FORMULATION AND EVALUATION OF CONTROLLED RELEASE TABLETS OF MONTELUKAST

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ABSTARCT

A controlled drug delivery system is usually designed to deliver the drug at the particular rate. The performance of a drug presented as a controlled release system depends upon its release from the formulation. Montelukast controlled release tablets were prepared by Direct compression method by using three different polymers Eudragit S 100, HPMC K4 M and HPMC K15 M as rate controlling polymer in three different ratios like 1:1, 1:2 and 1:3 to achieve desired release in later case. Physical characterization of tablet and powder blends used to form the matrix tablet was under taken using a range of experimental techniques. Granules were evaluated for Bulk density, Tapped density, Compressibility index and Hausner's ratio. Tablets were tested for weight variation, hardness, thickness and friability as per official procedure. The tablets were evaluated for *in-vitro* drug release profile. Dissolution studies of Montelukast controlled release tablets in media with different dissolution media 0.1N HCl, Phosphate buffer pH (6.8) as per US Pharmacopoeia. The dissolution data revealed that the ratio of polymers is very important to achieve an optimum formulation. The formulation of Montelukast CR tablets shown that formulation F5 with HPMC K4 M (10mg) shown good drug release profile.

KEYWORDS: Montelukast, Eudragit S 100, HPMC K4 M and HPMC K15 M, Controlled release tablets.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption.[1,2,3]

Controlled release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Greater attention is paid on development of oral controlled release drug delivery systems due to flexibility in designing of dosage form. The main challenges to oral drug delivery systems are to deliver a drug at therapeutically effective rate to desirable site, modulation of GI transit time and minimization of first pass elimination. Control release dosage form provides better maintenance of optimal and effective drug level for prolonged duration with less dosing frequency and side effects.[4,5]

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimised.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time the goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.[6]

The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetics, and pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by most

suitable route. The immediate release drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specified period of treatment.

MATERIALS AND METHODS

Montelukast Provided by SURA LABS, Dilsukhnagar, Hyderabad. Eudragit S 100 from Merck Specialities Pvt Ltd, Mumbai, India. HPMC K4 M from Merck Specialities Pvt Ltd, Mumbai, India. HPMC K15 M from Merck Specialities Pvt Ltd, Mumbai, India. MCC from Merck Specialities Pvt Ltd, Mumbai, India. PVP K30 from Merck Specialities Pvt Ltd, Mumbai, India. Magnesium stearate from Merck Specialities Pvt Ltd, Mumbai, India. Talc from Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Analytical method development:

Preparation of 0.1N HCl

Diluted 8.5mL of Concentrated Hydrochloric acid to 1000mL of Purified water and mixed

Preparation of 0.2M NaOH Solution

Dissolved 4g of Sodium hydroxide pellets in to 1000mL of Purified water and mixed

Preparation of pH 6.8 Phosphate buffer

Dissolved 6.805 g of Potassium dihydrogen phosphate in to 800mL of purified water and mixed added 112mL of 0.2M NaOH solution and mixed. Diluted to volume 1000mL with purified water and mixed. Than adjusted the pH of this solution to 6.8 with 0.2M NaOH solution.

a) Determination of absorption maxima:

100mg of Montelukast pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). And pH 6.8 Phosphate buffer UV spectrums were taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:

100mg of Montelukast pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5, 10, 15, 20 and 25 µg/ml of Montelukast per ml of solution. The absorbance of the above dilutions was measured at 265 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 1.The tablets were prepared as per the procedure given below and aim is to prolong the release of Montelukast. Total weight of the tablet was considered as 100mg.

Procedure:

1) Montelukast and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 1: Formulation composition for tablets

INGREDIENTS	FORMULATION CHART											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Montelukast	10	10	10	10	10	10	10	10	10	10	10	10
Eudragit S 100	5	10	15	20	-	-	-	-	-	-	-	-
HPMC K4 M	-	-	-	-	10	15	20	25	-	-	-	-
HPMC K15 M	-	-	-	-	-	-	-	-	20	25	30	45
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
PVP K30	8	8	8	8	8	8	8	8	8	8	8	8
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total Tablet Weight	100	100	100	100	100	100	100	100	100	100	100	100

All the quantities were in mg

RESULTS AND DISCUSSION

Standard Calibration curve of Montelukast:

Table 2: Concentration and absorbance obtained for calibration curve of Montelukast in 0.1 N hydrochloric acid buffers (pH 1.2**)**

S. No.	Concentration (µg/ml)	Absorbance* (at 285 nm)
1	0	0
2	5	0.127
3	10	0.237
4	15	0.341

5	20	0.448
6	25	0.557

It was found that the estimation of Montelukast by UV spectrophotometric method at λ_{max} 285 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml.

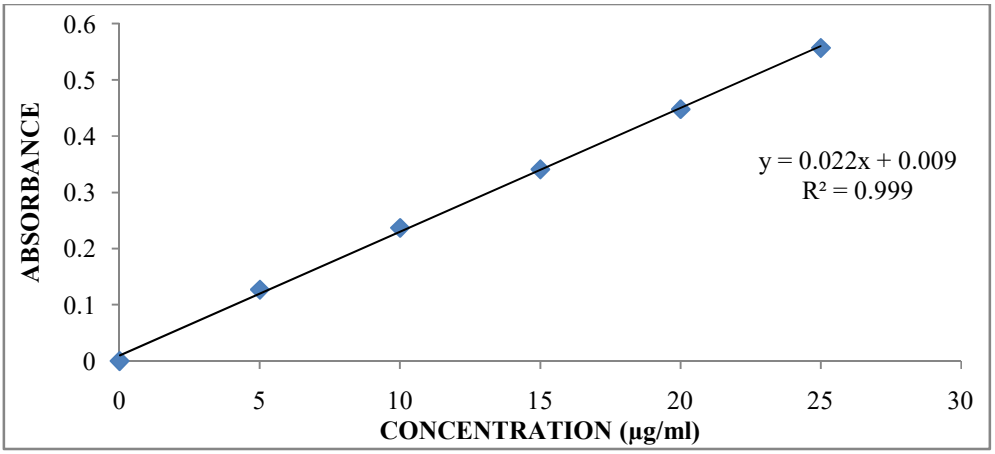

Fig 1: Standard graph of Montelukast in 0.1 N HCl

Table 3: Concentration and absorbance obtained for calibration curve of Montelukast in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 287 nm)
1	0	0
2	5	0.136
3	10	0.245

4	15	0.366
5	20	0.481
6	25	0.596

It was found that the estimation of Montelukast by UV spectrophotometric method at λ_{max} 287 nm in pH 6.8 Phosphate buffer. It had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5-25µg/ml.

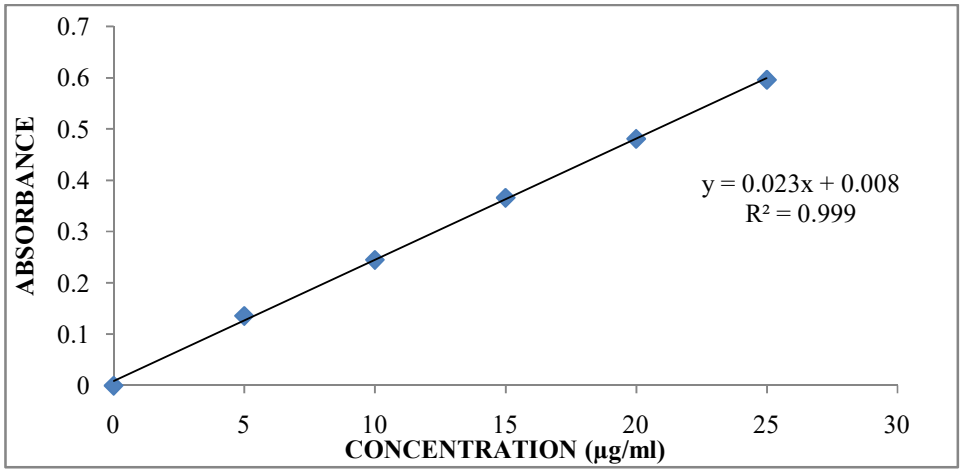

Fig 2: Standard graph of Montelukast in pH 6.8 Phosphate buffer

Evaluation Parameters for Controlled release tablets of Montelukast:

Evaluation:

Characterization of precompression blend:

The precompression blend Montelukast were characterized with respect to angle of repose , bulk density , tapped density , Carr's index and Hausner's ratio. Angle of repose was less than 28 °, Carr's index values were less than 11 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 foe all batches indicating good flow properties.

Table 4: Physical properties of precompression blend

Formulation code	Angle of repose (Ɵ)	Bulk density (gm/cm^3	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	39.90 ± 0.01	0.424 ± 0.001	0.517 ± 0.01	18.00 ± 0.01	1.21 ± 0.01
F2	40.13 ± 0.01	0.412 ±0.015	0.530 ±0.021	22.23 ± 0.01	1.29 ± 0.01
F3	19.98 ± 0.01	0.348 ±0.001	0.401 ± 0.001	13.22 ± 0.01	1.15 ± 0.01
F4	20.36 ± 0.015	0.523 ± 0.002	0.604 ± 0.017	13.41 ± 0.02	1.15 ± 0.01
F5	20.60 ± 0.015	0.382 ± 0.001	0.439 ± 0.002	12.98 ± 0.01	1.15 ± 0.01
F6	21.41 ± 0.01	0.421 ± 0.002	0.492 ± 0.002	14.43 ± 0.02	1.17 ± 0.02
F7	20.16 ± 0.015	0.465 ± 0.015	0.532 ± 0.001	12.59 ± 0.01	1.14 ± 0.01
F8	19.66 ± 0.02	0.332 ± 0.002	0.375 ± 0.015	11.46 ± 0.01	1.13 ± 0.01
F9	24.72 ± 0.01	0.345 ± 0.018	0.401 ± 0.012	13.97 ± 0.01	1.16 ± 0.02
F10	22.31 ± 0.015	0.386 ± 0.002	0.443 ± 0.015	12.87 ± 0.01	1.15 ± 0.01
F11	25.12 ± 0.015	0.373 ± 0.012	0.446 ± 0.03	16.67 ± 0.01	1.20 ± 0.01
F12	23.26 ± 0.001	0.409 ± 0.001	0.462 ± 0.001	11.47 ± 0.01	1.13 ± 0.01

Post compression Parameters:

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 5. The average weight of the tablet is approximately in range of 95.89 to 100.21mg, so the permissible limit is ±5% (100 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 5. The results showed that the hardness of the tablets is in range of 4.2 to 5.4 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-5 the result showed that thickness of the tablet is raging from 3.05 to 3.91 mm.

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 5. The average friability of all the formulations lies in the range of 0.16 to 0.32 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 95.83-100.02%.

Table 5: post compression parameter:

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (% loss)	Thickness (mm)	Drug content (%)
F1	98.25	4.6	0.26	3.31	98.35
F2	100.12	4.9	0.19	3.61	99.16
F3	99.87	5.1	0.22	3.78	100.02
F4	100.03	5.3	0.16	3.91	97.56
F5	96.38	4.6	0.25	3.37	99.38
F6	100.21	5.0	0.31	3.10	96.72
F7	98.87	4.7	0.29	3.13	95.83
F8	99.46	4.2	0.19	3.18	99.14
F9	97.59	5.2	0.26	3.05	98.76
F10	98.73	4.3	0.22	3.34	97.62
F11	96.46	4.9	0.28	3.27	99.21

F12	95.89	5.4	0.32	3.37	98.36

***In Vitro* Drug Release Studies**

***In-Vitro* Dissolution studies:** *In-Vitro* dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 12 hours. The samples were withdrawn at regular time intervals of 30 min, 1 hour, 2, 3,4,5,6,7,8,9, 10, 11 and 12 hours respectively. The results were displayed in table 6.

Table 6: *In -vitro* dissolution data

TIME (HRS)	CUMULATIVE % OF DRUG RELEASE											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	12.52	8.39	7.19	10.96	14.62	10.58	13.72	10.41	12.38	8.36	9.39	6.35
2	17.37	16.17	19.72	14.83	19.68	15.64	18.14	16.34	18.29	14.49	19.75	13.92
3	27.48	25.35	23.93	21.78	25.64	27.11	25.76	21.92	23.71	26.38	26.31	18.72
4	42.26	36.17	29.54	27.41	31.48	38.97	35.10	28.76	32.92	34.97	32.68	28.92
5	54.18	48.86	35.41	35.79	36.95	45.65	46.28	33.63	38.49	48.11	48.97	34.89
6	58.71	56.61	39.76	41.86	48.72	52.74	55.19	45.21	46.58	53.38	57.45	47.22
7	66.33	69.14	56.19	47.31	59.39	64.22	64.98	49.34	58.26	65.15	65.53	53.81

8	75.85	75.59	64.72	53.22	63.14	75.94	69.75	57.27	69.15	74.59	72.97	59.78
9	83.95	83.61	67.29	61.89	67.58	84.19	74.15	68.34	76.87	78.67	75.32	63.75
10	86.78	85.34	72.34	67.15	74.11	88.76	79.37	73.27	84.62	82.98	82.47	69.18
11	90.15	89.23	76.52	72.93	80.64	92.36	85.48	81.54	88.48	87.35	85.59	73.82
12	96.15	92.45	84.42	76.42	98.96	95.15	91.86	87.12	94.12	90.24	87.67	78.49

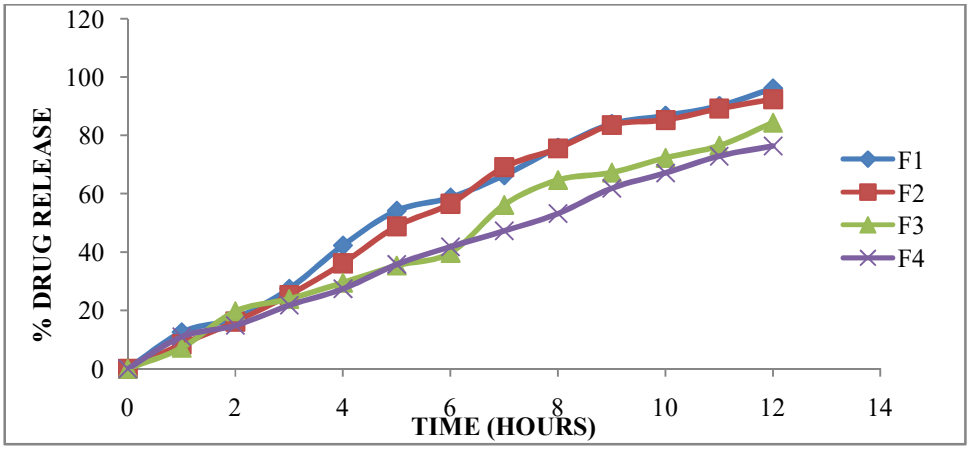

Fig 3: Dissolution profile of formulations prepared with Eudragit S 100 polymer

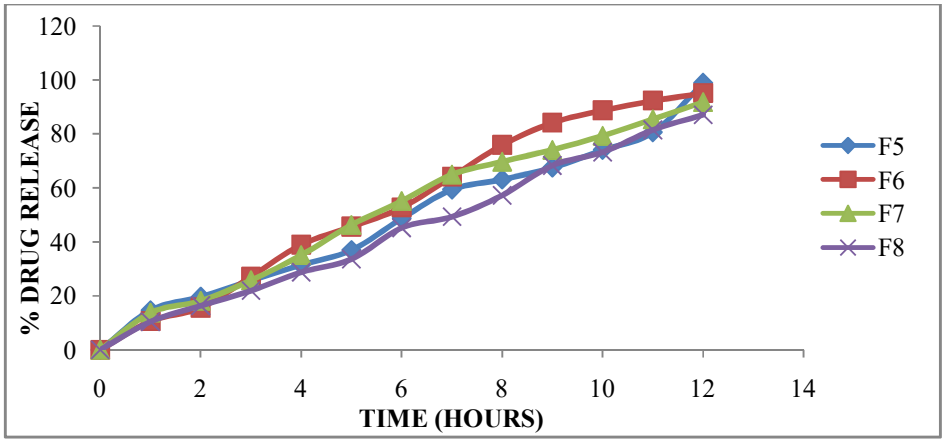

Fig 4: Dissolution profile of formulations prepared with HPMC K4 M polymer

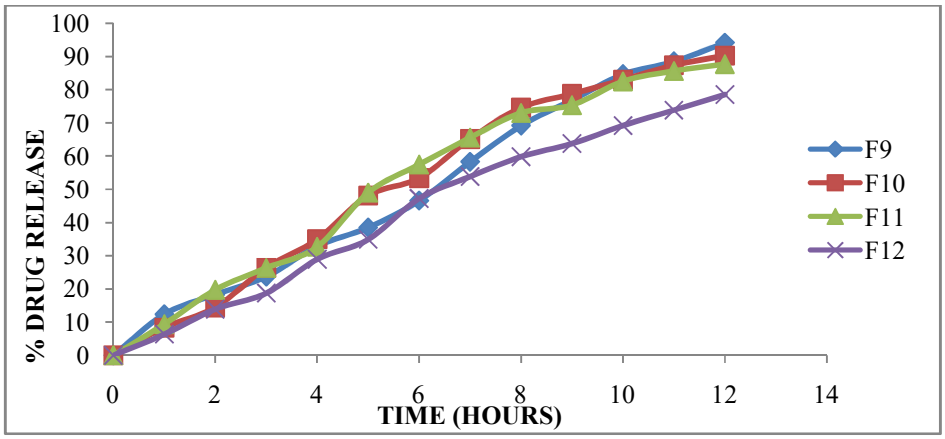

Fig 5: Dissolution profile of formulations prepared with HPMC K15 M as polymer

From the tabular column 6 it was evident that the formulations prepared with Eudragit S 100 as retarding polymer in high concentrations the polymer was unable to produce the required retarding action to the tablets. As the concentration of polymer low the retarding nature was also increased. Eudragit S 100 in the concentration of 5 mg showed good % drug release i.e., 96.15 in 12 hours.

Where as in case of formulations prepared with HPMC K4 M as retarding polymer, the formulations with 10 mg concentration of polymer showed complete drug release in 12 hours only, whereas the concentration of polymer increases the retarding nature decreased. The Formulation Containing HPMC K4 M in 10 Mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.96 %.

Where as in case of formulations prepared with HPMC K15 M as retarding polymer, the formulations with 20 mg concentration of polymer able to showed complete drug release in 12 hours, The Formulation Containing HPMC K15 M in 20 Mg Concentration showed good retarding nature with required drug release in 12 hours i.e., 94.12%.

From the above results it was evident that the formulation F5 is best formulation with desired drug release pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release mode

Table 7: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
14.62	1	1.000	1.165	0.000	1.931	14.620	0.0684	-0.835	85.38	4.642	**4.403**	0.238
19.68	2	1.414	1.294	0.301	1.905	9.840	0.0508	-0.706	80.32	4.642	4.315	0.327
25.64	3	1.732	1.409	0.477	1.871	8.547	0.0390	-0.591	74.36	4.642	4.205	0.436
31.48	4	2.000	1.498	0.602	1.836	7.870	0.0318	-0.502	68.52	4.642	4.092	0.550
36.95	5	2.236	1.568	0.699	1.800	7.390	0.0271	-0.432	63.05	4.642	3.980	0.661
48.72	6	2.449	1.688	0.778	1.710	8.120	0.0205	-0.312	51.28	4.642	3.715	0.926
59.39	7	2.646	1.774	0.845	1.609	8.484	0.0168	-0.226	40.61	4.642	3.437	1.204
63.14	8	2.828	1.800	0.903	1.567	7.893	0.0158	-0.200	36.86	4.642	3.328	1.314
67.58	9	3.000	1.830	0.954	1.511	7.509	0.0148	-0.170	32.42	4.642	3.189	1.453
74.11	10	3.162	1.870	1.000	1.413	7.411	0.0135	-0.130	25.89	4.642	2.958	1.683
80.64	11	3.317	1.907	1.041	1.287	7.331	0.0124	-0.093	19.36	4.642	2.685	1.956
98.96	12	3.464	1.995	1.079	0.017	8.247	0.0101	#DIV/0!	1.04	4.642	1.013	3.628

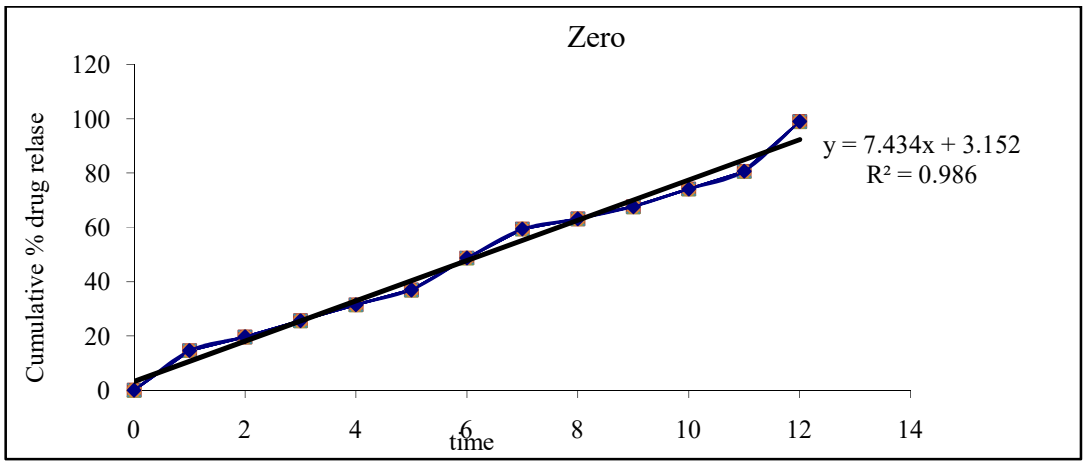

Fig 6 : Zero order release kinetics graph

From the above graphs it was evident that the formulation F5 was followed Zero order release mechanism.

FTIR

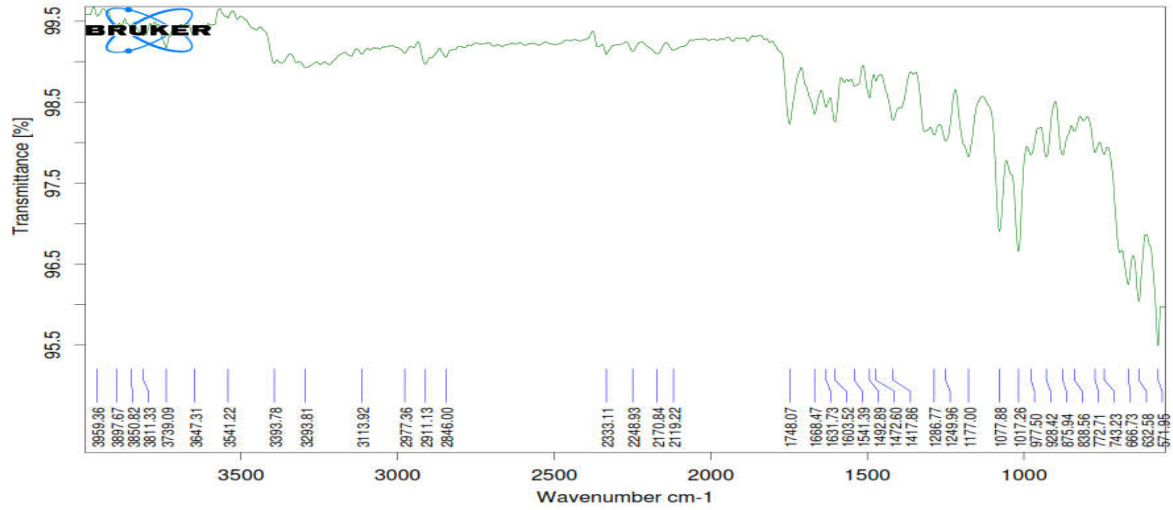

Fig no 7: FT-TR Spectrum of Montelukast pure drug

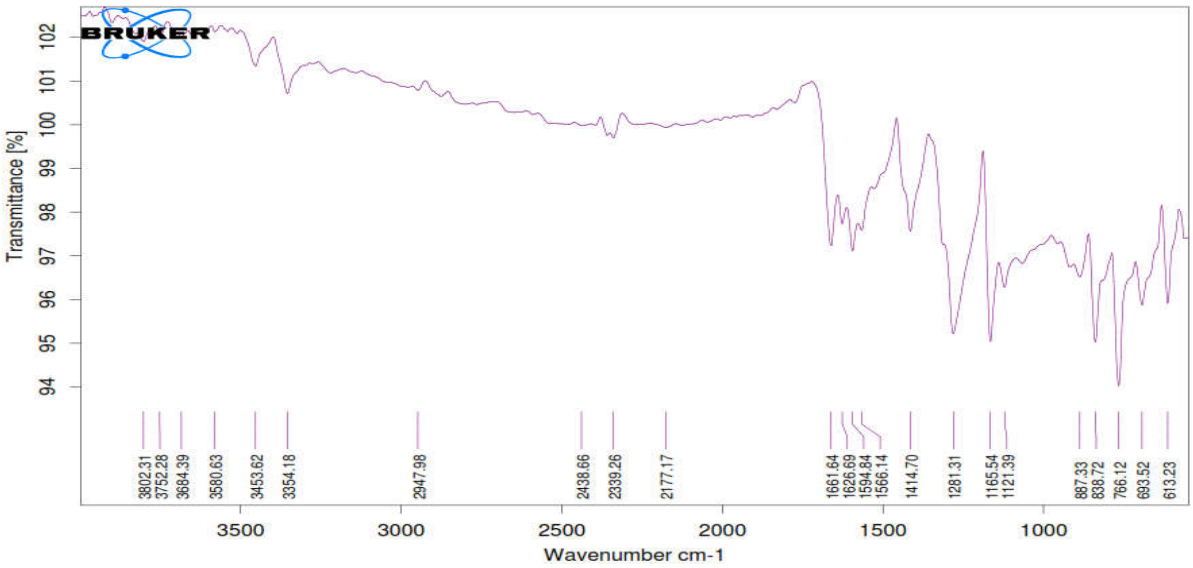

Fig No 8 :FT-IR Spectrum of Optimised Formulation

There is no incompatibility of pure drug and excipients. There is no disappearence of peaks of pure drug and in optimised formulation.

CONCLUSION

Montelukast, sold under the brand name Singulair among others, is a medication used in the maintenance treatment of asthma. It is generally less preferred for this use than inhaled corticosteroids. It is not useful for acute asthma attacks. Other uses include allergic rhinitis and hives of long duration. For allergic rhinitis it is a second-line treatment. The objective of the present study was to investigate the possibility of sustaining the Montelukast release from matrix tablet prepared by using different concentration of polymers.

The following conclusions can be drawn from the result obtained.

- ✓ FTIR studies revealed that there was no chemical interaction between drug and other excipients.
- ✓ All the formulations were subjected for various pre-compression studies such as angle of repose, bulk density; tapped density, Carr's index, Hausner's ratio and results revealed that the powder mixtures showed good to acceptable flow and compressibility properties.
- ✓ All the formulations were subjected for various post-compression studies such as weight variation, hardness, thickness, friability, drug content and *in-vitro* dissolution studies all other parameters were within the standard official specifications.
- ✓ Various formulations were developed by using release rate controlling polymers like Eudragit S 100, HPMC K4 M and HPMC K15 M by direct compression method.
- ✓ We conclude that from among all the developed formulations, F5 formulation controlled the drug release for longer period of time over 12 h when compare to other formulations. So, F5 was selected as the best formulation.
- ✓ To analyze the mechanism of drug release from the tablet, the *in-vitro* drug release data were fitted to Zero order, First order, Higuchi and Korsmeyer-Peppas model. It was observed that the release of drug followed Zero order release kinetics.

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