents in table no.8 and graph 4-8



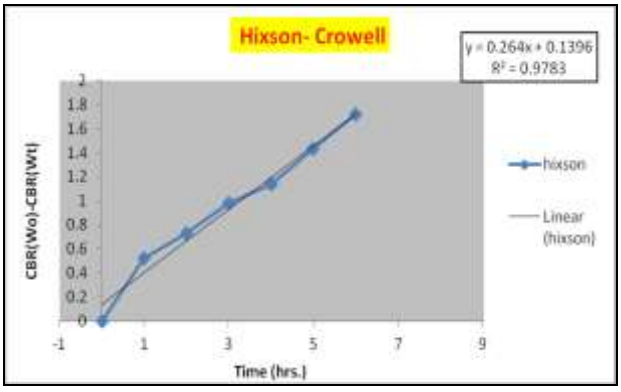


Graph No.4: Zero Order Plot **Graph No.5: First Order Plot**





Graph No.6: Higuchi Plot. **Graph No.7: Korsmeyer-Peppas Plot.**



Graph No.8: Hixson Crowell Plot

Table No.8 Release kinetics study of optimized formulation:

Code	Zero order R^2	First order R^2	**Higuchi R^2**	Korsmeyer Peppas model		Hixson Crowell R^2
				n	R^2	
DE5	0.9441	0.9705	**0.9939**	0.5803	0.9903	0.9783

k. In vitro Buccal Permeability Study: In vitro permeability study was performed by using Franz diffusion apparatus. Optimized DoE batch (DE5) was shows percentage drug permeability 22%, 43%, 59% and 76% after 1 hour, 3 hour, 6 hour and 9 hour respectively.

l. Analytical result of stability batch:

Optimized DOE batch (DE5) was incubated on accelerated stability condition (40^0 C/75% RH) for 1 month. After 1 month, stability samples were withdraw and evaluated. No

change in physical appearance or color of the formulation. Stability sample was estimated for drug content and In vitro drug release study. Formulation was found stable up to 1 month. Stability result given in mentioned table no. 13

Table No.13 Stability result of optimized formulation:

Parameters	Initial	1 Month
Description	No change	No change
Drug content (%)±SD	99.30±0.17	99.00±0.12
Invitro Drug Release at 8 Hours (%)±SD	98.90±0.5	99.10±0.8

CONCLUSION:

An attempt was made to fabricate and optimize oromucosal tablets of Rizatriptan Benzoate. Rizatriptan Benzoate was from triptan group of medicines. Migraine is neurovascular disorder in which patient suffers from moderate to severe headache. To avoid the repeated administration of immediate release dosage form attempt was to make buccal mucoadhesive sustained release tablets. Fourier transform infrared spectrometer was used to check the drug excipient compatibility study. FTIR study reveals that there was no drug excipients interaction. Physical parameters of compressed tablets like weight variation, hardness, thickness, friability were found satisfactory. HPMC K4M, Gum Acacia, Sodium alginate were used alone or in combination to extend mucoadhesive time and provide sustained drug release.

Among all the formulations, the DE5 formulation using polymers HPMC K4M and Sodium Alginate in the ratio (1:3) were exhibit significant bioadhesive properties, promising swelling index with optimum release profile. Swelling index test was performed on optimized formulation DE5.Pictorial representation of % swelling index mentioned in figure 8a to 8g

The optimized formulation DE5 was showed satisfactory surface pH. The pH of optimized formulation was found 6.79 ±0.35 and it could be used without risk of mucosal irritation.

Optimized formulation DE5 was effective in vitro permeation. In vitro dissolution studies showed that formulation DE5 containing HPMC K4M and Sodium Alginate was shows desired drug release of 99.00% over a period of 9 hours. Optimized formulations follow Higuchi model of drug release.

Design of experiment (DoE) applied by using 3^2 full factorial design (2 factor 3 level) was used to optimize and detect the effect of independent variable such as concentration of HPMC K4M(X1) and concentration of Sodium Alginate (X2) on dependent variables such as Mucoadhesive Strength (Y1), % Drug release (Y2), Swelling index (Y3).

Oromucosal tablet of Rizatriptan Benzoate was good choice for migraine. Oromucosal tablets can bypass the hepatic first pass metabolism with reduction in dosing frequency, reduction in the fluctuation of steady state concentration and reduction in side effect.

CONFLICT OF INTEREST: None

ACKNOWLEDGEMENT: The authors are grateful to principal of P.S.G.V.P. Mandal's College Of Pharmacy, Shahada for their valuable support to carry out the research work.

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