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FORMULATION AND EVALUATION OF BILAYER TABLET OF MONTELUKAST SODIUM AND DESLORATADINE IN THE TREATMENT OF ALLERGIC RHINITIS

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ABSTRACT

The present study was aimed to develop bilayer tablets of montelukast sodium as SR layer and Desloratadine as IR layer to treat seasonal allergic rhinitis. The bilayer tablets were formulated by combining montelukast sodium with desloratadine which gives additional benefits in comparison with either drug alone and could be considered for patients whose quality of life, impaired by persistent allergic rhinitis. The tablets were formulated using hydrophilic polymers such as HPMC K4M and ethyl cellulose in varying ratios to retard the drug release for a period of 12 hours. The immediate release layer of Desloratadine was formulated using pregelatinzed starch (5% and 10 %). All the formulations were evaluated for physical characteristics, drug content, dissolution, release kinetics and stability studies. The Drug- excipient interaction was investigated with FTIR spectroscopy. The study indicated. The formulated granules were evaluated for precompression studies which showes that the flow property was good. The formulated tablets were found to be within the limits with respect to Weight variation, Hardness, Thickness and Friability. The friability of IR tablets containing pregelatinzed starch 10% was found to be optimum. Nine batches of montelukast sodium formulations containing varying proportions of HPMC K4M and ethyl cellulose were subjected to in vitro dissolution study of SR tablet, optimized formulation were selected using DOE software and selected for bilayer tablets. The optimized formulations of both montelukast sosdium and desloratadine were compressed into bilayer tablets. The drug content of the bilayer tablets were estimated by simultaneous estimation method and it was found to be within the Pharmacopoeial limits. The release kinetics of the optimized tablets showed that it follows zero order release kinetics. The stability studies indicated that the bilayer tablets were stable and do not show any significant changes in the physical characteristics, drug content and dissolution. The results obtained were found to be within the limits.

KEYWORDS: Formulation, Evaluation, Bilayer Tablet, Montelukast Sodium, Desloratadine Allergic Rhinitis.

INTRODUCTION

Controlled release dosage form is a term used to describe the dosage forms having drug release features based on the time, course and/or location and which are designed to accomplish therapeutic or convenience objectives which are not offered by conventional release dosage forms. However, controlled release dosage form does not provide a rapid onset of action of drug entity. Whereas immediate release drug delivery system is intended to disintegrate rapidly and exhibits instant drug release. However, it is also associated with fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side-effects. Therefore, to compensate the dip in drug plasma concentration due to metabolism and excretion, it is necessary to administrate the dosage form several times per day. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms. Bilayered tablet is suitable for combination therapy, i.e., for sequential release of two different drugs, separate two incompatible substances and also for sustained release dosage form in which one layer is immediately released as a loading dose and second layer act as a maintenance dose.[1,2]

On the basis of these considerations, the bilayered tablet have been specially developed to provide two different release rates or biphasic release of a drug from a single dosage form in which one layer is formulated to obtain immediate release effect of the drug, with the aim of reaching a high plasma concentration in a short period of time while the second layer is designed as sustained released layer, which provides effective plasma concentration by a maintenance dose of drug for an extended period of time. The design of bilayered tablet dosage form holds many advantages over conventional dosage forms such as a reduction in frequency of drug administration, improved patient compliance, reduction

in drug level fluctuation in blood and quantitative reduction in total drug usage when compared with conventional therapy.[3,4,5,6]

The aim of the present investigation is to formulate and evaluate dual timed release bilayer tablet of Montelukast sodium and Desloratadine. The objectives are Allergy is a common problem among all age groups. Montelukast sodium is a leukotriene receptor antagonist used in the treatment of asthma and to relieve symptoms of seasonal allergies whereas desloratadine works by binding to a receptor, known as the histamine H1 receptor, and blocking a biochemical called histamine from binding to this receptor.[7,9] This prevents histamine from triggering a sequence of events that leads to things we commonly associate with hives and allergies in general, like itching, redness, and swelling. It is long acting tricyclic histamine antagonist with a selective H1 receptor histamine antagonist activity. The combining of montelukast with desloratadine gives additional benefits in comparison with either drug alone and could be considered for patients whose quality of life is impaired by persistent allergic rhinitis. Hence montelukast sodium which has a short half life of 2.7- 5.5 hours is prepared as a sustained release dosage form and desloratadine as immediate release layer to improve the patient compliance.

MATERIALS

Table 1: List of materials and their applications in the formulation.

S.No	Name of the material	Manufacture/ Supplier	Use in formulation
1.	Montelukast sodium	Neha chemicals (Hyderbad)	Active ingredient
2.	Desloratadine	Hindustan chemicals pvt.ltd	Active ingredient
3.	Microcrystalline Cellulose 102	Ankit pulps and boardspvt.ltd	Diluent
4.	Lactose Monohydrate	Manish global ingedientpvt.ltd	Diluent

METHODOLOGY

PREFORMULATION STUDIES

The Preformulation studies are conducted to establish the physiochemical characteristics of the drug and its compatibility with the excipients used. The Preformulation studies are necessary to formulate drug into stable, safe and effective dosage form.

Drug-excipient compatibility study

The drug and excipients selected for the formulation are evaluated for physical and chemicalcompatibility studies.

Chemical compatibility study by FTIR

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of a mixture there by we can study incompatibility with two compounds. Compatibility in between two pure drug and compatibility in between both drug and excipient has been investigated by FTIR. The IR spectra of the test samples were obtained by Pressed Pellet technique using Potassium bromide.

Potassium bromide pellet method

A small amount of finely ground solid sample is intimately mixed with about 100 times its weight of powdered potassium bromide. The finely ground mixture is then passed under very high pressure in a press (at least 25,000 psig) to form a small pellet(about 1-2 mm thick and 1 cm in diameter). The resulting pellet is transparent to IR radiation and is run as such.

CALIBRATION CURVE

MONTELUKAST SODIUM

10 mg of drug was weighed and transferred to a 100 mL volumetric flask and made upto volume using methanol. From the resulting solution 1, 3, 5, 7 and 9 mL were pipetted out into separate 50 mL volumetric flasks and made upto volume using methanol to represent 2, 6, 10, 14 and 18 µg/mL of the drug. The absorbance of the solutions was measured at 283nm taking methanol as blank using UV-Visible spectrophotometer. The calibration curve was then plotted taking concentration (µg/mL) along X-axis and absorbance along Y- axis.

DESLORATADINE

25 mg of drug was weighed and transferred to a 100 mL volumetric flask and made upto volume using methanol. From the resulting solution 1, 2, 3, 4 and 5 mL were pipetted out into separate 50 mL volumetric flasks and made upto volume using methanol to represent 5, 10, 15, 20 and 25 µg/mL of the drug. The absorbance of the solutions was measured at 269 nm taking methanol as blank using UV-Visible spectrophotometer. The calibration curve was then plotted taking concentration (µg/mL) along X-axis and absorbance along Y- axis.

FORMULATION OF SUSTAINED RELEASE OF MONTELUKAST SODIUM TABLET

Table 2: Materials used in the Formulation of Montelukast sodium.

INGREDIENT	M1	M2	M3	M4	M5	M6	M7	M8	M9
Dry mix									
Montelukast sodium	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Microcrystalline Cellulose 102	45.5mg	40.5mg	35.5mg	35.5mg	30.5mg	25.5mg	35.5mg	40.5mg	15.5mg
HPMC K4M	10mg	10mg	10mg	20mg	20mg	20mg	30mg	30mg	30mg
Ethyl cellulose	5mg	10mg	15mg	5mg	10mg	15mg	5mg	10mg	15mg
Lactose	24mg	24mg	24mg	24mg	24mg	24mg	24mg	24mg	24mg
Binder									
IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
PVP K30	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Extra granular									
Magnesium sterate	0.5mg	0.5mg	0.5mg	0.5mg	0.5mg	0.5mg	0.5mg	0.5mg	0.5mg

Wet granulation process steps for Montelukast sodium

Montelukast sodium tablet was prepared by wet granulation and using Design of experiment, optimization was carried out. Final optimized blend is used to compress Bilayer tablet.

1. The weighed quantities of intra granular material (montelukast sodium, microcrystalline cellulose, lactose monohydrate, hydroxy propyl methylcellulose K4M, Ethyl cellulose) sifted through Mesh #40.
2. Sifted intra granular materials are subjected to dry mix in a polyethylene bag and mixed for10 minutes.
3. Iso propyl alcohol was chosen as solvent for binder solution. The quantity of iso propyl alcohol was fixed based on 20% weight of intragranular material. Weighed quantities of polyvinyl pyrolidone K30, was passed through Mesh#40 and mixed in iso propyl alcohol to make binder solution.
4. The binder solution was poured over dry mix and was mixed together until granules with desired size were formed. The granules were then kept for drying at 55ºC in Hot air oven. Drying was continued till LOD reaches NMT 2.5%.
5. Dried granules were passed through mesh#20, and transferred to polyethylene bag and blended for 10min.
6. The extragranular material consist magnesium sterate passed through mesh#40
7. Finally sifted magnesium sterate transferred into the above granules and blended for 3 min.
8. The tablets were compressed by 12 station tablet compression machine using 6 mm flat shaped punches.

OPTIMISATION

To understand the influence of formulation variables on the quality of formulations with a minimal number of experimental trials and subsequent selection of formulation variables to develop an optimized formulation using established statistical tools for optimization.

Mathematical modeling, evaluation of the ability to fit to the model and response surface modeling were performed with employing Design-Expert® software (Version 11). In a full factorial design, all the factors are studied in all the possible combinations. Hence, 32 factorial designs were chosen for the current formulation optimization study.

Design of Experiment (DOE)

A two factor and three-level factorial design was used as the experimental design. The independent variables studied were amount of HPMC as X1 and Amount of ethyl cellulose as X2. Time taken for drug release at 50% as Y1 and drug release at 12^{th} hour as Y2 were considered as dependent variable.

Experimental Design

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 the choice of responses. Experimental runs were designed by Design Expert 11.0.1 [Stat Ease. Inc.] software following full factorial method. 32 full factorial design was applied for examining two variables (factors) at three levels with a minimum of 9 runs. Totally nine tabletformulations were prepared employing selected combinations of the two factors as per 3^2 Factorial and evaluated to find out the significance of combined effects of the two factor to select the best combination required to achieve the desired sustained release of montelukast sodium tablet.

Table 3: Experimental Design.

Factors: Formulation Variables	Levels (mg/tablet)		
	-1	0	+1
HPMC K4M	10	20	30
Ethyl cellulose	5	10	15
Response	**Goal**		
Time taken for drug release at 50%	Minimize		
Drug release at 12^{th} hour	Maximize		

FORMULATION OF IMMEDIATE RELEASE DESLORATADINE LAYER Formulation was carried out by trial and error method for IR layer of desloratadine. Totally two formulation, by direct compression. Final optimized blend is used to compress Bilayertablet.

Table 4: Materials used in the formulation of Desloratadine.

INGRIDENTS	D1	D2
Desloratadine	5 mg	5mg
Microcrystalline cellulose 102	66.30mg	71.30mg
Lactose monohydrate	10mg	10mg
Pre-gelatinzed starch	10mg	5mg
Croscaramellose sodium	5mg	5mg
Aerosil	1mg	1mg
Magnesium sterate	1mg	1mg
Talc	1mg	1mg
Erythrosine (colour)	0.7mg	0.7mg

Direct compression process steps for Desloratadine

- Microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, pregelatinsed starch was sifted through mesh#20 and transferred into the polyethylene bag and they were blended for 10 minutes.
- Erythrosine colouring agent and desloratadine was passed through mesh#40 and mixed for 5 minutes with the above blend.
- Magnesium sterate, talc, aerosil was passed through mesh#40 mixed for 2 minutes withthe above blend.

Formulation of Bilayer tablets of montelukast sodium and desloratadine

- Based on the above formulation, development and optimization, the optimized blend of montelukast sodium and desloratadine was used for bilayer tablet.
- Using 9 mm flat punch bilayer tablets of montelukast sodium and desloratadine were compressed.
- Weighted quantity of montelukast sodium granules and desloratadine was placed in separate hopper.
- First montelukast sodium granules were filled in die cavity and slight compression is applied and then desloratadine layer was filled over the montelukast sodium layer and final compression is given to form Bilayer tablet.

RESULT AND DISCUSSIONS

Chemical compatibility study by FTIR

The drug-drug interaction and drugs-excipients interaction was studied by FTIRspectroscopy. The results are given in the Figures below.

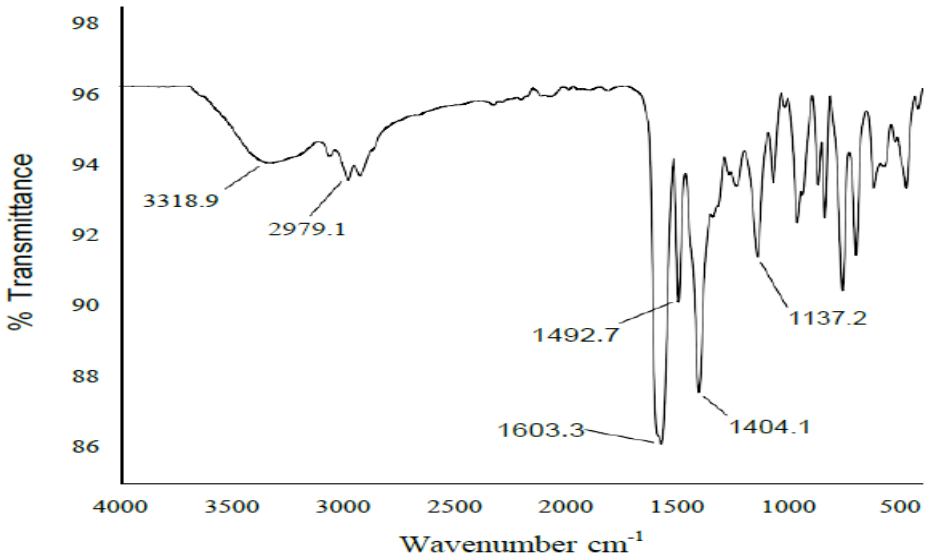

Fig 1: FTIR of Montelukast sodium.

Table 5: IR Spectral Interpretation Of Montelukast Sodium.

S.No	Wavenumber cm^{-1}	Interpretation
1	3318.9 cm^{-1}	N-H bending amine
2	2979.1 cm^{-1}	CH stretching alkene
3	1603.3 cm^{-1}	C=C stretching alkene
4	1492.7 cm^{-1}	C=C stretching ring
5	1404.1 cm^{-1}	CN stretching amine
6	1137.2cm^{-1}	CO stretching carboxylic acid

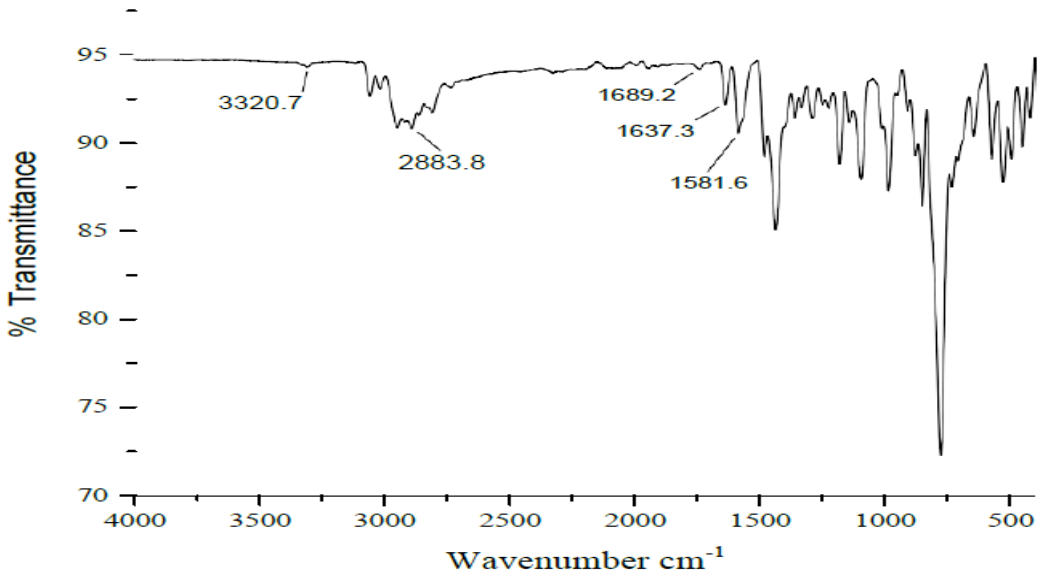

Fig 2: FTIR of Desloratadine.

Table 6: IR Spectral Interpretation of Desloratadine.

S.No	Wavenumber CM^{-1}	Interpretation
1	1637.3 cm^{-1}	C=C stretching alkene
2	1689.2 cm^{-1}	N-R stretching imines
3	1581.6 cm^{-1}	C=C stretching ring
4	2883.8 cm^{-1}	C-H stretching
5	3320.7 cm^{-1}	N-H bending amines

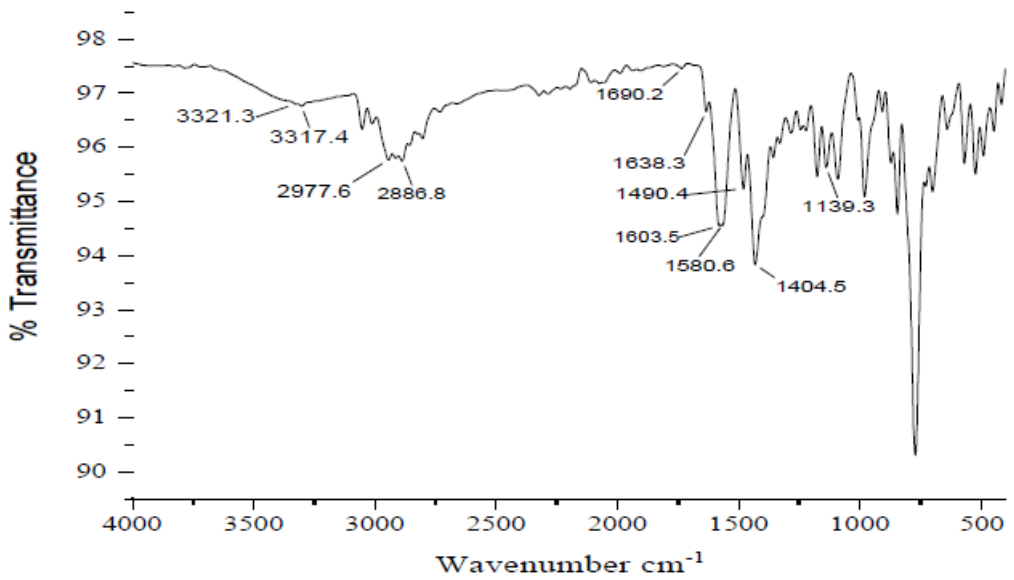

Fig 3: FTIR of Montelukast and Desloratadine.

Table 7: IR Spectral Interpretation of Montelukast sodium and Desloratadine.

S.No	Wave number cm^{-1}	Interpretation
1	3321.3cm^{-1},3318.9cm^{-1}	N-H bending amines
2	2977.6 cm^{-1}	N-H bending amines
3	2886.8cm^{-1},1690.2cm^{-1}	C-H stretching
4	1638.3cm^{-1},1603.5cm^{-1}	C=C stretching alkene
5	1580.6cm^{-1} ,1490.4cm^{-1}	C=C stretching ring
6	1404.5 cm^{-1}	CN stretching amine
7	1139.3 cm^{-1}	CO stretching carboxylic acid

Inference

The FTIR peak of spectra for Montelukast sodium and Desloratadine showed no shiftand no disappearance of the characteristic peaks suggesting that there is no interaction betweenthe two drugs.

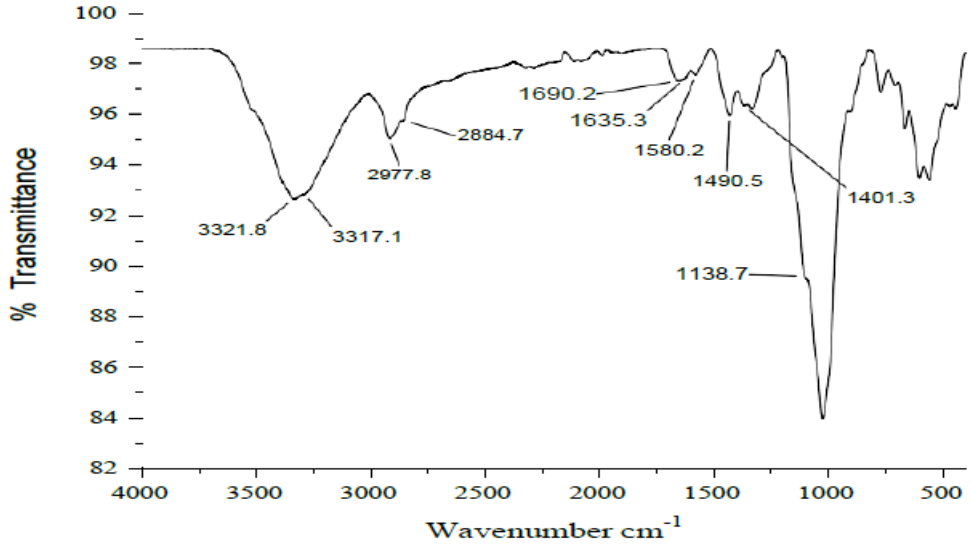

Fig 4: FTIR of Montelukast sodium and Desloratadine.

Table 8: IR Spectral Interpretation of Montelukast sodium and Desloratadine.

S.No	Wavenumber cm^{-1}	Interpretation
1	3321.8 cm^{-1} 3317.1 cm^{-1} 2977.8 cm^{-1}	N-H bending amines
2	2884.7cm^{-1}	C-H stretching
3	1690.2cm^{-1}	N-R stretching imines
4	1635.3cm^{-1}	C=C stretching alkene
5	1580.2cm^{-1} 1490.5 cm^{-1}	C=C stretching ring
6	1138.7cm^{-1}	CO stretching carboxylic acid
7	1401.3cm^{-1}	CN stretching amine

Inference

The FTIR peak of Spectra for Bilayer formulation showed no shift and no disappearance of the characteristic peaks suggesting that there is no interaction between the two drugs and also with the excipients in the final formulation.

Calibration Curve of montelukast sodium

The calibration curve of montelukast sodium in methanol is given in Table 9 & 10 and Fig 10 & 11.

Table 9: Data for calibration curve of montelukast sodium in 283 nm.

Concentration (µg/mL)	Absorbance at 283 nm
2	0.078
6	0.241
10	0.380
14	0.538
18	0.765

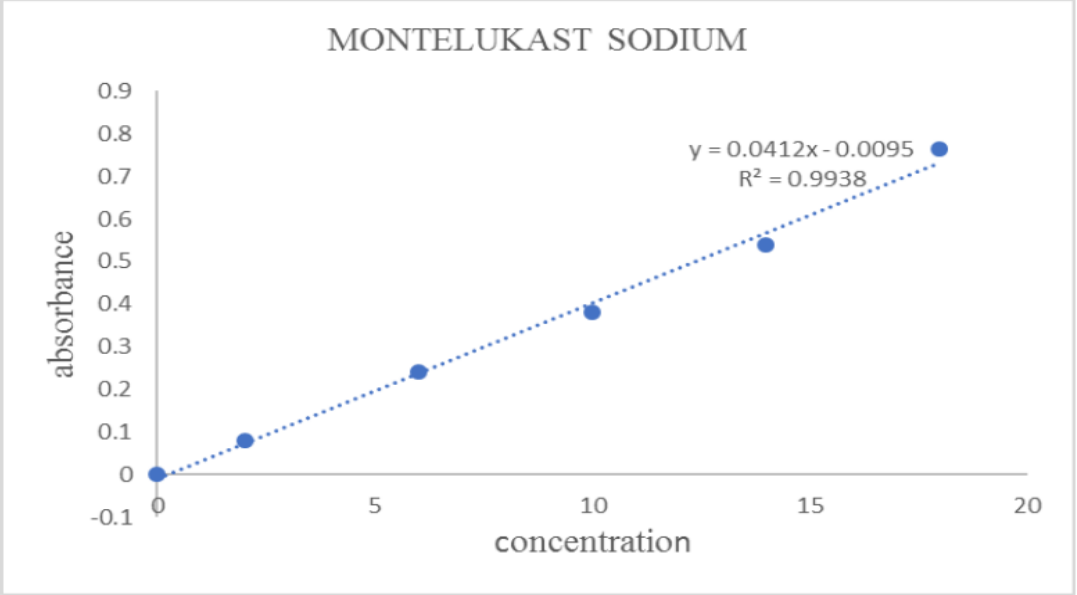

Fig 5: Calibration Curve of montelukast sodium in 283 nm.

Table 10: Data for calibration curve of montelukast sodium in 269 nm.

Concentration (µg/mL)	Absorbance at 269 nm
2	0.666
6	0.189
10	0.297
14	0.445
18	0.590

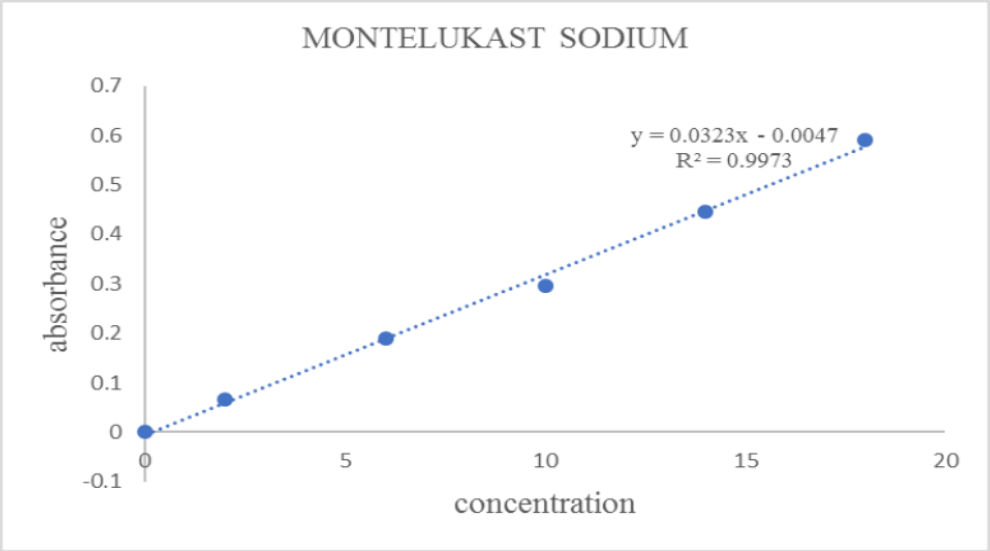

Fig 6: Calibration Curve of montelukast sodium in 269 nm.

It was found that the solution of montelukast sodium in methanol show linearity (R^2 = 0.9938) in absorbance at concentrations of 2 -18 (µg/mL) and obey Beer Lambert Law.

Calibration Curve of Desloratadine

The calibration curve of desloratadine in methanol is given in Table 11 & 12.

Table 11: Data for calibration curve of Desloratadine in methanol.

Concentration (µg/mL)	Absorbance at 269 nm
5	0.125
10	0.252
15	0.391
20	0.496
25	0.628

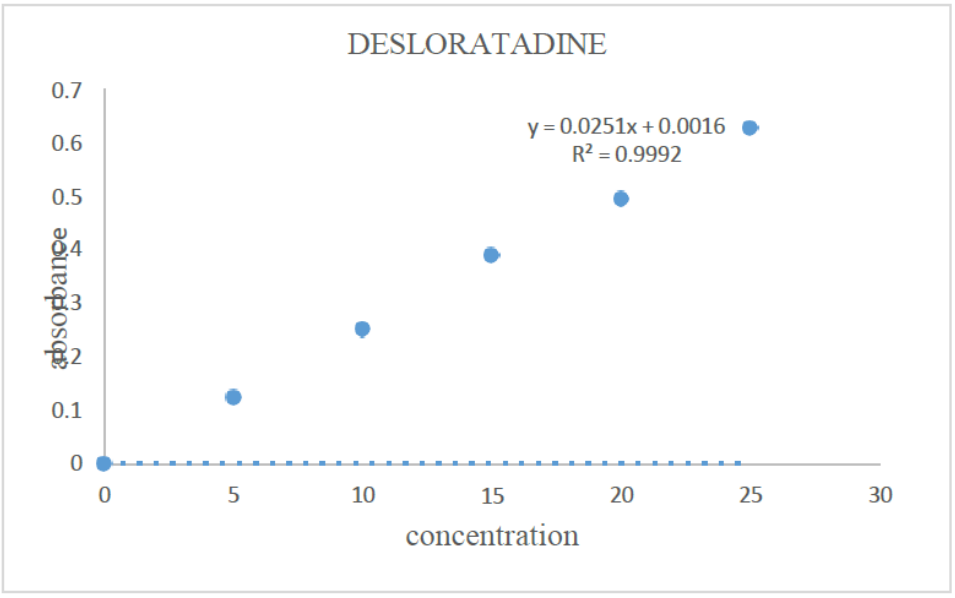

Fig 7: Calibration curve of Desloratadine in 269 nm.

Table 12: Data for calibration curve of Desloratadine in methanol.

Concentration (µg/mL)	Absorbance at 283 nm
5	0.072
10	0.144
15	0.217
20	0.278
25	0.342

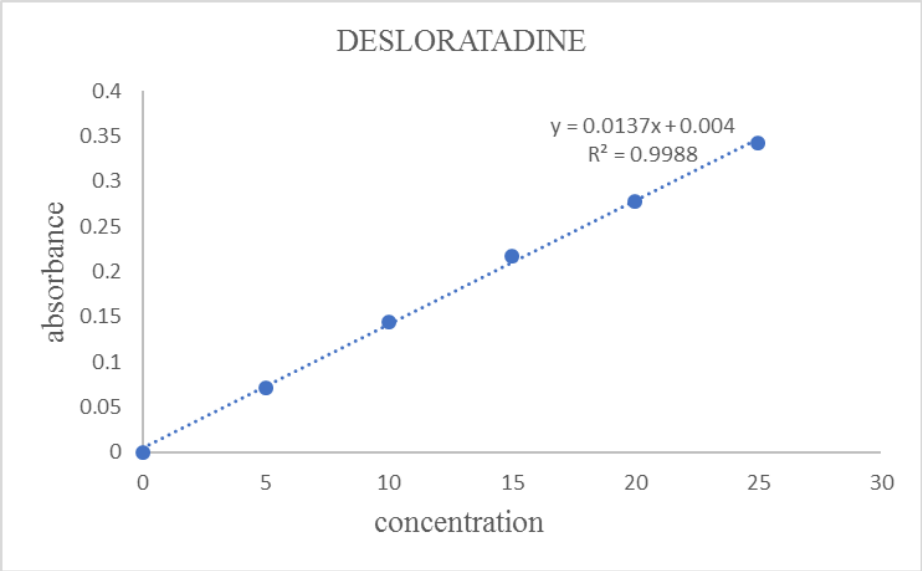

Fig: 8. Calibration curve of Desloratadine in 283 nm.

It was found that the solution of Desloratadine in methanol show linearity (R2 = 0.9992) in absorbance at concentrations of 5 -25 (µg/mL) and obey Beer Lambert Law.

Precompression study of montelukast sodium

Montelukast sodium tablet

The formulated blends of montelukast sodium were evaluated for pre compression parameters. The results are given in Table 13.

Table 13. Precompression of montelukast sodium.

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
M1	0.307±0.008	0.364±0.002	14.74±0.89	1.16±0.01	22.4±1.27
M2	0.298±0.006	0.357±0.001	15.41±0.93	1.18±0.03	21.3±1.21
M3	0.302±0.004	0.373±0.003	15.28±0.89	1.17±0.02	26.8±0.82
M4	0.305±0.002	0.354±0.002	14.52±0.79	1.16±0.01	24.8±0.86
M5	0.298±0.007	0.362±0.002	15.69±0.83	1.16±0.03	26.2±1.96
M6	0.306±0.008	0.356±0.001	15.65±0.99	1.19±0.01	23.9±1.92
M7	0.300±0.009	0.362±0.003	15.45±0.90	1.16±0.01	25.4±1.32
M8	0.303±0.005	0.357±0.001	14.51±0.89	1.17±0.02	24.6±0.95
M9	0.299±0.006	0.354±0.003	14.33±0.91	1.19+0.01	26.2±0.88

The bulk density of the montelukast sodium blend ranged from 0.298 g/mL to 0.307 g/mL and the tapped density ranged from 0.354 g/mL to 0.373 g/mL. The compressibility index of the blend ranged from 14.33% to 15.69% and Hausner's ratio ranged from 1.16 to 1.19. The angle of repose of the ranged from 21.3 to 26.8. Hence the entire formulations blend was found to be good, passable flow property.

Post Compression Study of Montelukast sodium

The formulated montelukast sodium tablets were evaluated for post compression parameters. The results of weight variation, thickness, hardness, friability and assay are givenin the Table 14.

Table 14. Post compression of montelukast sodium.

Trial	Weight Variation (%)	Thickness(mm)	Hardness (kg/cm^2)	Friability(%)	Assay (%w/w)
M1	102±0.13	2.37±0.21	3.22±0.17	0.35±0.12	99.05±0.21
M2	100±0.26	2.41±0.25	3.37±0.21	0.40±0.09	101.12±0.14
M3	103±0.21	2.36±0.23	3.14±0.18	0.32±0.05	98.6±0.21
M4	99±0.56	2.39±0.21	3.20±0.20	0.41±0.07	102±0.25
M5	101±0.62	2.41±0.26	3.18±0.14	0.38±0.03	100.8±0.25
M6	98±0.27	2.42±0.25	3.41±0.18	0.49±0.11	98.4±0.11
M7	103±0.47	2.35±0.27	3.32±0.25	0.36±0.02	99.7±0.19
M8	100±0.37	2.43±0.26	3.14±0.23	0.43±0.17	101.4±0.27
M9	98±0.34	2.38±0.21	3.47±0.24	0.36±0.09	98.7±0.12

Weight variation

The percentage weight variations for all formulations were tabulated in the Table 18. The formulated batches passed weight variation test as the Percentage weight variation was within the pharmacopoeial limits.

Thickness

The measured thickness of tablets of each batch ranged between 2.35±0.27 to 2.43±0.41mm. The value shows that formulated tablets have uniform thickness. The parameters were reported in the Table 14

Hardness

The measured hardness of tablets of each batch ranged between 3.14±0.27 to 3.47±0.24 Kg/cm^2. This ensures good handling characteristics of all batches.

Friability

The values of friability test were ranges from 0.32±0.05 to 0.49±0.11. The % friabilitywas less than 1% in all the formulations which ensure that all the tablets were mechanically stable.

Assay

The assay of the formulations ranged between 98.4±0.11 to 102±0.25%w/w. The values are within the pharmacopoeial limits.

***In-Vitro* dissolution**

The *in-vitro* dissolution of all the montelukast sodium tablet are given in the table 19.

Table : 15. *in-vitro* dissolution test

Time point	M1	M2	M3	M4	M5	M6	M7	M8	M9
1 HOURS	24.07	19.68	17.45	10.79	09.32	07.55	8.85	07.15	04.53
2 HOURS	38.97	30.97	27.21	13.21	11.30	09.33	11.99	09.57	06.09
3 HOURS	45.75	36.18	34.15	22.45	20.59	21.78	18.38	16.96	17.85
4 HOURS	53.56	44.52	42.45	28.50	26.90	28.76	23.50	23.79	21.57
5 HOURS	59.03	49.22	47.38	35.23	31.67	39.84	31.98	30.25	35.70
6 HOURS	65.77	56.79	54.23	44.32	39.56	46.70	39.60	39.57	41.58
7 HOURS	71.28	61.89	63.85	51.54	48.99	54.49	48.97	46.68	50.68
8 HOURS	77.15	67.50	69.67	59.77	56.51	63.57	57.65	53.97	59.74
9 HOURS	82.65	73.45	75.54	64.17	60.57	72.49	66.80	65.10	68.51
10 HOURS	88.50	78.31	79.75	72.15	69.50	78.12	70.69	71.78	76.82
11 HOURS	91.80	85.66	83.40	84.70	80.83	83.87	79.25	75.37	80.55
12 HOURS	95.35	89.69	87.69	86.69	83.18	88.51	82.68	80.85	82.22

The dissolution profiles of montelukast sodium studied in phosphate buffer 6.8. The drug release of the formulations were determined. The cumulative drug releases for formulations were ranges from 82.22% to 95.35%. The effects of independent variables on cumulative drug release were investigated as per optimized response parameters.

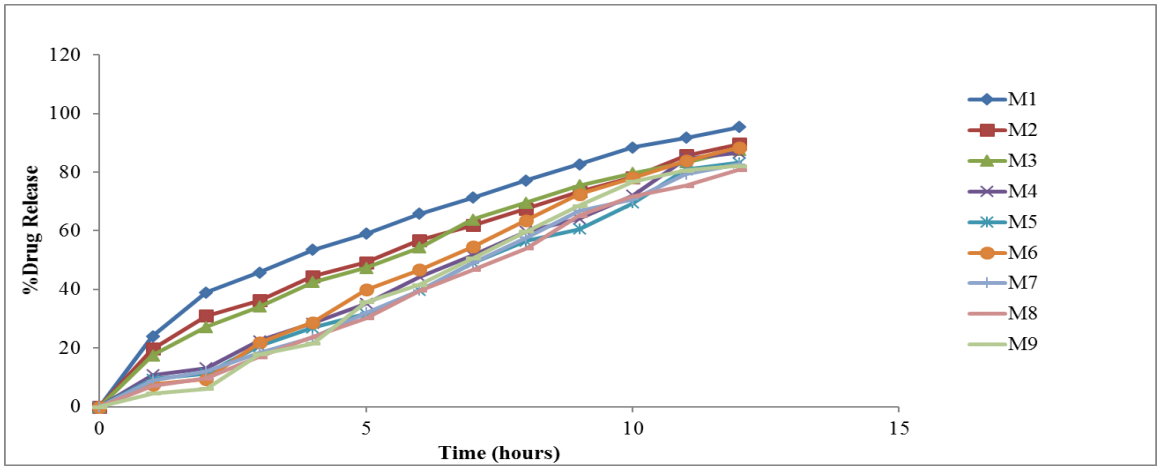

Fig: 9. *In-vitro* dissolution of Montelukast sodium formulations.

Optimization by 3^2Factorial Design

On the basis of defined constraints for each independent variable, the Design Expert® Software version 11 automatically generated the optimized formulation. The experiments were performed and the responses were obtained.

Table 16: Result of independent variable and dependent variable according to 3^2 FactorialDesign.

Run S.NO	Factor 1	Factor 2	Response 1	Response 2
	HPMC	ETHYLCELLULOSE	Time taken for 50 % drug release	Drug releaseat 12 hours
	mg/tablet	mg/tablet	minutes	%
1	20	5	408	86.69
2	30	5	435	82.55
3	10	15	324	87.69
4	20	10	438	83.18
5	10	10	294	89.83
6	10	5	216	95.35
7	30	15	420	82.22
8	20	15	390	88.51
9	30	10	438	80.95

Time taken for 50% drug release

The Fig illustrates, when the amount of hpmc increase, time taken for 50 percent drug release increased and time taken for 50 percent drug release increased when the amount of ethyl cellulose increase.

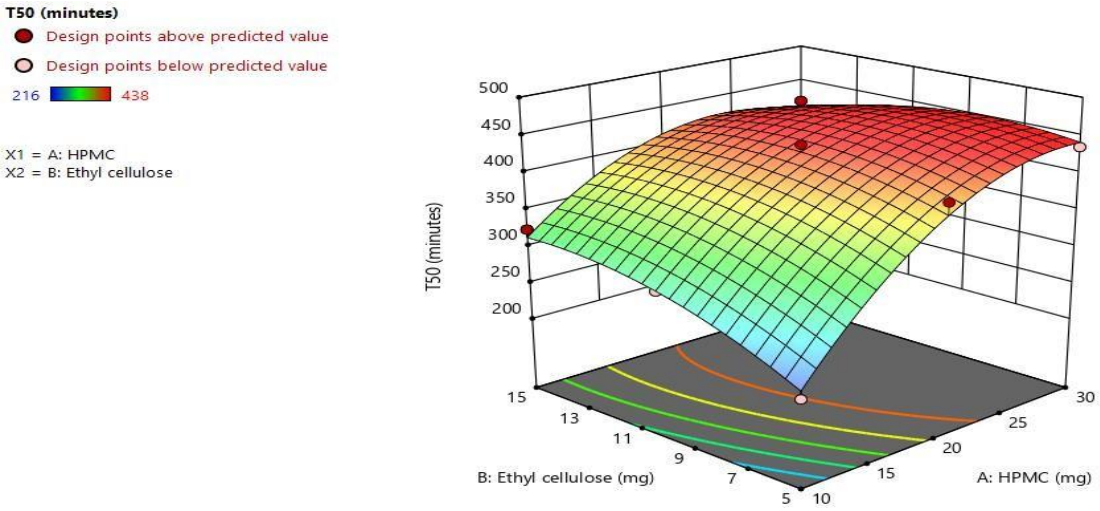

Fig 10: Effect of HPMC and ethyl cellulose on time taken for 50% drug release presented by response surface plots.

Drug release at 12 hours

The Fig illustrates, when the amount of HPMC increase, time taken for drug release at 12 hours release increased and time taken for drug release at 12 hours increased with when the amount of ethyl cellulose increase.

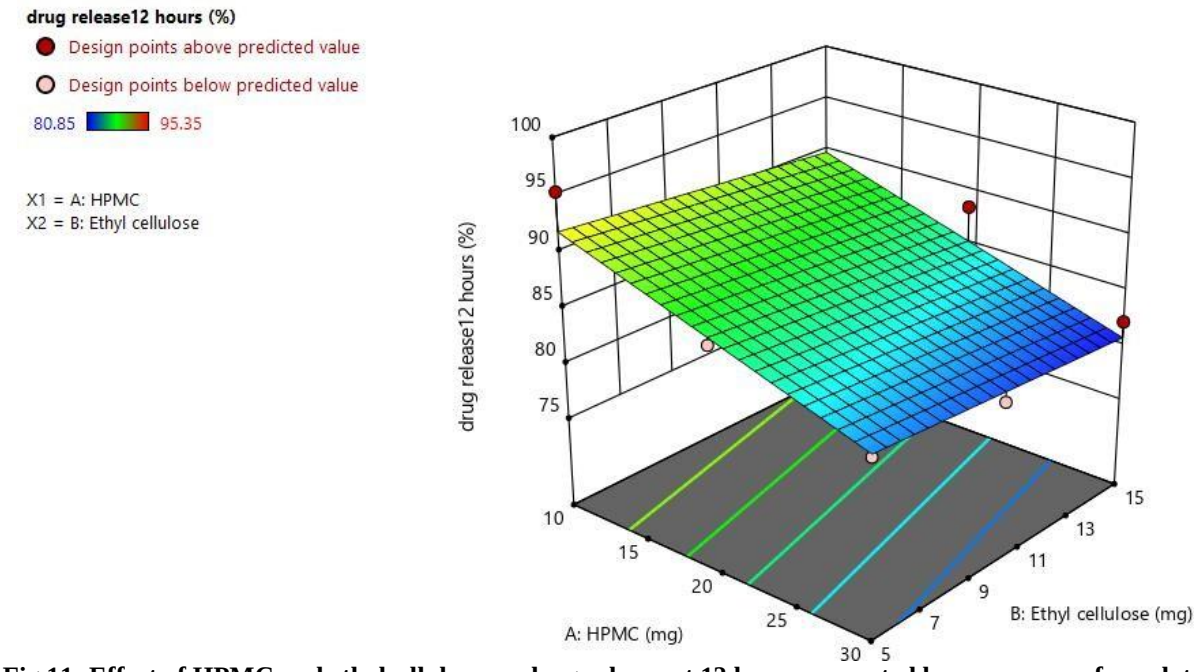

Fig 11: Effect of HPMC and ethylcellulose on drug release at 12 hours presented byresponse surface plots.

ANOVA

Table represents the statistical parameters such as adjusted R2, predicted R2, model P values, adequate precision and %CV. Based on Table 28 the responses time taken for 50% drug release, drug release at 12th hour was well fitted to the linear model with P value of <0.0500. Table 23 shows adjusted R2 for Y1 and Y2 which is in reasonable agreement with the predicted R2. Adequate precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable ratio indicating an adequate signal. This model can be used to navigate the design space. The results show that 90% of response variations in drug release, disintegration time could be described by Factorial design as a function of main composition. So it can be concluded that linear model was suitable model for analysis and could show very good interaction between time taken for 50% drug release and drug release at 12 hours of montelukast sodium tablets.

Table 17: Response model and statistical parameters obtained from ANOVA for 3^2 factorialdesign.

Responses	Adjusted R2	PredictedR2	Model Pvalue	Adequateprecision	%CV
Time taken for 50 % drug release	0.6416	0.3583	0.0194	11.5013	6.29
Drug release at 12 hours	0.6783	0.4299	0.0140	7.3482	3.04

Point Prediction

The montelukast sodium tablets were formulated and responses were measured. The software generated the optimized formulation and predict the response based on the constraint. Then batch was formulated based on the suggested formulation and response were obsereved. The observed values of responses were compared to the predicted values of the response and % error was calculated to validate the method. The observed value of Y1 and Y2 were in a close agreement to the predicted one. By this the validity of optimization procedure was proven. The point prediction has been shown in then Table 18.

Desirability of optimum formulation was 0.936. When desirability value is between 0.8 and 1, the formulation quality is regarded to be acceptable and excellent. When this value is <0.63, the formulation quality is regarded as poor.

Table 18: Optimum formulation derived by Factorial design.

Factor	HPMC	Ethyl cellulose	Desirability
Optimum formulation	16.76	9.61	0.936

Table 19: Point Prediction for Montelukast sodium tablets.

Point Prediction	Time taken for 50% drug release	Drug release at 12 hours (min)
Predicted	395.5	87.87
Observed	398.5	89.20
% error	0.75	1.513

% error = (observed value-predicted value)/predicted value x 100.

Table 20: Post Compression report of Optimized montelukast sodium tablets.

Trial	Weight Variation (%)	Thickness (mm)	Hardness(kg/cm^2)	Friability (%)	Assay (%w/w)
Optimized Formulation	100±0.38	2.38± 31	3.35±0.21	0.41±0.07	99.7

Fig 12: Optimized formulation of Montelukast sodium.

From the above parameter of optimized formulation trial it had been concluded that blend of the above trial is used for formulating with Desloratadine as Bilayer tablets.

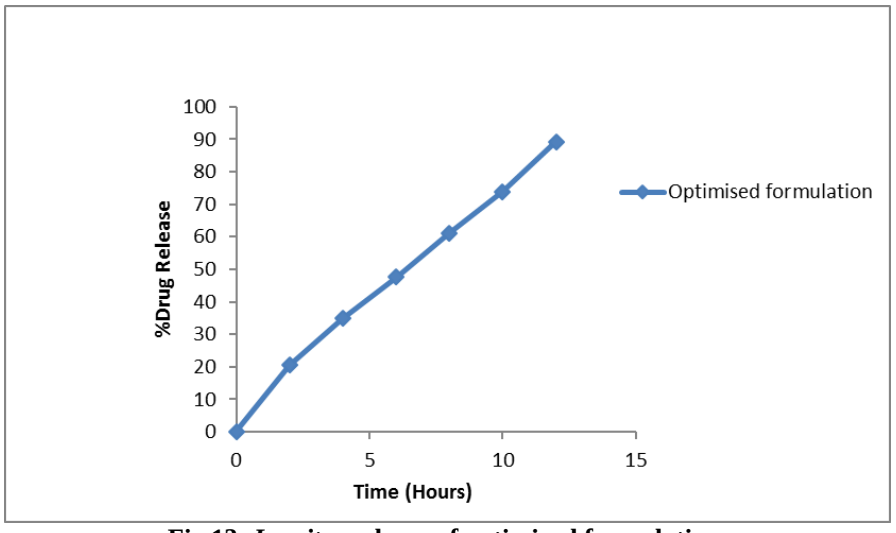

Fig 13: *In- vitro* release of optimized formulation.

FOR DESLORATADINE TABLET

Recompression Study of Desloratadine

The formulated blends of desloratadine were evaluated for pre compressionparameters. The results are given in the Table 21.

Table 21: precompression study of Desloratadine tablet.

Formulation	Bulk density (gm/ml)	Tappeddensity (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle ofrepose (θ)
D1	0.4221±0.013	0.4751±0.015	10.44±0.247	1.12±0.025	25.49±0.20
D2	0.4215±0.016	0.4640±0.013	11.09±0.239	1.11±0.021	24.43±0.21

The bulk density of the montelukast sodium blend ranged from 0.4215 g/mL to 0.4221 g/mL and the tapped density ranged from 0.4751 g/mL to 0.4640 g/mL. The compressibility index of the blend ranged from 10.44% to 11.09% and Hausner's ratio ranged from 1.11 to 1.12. The angle of repose of the ranged from 24.43 to 25.498. Hence the entire formulations blend was found to be good, passable flow property.

Post Compression Study of Desloratadine

Table 22: post compression study of Desloratadine.

Trial	Weight Variation (%)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintigration time (sec)	Assay (%w/w)
D1	101.4mg	2.32	3.5±0.20	0.7	10 sec	98.37
D2	100mg	2.36	4 ±0.52	0.3	12 sec	99.84

Weight Variation

The percentage weight variations for all formulations were tabulated in Table. All the formulated batch passed weight variation test as the Percentage weight variation was within the pharmacopoeial limits which ranges from 101.4mg to 100mg.

Thickness

The measured thickness of tablets of each batch have uniform thickness. The batches ranges from 2.3 mm to 2.4 mm.

Hardness

The measured hardness of tablets of each batch ranged between 3.5±0.20 to 4±0.52.

Friability

The values of friability test were tabulated in Table No. The %friability of each batch was ranged between 0.3 to 0.7%.

Assay

The assay of the formulations ranged between 92.37 - 97.84% w/w. The values are within the limits. The results were shown in Table 22.

Disintegration time

The disintegration time of all the batches were found between 10 to 12 seconds and results were shown in Table 22.

***In-Vitro* dissolution**

The *In-vitro* dissolution of all the desloratadine tablet are given in the table 23.

Table 23: *In-vitro* dissolution of Desloratadine tablet.

Time	D1	D2
10mins	47.54	45.73
20mins	68.36	63.57
30mins	85.47	82.89
40mins	93.21	92.64
45mins	98.42	95.37

The dissolution profiles of desloratadine tablet were studied in phosphate buffer 6.8. The drug release of the formulations were determined and given in Table 23 and plotted in Fig.19. The cumulative drug releases for formulations were found within the range of 98.42 - 95.37 %. From the above observation it has been clear that trial D1 shows, lower hardness and high friability (0.7). So trial D2 was formulated using 10% dry binder (pregelatinized starch) all the post compression parameter was within the acceptable range. Hence trial D2 was chosen as optimized formulation. Thus for the further formulation of bilayer tablet, the blend of trial D2 was used.

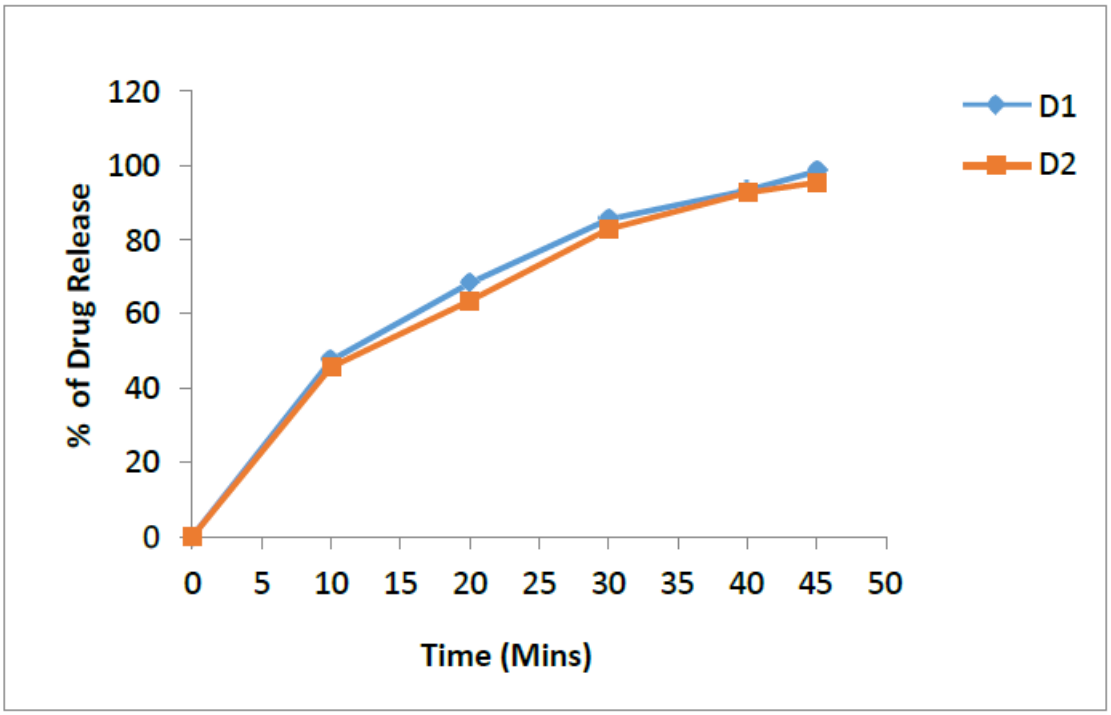

Fig 14: *In-vitro* dissolution of Desloratadine formulation.

Post Compression Study Of Bilayer Tablets

The compressed bilayer tablets were evaluated for following parameters and the values are given in the table 24.

Table 24: Post Compression Study of Bilayer Tablets.

Weight variation	Thickness	Hardness	Friability	Disintegration time	Assay (Simultaneous EstimationMethod)	
					Montelukast sodium	Desloratadine
200.4	3.12	6±0.12	0.42	12 sec	99.52	99.86

Fig : 15. Optimized Formulation of Desloratadine.

Table 25: *In - Vitro* dissolution of Bilayer tablet of Montelukast sodium and Desloratadine.

Time	Desloratadine
10mins	43.21
20mins	64.48
30mins	81.37
40mins	93.65
45mins	94.37

Time	Montelukast sodium
1 Hours	11.25
2 Hours	19.42
3 Hours	25.45
4 Hours	32.83
5 Hours	40.95
6 Hours	48.61
7 Hours	53.45
8 Hours	63.24
9 Hours	66.90
10 Hours	71.89
11 Hours	83.78
12 Hours	87.20

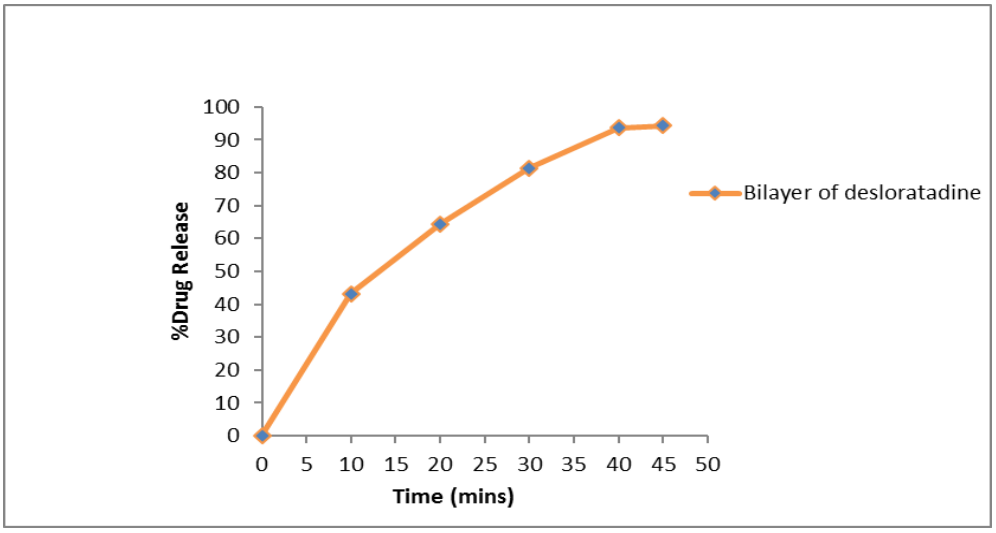

Fig 16: *In - Vitro* dissolution of optimized formulation of Desloratadine.

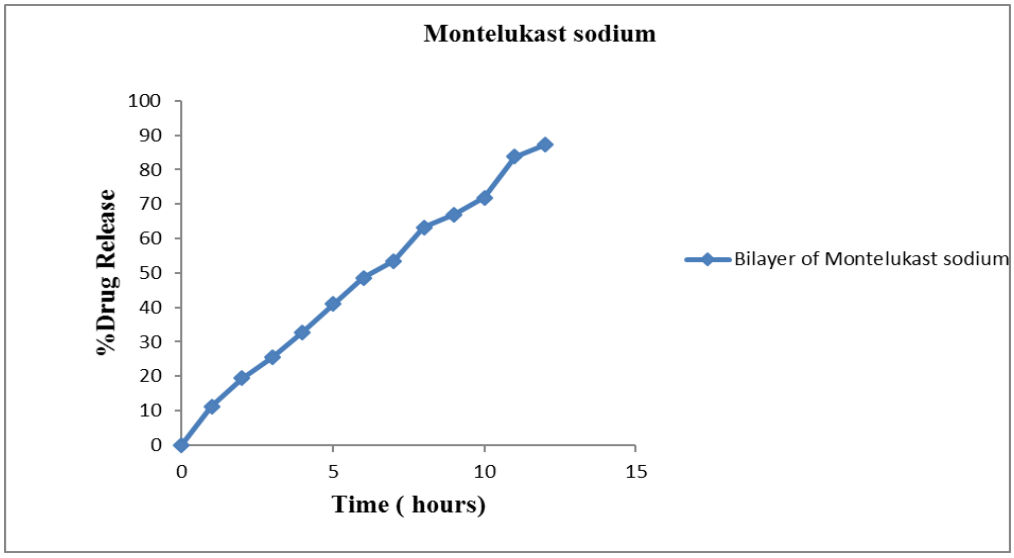

Fig: 17. *In – Vitro* dissolution of optimized formulation of Montelukast sodium.

- Friability was less than 1% ensuring that the tablets were mechanically stable.
- The measured thickness of tablets were uniform in size.
- The Disintegration time for Desloratadine were found to be 12 sec seconds.
- The percentage of drug content for was found to be 99.52% for montelukast sodium and 99.86% for desloratadine, it complies with official specifications.
- The Bilayer tablets showed release of 87.20 % of montelukast sodium (SR) in 12 hours and 94.37 %

of Desloratadine in 45 minutes.

Fig 18: Optimized formulation of Bilayer tablets.

***IN-VITRO* KINETICS STUDY**

The values obtained from *in vitro* dissolution of montelukast sodium from bilayer tablets were fitted in various kinetics models. The results are given in the Table 26.

Table 26: *In vitro* release kinetics of bilayer tablets.

S.no	Time (hrs)	% Drugrelease	Zero order kinetics	First order Log % drug remaining	Higuchi Squareroot of time	Pepas Log % oftime	Hixon Cube root of drug release
1	2	20.42	79.58	1.9008	1.4142	0.3010	2.7332
2	4	34.83	65.17	1.8140	2	0.6020	3.2657
3	6	47.61	52.39	1.7192	2.4494	0.7781	3.6243
4	8	61.24	38.76	1.5883	2.8284	0.9030	3.9416
5	10	73.89	26.11	1.4168	3.1622	1	4.1962
6	12	89.20	10.8	1.0334	3.4641	1.0791	4.4680

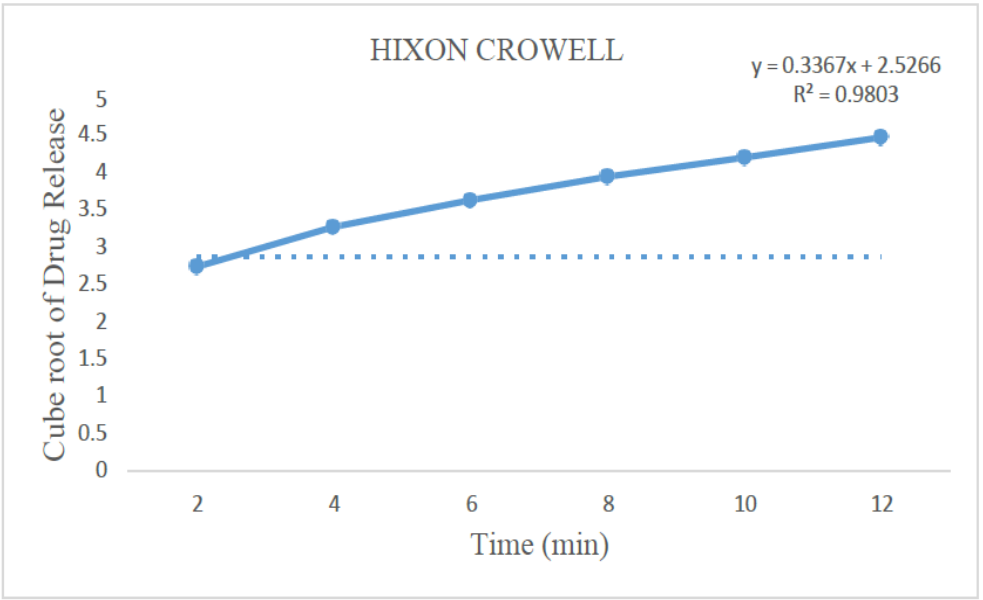

Fig: 19. Hixon crowell.

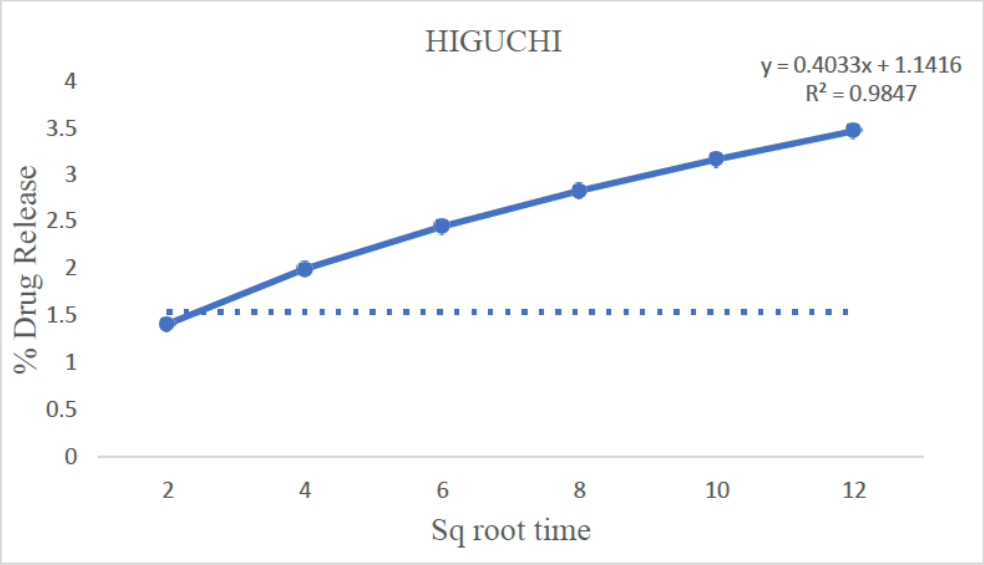

Fig 20: Higuchi.

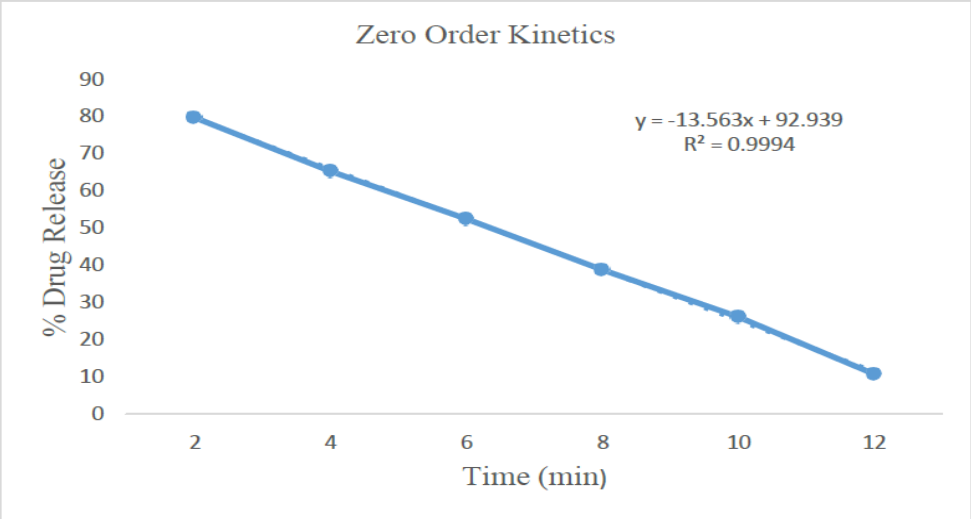

Fig 21: zero order kinetics.

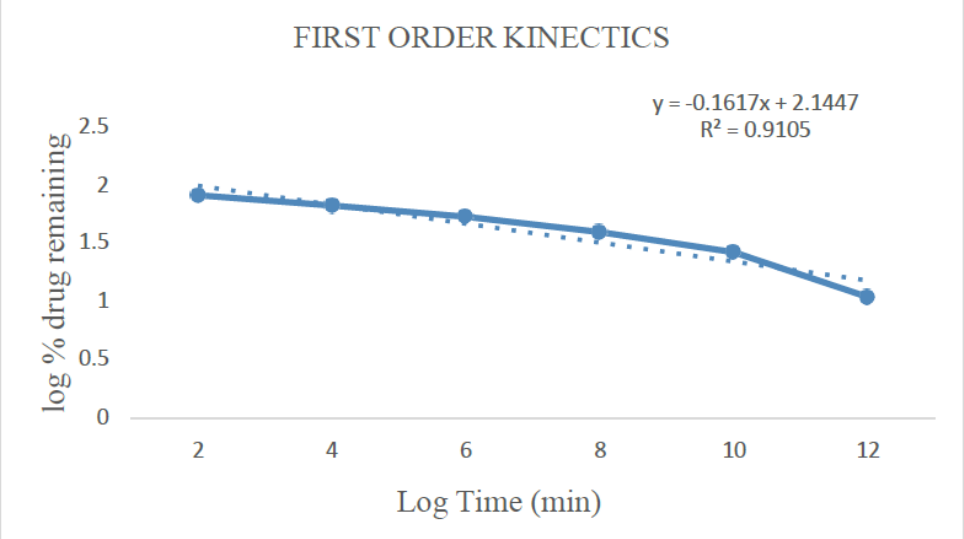

Fig 22: First order kinectics.

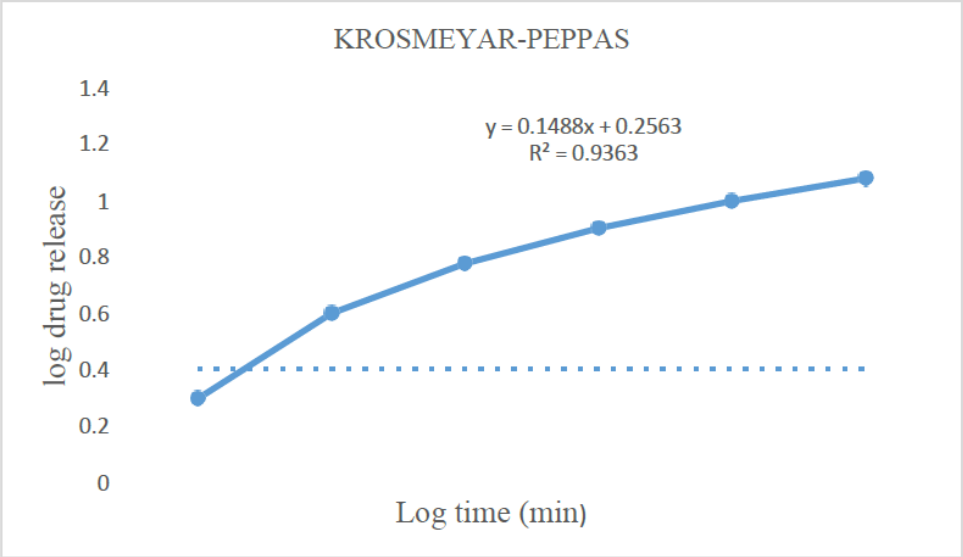

Fig 23: krosmeyar- peppas.

Determination of drug release mechanism of optimized bilayer tablets

- From the drug release kinetic study the results indicates that the in-vitro release of bilayer tablets is fitted with various models such as zero order kinectics, first order kinectics, hixon crowell, krosmeyar- peppas.
- The models were evaluated based on the slope and regression (R^2) values, the respective R^2 and N values of models were given in the table 31.
- The in-vitro drug release of the optimized bilayer formulation is best fitted and found to follow zero order kinetics with a higher R^2 value of 0.9994.

STABILITY STUDIES

Stability studies were carried out of the optimized 9 formulation at 40°C ± 2°C & 75 % ± 5 % RH for 30 days as per ICH guidelines. At various time intervals (initial, 15 days & 30 days), samples were evaluated for appearance, average weight (mg), drug content (%). There was no major change in the evaluation parameters. The results were shown in Table 32.

Table 27: Stability results of Bilayer tablet.

Parameters	Storage condition 40°C ± 2°C & 75 % ± 5 % RH		
	Intial	15 days	30 days
Appearance	No changes	No changes	No changes
Average weight(mg)	200.4	200.4	200.4
Assay 1.Montelukast sodium(%) 2.Desloratadine(%)	 99.52 99.86	 99.45 99.74	 99.28 99.51

CONCLUSION

The present study was aimed to develop bilayer tablets of montelukast sodium as SR layer and Desloratadine as IR layer to treat seasonal allergic rhinitis. The bilayer tablets were formulated by combining montelukast sodium with desloratadine which gives additional benefits in comparison with either drug alone and could be considered for patients whose quality of life, impaired by persistent allergic rhinitis. The tablets were formulated using hydrophilic polymerssuch as HPMC K4M and ethyl cellulose in varying ratios to retard the drug release for a period of 12 hours. The immediate release layer of Desloratadine was formulated using pregelatinzed starch (5% and 10 %).

All the formulations were evaluated for physical characteristics, drug content, dissolution, release kinetics and stability studies.

- The Drug- excipient interaction was investigated with FTIR spectroscopy. The study indicated that there was no interaction between the drugs and the excipients used in theformulations.
- The formulated granules were evaluated for precompression studies which showes that the flow property was good.
- The formulated tablets were found to be within the limits with respect to Weight variation, Hardness, Thickness and Friability.
- The friability of IR tablets containing pregelatinzed starch 10% was found to be optimum.
- Nine batches of montelukast sodium formulations containing varying proportions of HPMC K4M and

ethyl cellulose were subjected to *in vitro* dissolution study of SR tablet, optimized formulation were selected using DOE software and selected for bilayer tablets.

- The optimized formulations of both montelukast sosdium and desloratadine were compressed into bilayer tablets.
- The **drug content** of the bilayer tablets were estimated by simultaneous estimation method and it was found to be within the Pharmacopoeial limits.
- The **release kinetics** of the optimized tablets showed that it follows zero order releasekinetics.
- The **stability studies** indicated that the bilayer tablets were stable and do not show any significant changes in the physical characteristics, drug content and dissolution. The results obtained were found to be within the limits.

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