World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org

SJIF Impact Factor: 7.409

FORMULATION AND DEVELOPMENT OF CONTROLLED RELEASE TABLETS OF MONTELUKAST SODIUM

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Article Received on 25/04/2025 **Article Revised on 14/05/2025** **Article Accepted on 04/06/2025**

ABSTRACT

Montelukast sodium is a Leukotriene receptor antagonist used for the maintenance treatment of Asthma and to relieve symptoms of seasonal allergies and it's a BCS class II drug with half-life of 2.7 to 5.5 hrs. Mean oral bioavailability is about 64%. The objective of this study was to develop the Sustained release matrix tablets of Montelukast sodium by Direct Compression method using various polymers such as Xanthan gum, Ethyl cellulose and Eudragit RSPO in various concentrations. The drug excipient mixtures were subjected to pre- formulation studies. FTIR study was shown there was no interaction between drug and polymers. Optimization was carried out using Stat- Ease software. A randomized 2^3 full factorial design was selected. Based on Central composite design the polymers concentration should be optimized. The formulation F1 to F9, the polymer ratio was optimized as low and high level with QbD. The tablets were subjected to physicochemical evaluation, *in vitro* drug release, kinetic and stability studies. The physicochemical properties of tablets were found within the limits. And all the formulations (F1to F9) shows the drug release between 89.92% and 93.89%. The optimized formulation F10 showed maximum drug release of 95.49% at the end of 12hrs. The drug release kinetic data confirmed that all the formulation (F1 to F10) fit in Higuchi model which shows the highest R^2 value of 0.966 to 0.995. The results of *in vitro* release data were fitted to the Korsmeyer Peppa's equation to analyse pattern of the drug release from polymeric system. The slope (n) value was found between 0.539 – 0.682, indicating that the drug release follows non-Fickian release mechanism. It can be concluded that combination of Eudragit RSPO with other polymer (F10) shows stable and better duration of release rate, when compared to individual polymer.

KEYWORDS: Montelukast sodium, Xanthan gum, Ethyl cellulose, Eudragit RSPO, Optimized-(F10), QbD, Sustained release, Higuchi model, Non-Fickian release.

INTRODUCTION

Oral drug delivery is the most widely utilized routes for administration among other routes.[1] Asthma is a chronic obstructive lung disease characterized by airway inflammation and hyperactivity. Clinical and epidemiological studies verify that asthma is several hundred folds more likely at night than during day with the disturbance of sleep. A drug delivery system would deliver drug at night but releasing drug upto morning hours would be ideal.[2]

Montelukast sodium is a highly selective and competitive antagonist of Leukotriene receptors. Leukotrienes are the important mediators of inflammation. They bring about bronchospasm, mucosal oedema, increase in the influx of inflammatory cells and respiratory mucus production by their action of leukotriene receptor especially on the cysteinyl leukotriene receptor cysLT1 in the lungs and bronchial tubes. Montelukast works by blocking the action of Leukotriene D4 in the lungs by binding to it. It reduces the bronchial constriction caused by Leukotriene which results in less inflammation and also relaxation of smooth muscles.[3]

MATERIALS AND METHODS

Materials

Montelukast sodium, Xanthan gum, Ethyl cellulose, Eudragit RSPO, Lactose, Microcrystalline cellulose, Magnesium stearate and Talc.

Methods

I. Drug-Excipient Compatibility studies

FT-IR: Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drug, Polymers and drug-polymer mixture were subjected to FTIR studies using Schimadzu FTIR spectrometer model to investigate the Drug-Polymer interactions. The IR spectra of the test samples were

obtained by pressed pellet technique using Potassium bromide and the ratio of the sample is 1: 100.[4]

II. Optimization Design of Experiment

Design of experiments (DOE) is a systematic method to determine the relationship between factors affecting a process and the output of that process.[5]

Stat-Ease DOE software: 3 steps
1. Design Experiment Design
2. Analyze data design
3. Visualize results design.[6]

ANOVA

Analysis of variance (ANOVA) is an analysis tool used in statistics that splits an observed aggregate variability found inside a data set into two parts: systematic factors and random factors. The systematic factors have a statistical influence on the given data set, while the random factors do not. Analysts use the ANOVA test to determine the influence that independent variables have on the dependent variable in a regression study. Fisher's statistical test using ANOVA was performed to evaluate the significance of the reduced linear model.[7]

Contour plot

A contour plot is a graphical technique for representing a 3-dimensional surface by plotting constant *z* slices, called contours on a 2-dimensional format. That is, given a value for *z*, lines are drawn for connecting the (x, y) coordinates where that *z* value occurs. The contour plot is an alternative to a 3-D surface plot.[8]

3D Surface interpretation

3D response surface and contour plots were made to investigate the relationship between different variables and response, in order to obtain the optimal formulation conditions that would maximize the yield. Three-dimensional (3D) response surface and contour plot showing the effect of Polymers.[9]

III. Construction of standard curve for Montelukast Sodium Preparation of stock solution

100 mg of pure Montelukast Sodium was accurately weighed and transferred to 100 ml volumetric flask. Drug was dissolved in phosphate buffer pH 7.4 along with 0.5% SDS and the volume was made upto 100 ml.

Preparation of standard solution

From this 10 ml of the solution was taken in a 100 ml volumetric flask and make upto 100 ml using phosphate buffer pH 7.4 along with 0.5% SDS. From this 10ml of the solution was taken and made upto 100 ml using phosphate buffer pH 7.4 along with 0.5% SDS. From the above solution 2, 4, 6, 8 and 10 ml was taken and made upto 10ml using phosphate buffer pH 7.4 along with 0.5% SDS to obtain concentration in range of 2-10 µg/ ml. The spectra were recorded, absorbance was measured at 347 nm and the standard curve was plotted.[10]

IV. Formulation of Tablets

A total number of ten formulations were prepared by direct compression method. Sustained release tablets of Montelukast sodium were prepared by using drug and various concentrations of polymers (Xanthan gum, Ethyl cellulose and Eudragit RSPO) while Lactose used as filler; Microcrystalline cellulose was used as diluent; Magnesium stearate was incorporated as lubricant and talc as anti-adherent. All ingredients were passed through a #100 sieve, weighed, and blended. The lubricated formulations were compressed by a direct compression technique, using 6/32 mm punches in a rotary tablet press.[2]

Composition of various tablet formulations (F1 to F10) Table: 1.

S. no	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Montelukast sodium	10	10	10	10	10	10	10	10	10	10
2.	Xanthan Gum	10	15	20	-	-	-	-	-	-	15.5
3.	Ethyl cellulose	-	-	-	10	15	20	-	-	-	13.6
4.	Eudragit RSPO	-	-	-	-	-	-	10	15	20	14.47
5.	Lactose	44	39	34	44	39	34	44	39	34	10.43
6.	MCC	30	30	30	30	30	30	30	30	30	30
7.	Magnesium stearate	3	3	3	3	3	3	3	3	3	3
8.	Talc	3	3	3	3	3	3	3	3	3	3

V. Pre- compression parameter Angle of repose

For determination of angle of repose (θ), the blend was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2cm above surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel.

$$\theta = \tan^{-1}(h/r)$$

Where,
h = height of the pile in cm r = radius of the pile in cm

Bulk density

It is the ratio of the total mass of powder to the bulk volume of the powder. It was measured by pouring the weighed powder into a measuring cylinder and the initial weight was noted. This initial volume was called bulk volume. Bulk density was calculated according to the formula mentioned below. It is expressed in gm/ ml.

$$\rho_b = M / V_b$$

Where,
M = mass of the powder
V_b = Bulk volume of the powder

Tapped density

It is the ratio of total mass of the powder to the tapped volume of the powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for 50 times on a wooden surface at a 2 second interval and the volume attained is the tapped volume. It is expressed in gm/ml and is given by

$\rho_t = M / V_t$

Where,

M = mass of the powder

V_t = tapped volume of the powder

Carr's index

It indicates powder flow properties. It is measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and is given by.

$$CI = \frac{\rho t - \rho b}{\rho t} \times 100$$

Where,

ρ_t = tapped density ρ_b = bulk density

Hasuner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$HR = \rho_t / \rho_b$

Where,

ρ_t = tapped density

ρ_b = bulk density.[11,12,13]

VI. Post - compression Parameters Thickness

Vernier caliper scale was used for the determination of the thickness of tablets, which gives accurate measurements and provides information of the variation between the tablets.[14]

Hardness

Hardness test is defined as the force which is required to break a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared tablet was determined by using Monsanto hardness tester. It was expressed in kg/cm^2.

Friability

Friability of the prepared tablets was determined by using Roche Friabilator. Pre- weighed 10 no's of tablets was placed in the friability apparatus and subjected to 25 rpm in 4 mins. Tablets were dedusted and reweighed.

$$\% \text{ Friability} = \frac{\text{Intial weight of the tablets} - \text{Final weight of the tablets}}{\text{Final weight of the tablets}} \times 100$$

Drug content analysis

5 tablets were taken and crushed to get a fine powder. Weigh 30mg of the powdered tablet and transferred into 100 ml volumetric flask, dissolve and make upto 30ml using phosphate buffer pH 7.4 along with 0.5% SDS. 15 µg/ml was prepared using phosphate buffer pH 7.4 along with 0.5% SDS and compared with pure drug.[2]

Weight variation

The weight variation study was performed by weighing 20 tablets individually and finding the average weight. The deviation of the weight of the tablets from the average weight was determined as the weight variation. Not more than 2 of individual weight of tablets out from the average weight by more than the percentage deviation and none deviate by more than twice the percentage.[14]

***In-Vitro* drug release studies**

The release of Montelukast sodium from the tablets was studied in 900 ml of phosphate buffer pH 7.4 along with 0.5% SDS upto 12 hrs. An aliquot 1 ml was withdrawn at specific time intervals and replaced by an equal volume of dissolution medium. Then the samples were diluted upto 10 ml with the dissolution medium and analysed for Montelukast sodium content by UV-Visible Spectrophotometer at 347nm.[2,14]

VII. Kinetic Analysis of *In vitro* release study

The Experimental results of the release studies were fitted according to,

1. Zero-order kinetic model – Cumulative percentage drug release versus time.
2. First-order kinetic model – Log cumulative drug remaining versus time.
3. Higuchi's model – cumulative percent drug release versus square root of time
4. Korsmeyer equation/ Peppa's model – Log cumulative percent drug released versus log time.[15,16]

VIII. Stability studies

The stability studies carried out as per the ICH guidelines and the optimized formulation (F10) were placed in stability chamber.

- Stability chamber 1 = 30° C and 60% RH
- Stability chamber 2 = 35° C and 65% RH
- Stability chamber 3 = 45° C and 75% RH

The prepared tablets were place in the stability chambers. The sample should be withdrawn at a specific period of time (0, 1st, 3rd and 6th month). Then the tablets were tested for its Hardness, Friability, Drug content and *In-vitro* drug release studies.[17]

RESULTS

I. Compatibility studies

The FT-IR spectra of the Montelukast sodium and physical mixture of drug and polymer are represented in the following figures. The most intensive absorption band of N–H bend observed in the range of 3500^{-1}, N–H stretching in the range of 1500 cm^{-1}. The most intensive absorption band of OH group, C=O and CH observed in the range of 3400, 1050 and 2900 cm^{-1}.

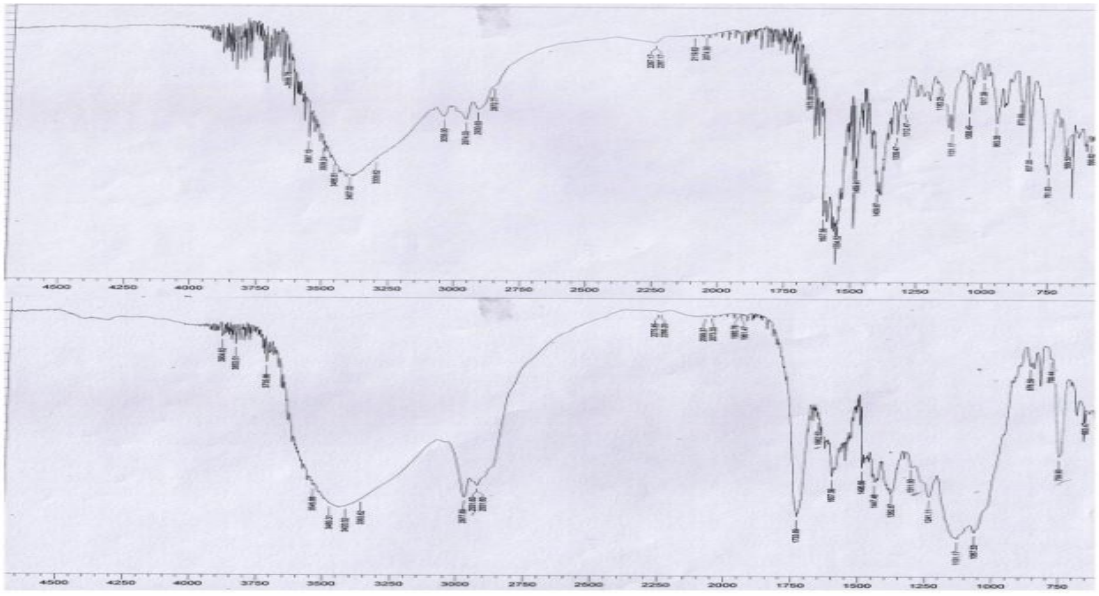

Fig. 1.

N–H bend and N–H Stretch observed in 3480.31 and 1496.66 cm^{-1}. OH stretching, C=O stretching, CH stretching and COOH group observed in 3420.52, 1067.53, 2931.60 and 1733.89. All the functional group in Montelukast sodium are maintained in the sustained release formulation. None of the functional groups of either drug or polymer have undergone any chemical reactions. All the functional groups are intact. Hence it is confirmed that no chemical reactions have taken place.

II. Optimization ANOVA

The ANOVA result shows that the F- value of 0.24 for lack of fit, p- Value of 0.0218 and R^2 value of 0.2595 for dissolution and hardness.

Contour Plot

The standard value for contour plot should lies between 0.8-1.0. Fig. 2 indicates desirability of the selected model was within the limit (0.942).

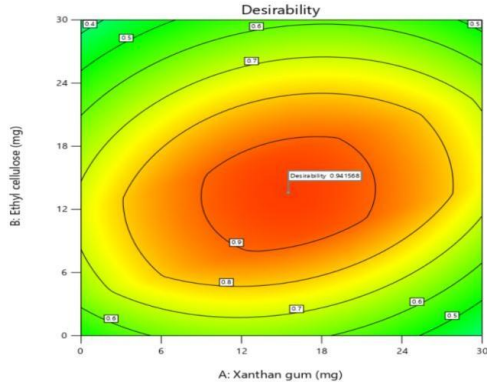

Fig. 2.

3D interpretation plot

The 3D interpretation plot (Fig. 3) indicates factor (A, B and C), Xanthan gum, Ethyl cellulose and Eudragit RSPO respectively, then the values shows 15.5, 13.6 and 14.47 mg. The above said range was within the optimized limit.

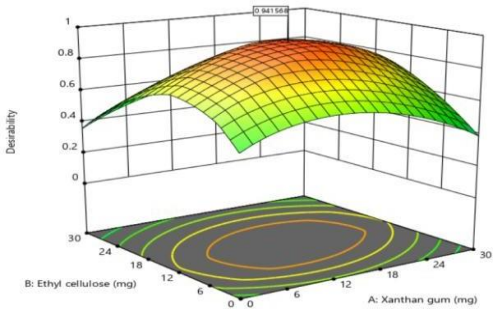

Fig. 3.

III. Standard curve of Montelukast Sodium Table: 2.

Concentration (µg/ ml)	Absorbance (347nm)
0	0
2	0.248
4	0.456
6	0.704
8	0.906
10	1.110

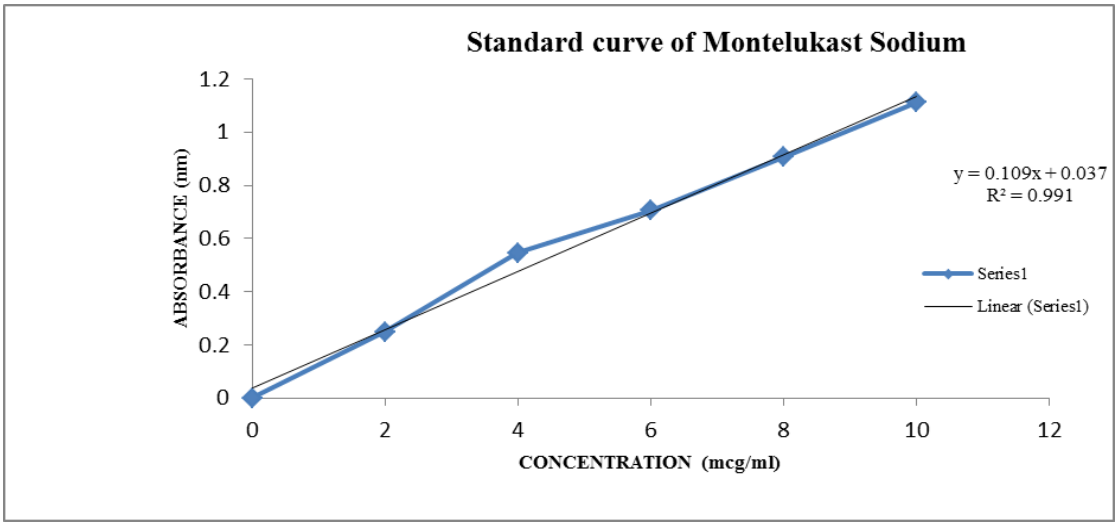

Fig. 4

IV. Pre-Compression parameter Table: 3.

Formulation code	Angle of Repose	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	Carr's Index (%)	Hausner's ratio
F1	33.5±1.5307	0.524±0.0127	0.663±0.0095	20.96±0.8015	1.26547±0.0127
F2	32.3±1.3076	0.551±0.0058	0.671±0.0005	17.91±0.8519	1.21835±0.0125
F3	34.3±1.7058	0.530±0.0055	0.664±0.0011	20.25±0.83	1.25418±0.0130
F4	32.8±1.8330	0.544±0.0075	0.666±0.0028	18.39±0.8164	1.22560±0.0123
F5	32.1±0.3	0.535±0.0036	0.655±0.0020	18.39±0.3510	1.22557±0.0052
F6	33.4±0.4	0.541±0.0050	0.668±0.0047	19.03±0.7823	1.23527±0.0119
F7	33.9±1.6093	0.528±0.0064	0.668±0.0066	20.94±0.4361	1.26502±0.0069
F8	31.0±1.4177	0.553±0.0098	0.668±0.003	17.10±1.5569	1.20676±0.0225
F9	30.3±0.9539	0.579±0.023	0.673±0.0117	13.92±2.2136	1.16238±0.0299
F10	31.3±0.4725	0.573±0.0095	0.660±0.0011	13.22±1.3209	1.15261±0.0175

All the values are expressed as mean ± S.D, n= 3

V. Post-Compression parameter Table: 4

Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Weight variation (mg)
F1	4.133±0.2081	5.33±0.2108	0.51±0.0208	93.33±0.6636	100.75±3.0065
F2	4.233±0.3785	5.7±0.2001	0.42±0.0207	94.21±0.4278	100.1±3.2428
F3	4.0±0.1	5.56±0.1527	0.44±0.0152	95.02±0.5548	99.35±2.4767
F4	4.2±0.1732	5.36±0.1527	0.47±0.01	94.76±0.5770	99.65±2.7582
F5	4.133±0.2081	5.5±0.1	0.39±0.0208	94.39±0.4708	99.4±3.2019
F6	4.10±0.3605	5.63±0.2081	0.49±0.0450	92.68±0.3306	99.55±3.4561
F7	4.33±0.1001	5.4±0,1	0.40±0.02	94.43±0.8399	100.05±2.6252
F8	4.2±0.1	5.8±0.0577	0.39±0.0416	95.32±1.0850	100.3±3.4043
F9	4.30±0.1	5.7±0.1527	0.42±0.0152	96.57±0.4592	101.1±3.3229
F10	4.33±0.0577	5.96±0.1527	0.32±0.0152	98.66±0.6490	101.75±2.5318

All the values are expressed as mean ± S.D, n= 3

Comparative *In-Vitro* release profile of Montelukast sodium from F1 to F10 Table: 5

TIME (HRS)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)	F10 (%)
0	0	0	0	0	0	0	0	0	0	0
0.5	22.28	19.09	17.5	23.87	17.5	15.11	19.09	15.11	15.11	14.32
1	27.07	23.87	22.28	27.85	24.66	21.48	29.44	23.87	21.48	19.8
2	39.78	33.42	38.19	38.19	35.8	27.85	38.99	29.44	38.99	25.46
3	47.74	46.15	43.76	49.33	46.94	44.56	50.13	38.19	54.11	38.99
4	62.06	59.68	55.7	63.66	58.09	56.49	59.68	49.33	59.68	51.72
5	75.59	67.63	65.25	76.39	65.25	63.66	70.82	59.68	64.45	62.06

6	83.55	76.39	71.01	85.14	75.57	72.41	74.8	66.04	77.98	68.43
7	87.53	82.75	81.16	89.12	81.96	80.37	83.55	75.59	81.16	71.61
8	90.71	87.53	85.14	92.3	86.73	84.35	89.12	85.14	87.53	75.59
9		91.51	87.53		91.51	88.32	92.3	93.89	90.71	79.57
10			92.3			89.92			93.1	86.73
11										90.71
12										95.49

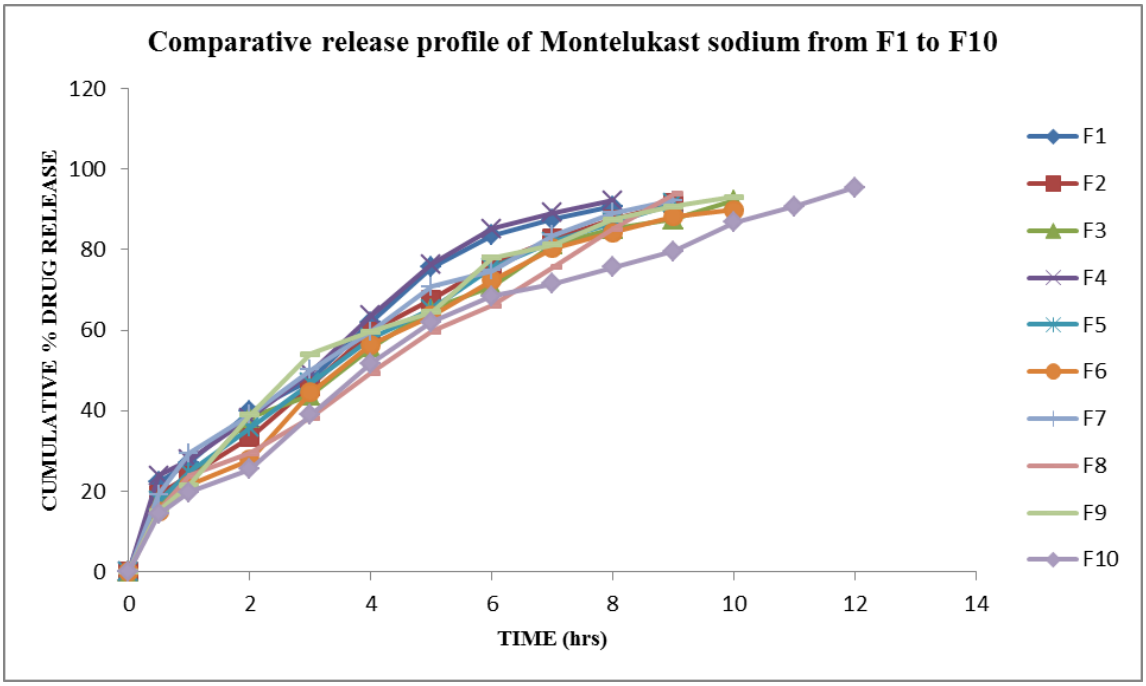

Fig. 5.

VI. Kinetic analysis of formulation F1 to F 10 Table: 6.

Form. code	Zero order plot	First order plot	Higuchi plot	Korsmeyer Peppa's plot		Possible mechanism of drug release
	R^2	R^2	R^2	R^2	n	
F1	0.913	0.982	0.984	0.978	0.552	Higuchi release, non-fickian mechanism
F2	0.899	0.985	0.987	0.984	0.587	Higuchi release, non-fickian mechanism
F3	0.895	0.984	0.991	0.992	0.588	Higuchi release, non-fickian mechanism
F4	0.933	0.978	0.982	0.969	**0.539**	Higuchi release, non-fickian mechanism
F5	0.906	0.981	0.991	0.996	0.593	Higuchi release, non-fickian mechanism
F6	0.904	0.980	0.982	0.983	0.637	Higuchi release, non-fickian mechanism
F7	0.843	0.980	**0.995**	0.996	0.549	Higuchi release, non-fickian mechanism
F8	0.953	0.895	**0.966**	0.981	0.623	Higuchi release, non-fickian mechanism
F9	0.839	0.988	0.989	0.987	0.630	Higuchi release, non-fickian mechanism
F10	0.882	0.948	0.984	0.982	**0.682**	Higuchi release, non-fickian mechanism

VII. Stability Studies

The freshly prepared samples were analysed (0 month)

Table: 7.

Formulation code	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	% *In vitro* drug release
F10	5.96	0.32	98.66	95.49 %

The samples were taken on 1st month and analysed for the following.

Table: 8.

Batch	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	% *In vitro* drug release
Batch 1	5.95	0.34	98.41	95.03
Batch 2	5.94	0.35	98.39	94.95
Batch 3	5.91	0.36	98.15	94.27

Then the samples are further taken on 3rd month and analyzed for the following.

Table: 9.

Batch	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	% *In vitro* drug release
Batch 1	5.93	0.35	98.35	94.67
Batch 2	5.89	0.37	98.28	94.31
Batch 3	5.87	0.39	98.05	93.89

Then the samples are further taken on 6th month and analysed for the following.

Table: 10.

Batch	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	% *In vitro* drug release
Batch 1	5.81	0.37	97.34	94.17
Batch 2	5.84	0.38	97.64	93.75
Batch 3	5.85	0.40	97.05	93.28

DISCUSSION

In the present study Sustained release Montelukast sodium matrix tablets were prepared by using different polymers at various concentrations by direct compression method.

The compatibility study of drug and polymer composition was studied by using FT-IR. The spectrum of drug and polymer showed the major characteristics of absorption bands of polymers in Xanthan gum, Ethyl cellulose and Eudragit RSPO with negligible difference of absorption band values. So, FT-IR spectra shows there is no change in nature and position of absorption band, which indicates no chemical reaction between Montelukast sodium with Xanthan gum, Ethyl cellulose and Eudragit RSPO.

Optimization was carried out using Stat-Ease software. A randomized 2^3 full factorial design was selected. Based on Central composite design the polymers concentration should be optimized. The optimized formula should be selected on the basis of ANOVA for reduced linear model, Desirability and lack of fit value. Stability studies were carried out for optimized formulation and are complies within the limit.

The physical characteristics of tablets were evaluated for thickness, hardness, friability, weight variation and Drug content. All the batches showed uniform thickness. The parameters like hardness, friability and weight variation test were within the acceptable limit. Hence, all the tablets are uniformity in weight. The drug content of Montelukast sodium in all the formulations was present within the acceptable limit which indicates the uniformity of drug present in all the formulation.

In vitro drug release characteristics were studied in 900 ml of phosphate buffer pH 7.4 using 0.5% SDS for upto 12 hrs; using USP dissolution apparatus type II (paddle type). The results of *in vitro* drug release studies for formulation F1 to F9 ranges from 89.92 to 93.89%. Also the result of *in vitro* drug release study indicates that the optimized formulation F10 shows the higher drug release rates of 95.49% upto 12hrs.

To know the mechanism of drug release from these formulations, the data were treated according to zero order, first order, Higuchi model and Korsemeyer peppa's model. The formulations F1 to F10 shows higher regression value for Higuchi release kinetics. The *in vitro* release profiles of drug from all the formulations could be best expressed in Higuchi's equation, as the plot shows regression value of 0.966 to 0.995. To confirm the release mechanism, the data were fitted in korsemeyer peppa's equation, with slope values (n) ranges from 0.539 to 0.682. This result suggests that the release of

drug follows non-Fickian mechanism.

CONCLUSION

The study was concluded that the Sustained release matrix tablets containing Montelukast sodium were prepared by direct compression method and their evaluation tests were carried out. The *in-vitro* release study of the optimized formulation F10 was found to be a most promising formulation and maintained excellent release of 95.49% at the end of 12hrs. All the formulation F1 to F10 follows Higuchi's model of drug release. The results of the *in-vitro* data were fitted to the Korsmeyer Peppa's equation, the 'n' value was found between 0.539 to 0.682, indicating that the drug release follows non - Fickian release mechanism. The stability studies of the optimized formulations show that there were no significant changes in the formulation. It can be concluded that the combination of Eudragit RSPO with other polymer (F10) shows better duration of release rate when compared to individual polymer.

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