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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF MONTELUKAST SODIUM

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ABSTRACT

The objective of this study was to develop sustained release tablets of Montelukast sodium by direct compression method using various polymers. The drug excipient mixtures were subjected to pre-formulation studies. The tablets were subjected to physicochemical studies, *in- vitro* drug release, kinetic studies and stability studies. FTIR and DSC studies shown there was no interaction between drug and polymers. The physicochemical properties of tablets were found within the limits. Montelukast sodium is a leukotriene receptor antagonist used for the maintenance treatment of asthma. The drug release from formulations was extended for a period of 12 hrs. The kinetic treatment showed that the release of drug follows first order models. The optimized formulations were subjected to stability studies and shown there were no significant changes in drug content, physicochemical parameters and release pattern. Results of the present study indicated the suitability of the above mentioned polymers in the preparation of sustained release formulation of Montelukast sodium.

Keywords: Montelukast sodium, Sustained release, Matrix tablets, direct compression

INTRODUCTION

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing [1,2]. Nevertheless, it is probable that at least 90% of all drugs used to produce systemic effects are administered by oral route **(see Figure 1).**

Chronotherapeutic refers to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harm. Asthma is a chronic obstructive lung disease characterized by airways, inflammation and hyperactivity. In most patients, the condition worsens at night with acute exacerbation being most common. Clinical and epidemiological studies verify that asthma is several hundred folds more likely at night than during the day with disturbance of sleep. The worsening of asthma at night commonly referred to as nocturnal asthma (NA). A drug delivery system administered at bed time but releasing drug during morning hours would be ideal in this case. The possibility of deferring the drug release for a programmed time interval after oral administration of the dosage form is to perform chronotherapy is quite appealing for those diseases the symptoms of which recur mainly at night times or in the early morning, such as asthma [3,4].

The montelukast is a leukotrine receptor antagonist (LTRA) used for the maintenance treatment of asthma, chronic asthma attacks and to relive symptoms of seasonal allergies [5]. The main drawback of conventional Montelukast sodium formulation is that it undergoes hepatic first pass metabolism. Thus, it shows plasma or biological half-life 2.5 to 5.5 hrs [6], thereby decreasing bioavailability upto 64% [7]. Therefore, to improve the biological half-life and to improve patient compliance, a sustained release formulation of Montelukast sodium is desirable.

For sustained release systems, the oral route of drug administration has received the most attention as it is natural, uncomplicated, convenient and safer route. The aim of the present work was to prepare sustained release matrix tablets of Montelukast sodium using various concentrations of polymers such as HPMC (E15), HPC (M) and ethyl cellulose by direct compression method and to study the effect of in-*vitro* release characteristics, kinetics of the prepared formulations and stability studies.

MATERIALS AND METHODS

Materials: Montelukast was obtained as a gift sample by Zydus health care (East Sikkim), and Morepen Pharma Pvt. Ltd, Solan (H.P). HPMC and Microcrystalline cellulose were purchased from Rajesh chemicals, Mumbai. Ethyl cellulose was purchased from Loba Chemie Pvt. Ltd, Mumbai. Hydroxyl propyl cellulose, Magnesium stearate and Talc were purchased from Himedia Chem Lab, Mumbai.

Experimental Methods

Drug-excipient compatibility studies: Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the pre-formulation stage during the development of solid dosage form. Therefore, the pure drug and the formulations mixed with polymers were subjected to infra-red (IR) and Differential Scanning Calorimeter (DSC) studies. The pure drug and formulations mixed with polymers were separately mixed with IR grade potassium bromide in a ratio (1:100) and pellets were prepared by applying 10 metric ton of pressure in hydraulic press. The pellets were then scanned over range of 4000-400cm^{-1} in FTIR instrument. Differential Scanning Calorimeter (DSC) allows the fast Evaluation of possible incompatibilities, because it shows changes in the appearance, Shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug, other excipients and final tablet were recorded. The thermal analysis was performed over a temperature range of 30°C to 250°C **[8,9]**.

Preformulation studies

Micromeritic properties *[10]*

Angle of repose: The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which was kept 2cm above graph paper that is placed on a flat horizontal surface. With r being the radius, of base of conical pile, angle of repose can be determined by following equation: $\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose, **h** is height of pile and **r** is radius of base of the pile

Bulk density and tapped density: Both loose bulk density and tapped bulk density were determined. A quantity of 2gm of granules from each formula, previously light Shaken for the break of any agglomerates formed, was introduced into the 10ml of measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall down its own weight from the hard surface from a height of 2.5cm at 2 sec Intervals. The tapping was continued until no further change in the volume was noted.

LBD and TBD were calculated using the following formulas:
LBD: Weight of the powder/volume of the packing.
TBD: Weight of the powder/Tapped volume of the packing.

Compressibility index: The compressibility index of the granules was determined by Carr's
Compressibility index
Carr's index (%) = [(TBD-LBD) * 100] / TBD

Where, LBD: Weight of the powder/volume of the packing.
TBD: Weight of the powder/Tapped volume of the packing.

Hausner's ratio: Hausner's ratio can be determined by the following equation,
Hausner's ratio = TBD / LBD
Where, TBD -Tapped bulk densities & LBD- Loose bulk densities

Preparation of tablets: According to the formula given in **Table 1**. A total number of four formulations were prepared by direct compression method. Sustained release matrix tablets of Montelukast sodium were prepared by using drug and various concentrations of polymers. HPMC (E15), HPC (M) and ethylcellulose were used as matrix forming material, while 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 using 8 mm flat round convex punches in a rotary tablet press (Rimek mini press, model RSB-4, M/S: Karnavathi engineering, Ahmadabad) **[11].**

Evaluation of physical properties of matrix tablets [12]:

Hardness test: The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in kg/cm^2. Six tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability: A friability test was conducted on the tablets using a veego friabilator. Twenty tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The drum was rotated at 25 rpm for 4 minutes after which the tablets were removed. Any loose dust was removed from the tablets as before and the tablets were weighed again (W_{final}).The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

% Friability of tablets less than 1% is considered acceptable.

Weight variation: The weight variation test was conducted by weighing 20 randomly selected tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The specification of weight variation is 10%.

Uniformity of thickness: The tablet thickness was measured using screw gauge.

Drug content uniformity: Five tablets weighted and crushed in a mortar then weighed powder contained equivalent to 10 mg of drug transferred in 100ml of 0.5% of SLS solution to give a concentration of 100µg/ml. Take 15ml of this solution and diluted it up to 100ml with 0.5% of SLS solution to give a concentration of 15µg/ml. Absorbance measured at 342nm using UV- visible spectrophotometer.

In Vitro-Release Testing [13,14]: The *in-vitro* release pattern of sustained release matrix tablets was studied as per method given by Chaudhari *et al* [14]. *In-vitro* dissolution studies of tablets were performed at 37±0.5°C using 0.5% w/v aqueous solution sodium lauryl sulfate in USP II paddle method at 50 rpm. 5 mL of filtered aliquot was manually withdrawn at pre determined time intervals and replaced with 5 mL of fresh 0.5% sodium lauryl sulfate solution maintained at the same temperature. The samples were analyzed at 342nm using a UV spectrophotometer.

Kinetics of in-vitro drug release [15,16,17]: To study the release kinetics in-vitro release data was applied to kinetic models such as zero-order, first order, Higuchi and Korsemeyer-Peppas.

Zero-order,

$C = K_o t$ (1)

expressed in units of concentration/time, K_o is zero order release constant and t is the time in hrs.

First-order,

$\log C = \log C_o - Kt/2.303$ (2)

Where C is the concentration, C_o is the initial concentration of drug, K is the first-order rate constant, and t is the time.

Higuchi,

$Q_t = K_H \cdot t^{1/2}$ (3)

Where Q_t is the amount of release drug in time t, K is the kinetic constant and t is the time in hrs.

Korsmeyer peppas,

$Mt / M_\infty = K \cdot t^n$ (4)

Where Mt represents amount of the released drug at time t, M is the overall amount of the drug (Whole dose). The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n = 0.5, then the drug release mechanism is Fickanian diffusion. If n < 0.5 the mechanism is quasi-Fickanian diffusion, and 0.5 < n < 0.5, then it is non-Fickanian or anamolous diffusion and when n = 1.0 mechanism is non-Fickanian case II diffusion, n > 1.0 mechanism is non-Fickanian super case II.

Stability studies [8]: Accelerated stability study was carried out to observe the effect of temperature and relative humidity on selected formulation (F3), by keeping at 40°± 2°C, in air tight high density polyethylene bottles for three months, at RH 75±5%. Physical evaluation was carried out in each month.

RESULTS AND DISCUSSION

Drug excipients interaction studies: Drug taken for the present study of formulation is Montelukast sodium. It has got tertiary hydroxyl groups which have exhibited a broad peak around 3300 cm^{-1} and a carboxylic acid peak which is in the form of a salt has exhibited a strong peak near 1700 cm^{-1}. Numbers of aromatic C-H peaks are also observed between 2900 cm^{-1} to 3000 cm^{-1}. These are the characteristic absorption peak of Montelukast sodium **(Figure 2)**. The formulation F-3 contains Montelukast sodium, HPMC (E15), HPC (M) and ethylcellulose. The HPMC (E15) contains number of hydroxyl groups in a molecule which is indicated by broad hump at 3500 cm^{-1} which is the expected place wherein many hydroxyl groups can observe. Similarly, to above

instead of aromatic C-H number of aliphatic C-H are observed near 2900 cm^{-1}. The HPC (M) exhibited a hydroxyl group which is indicated by a broad peak around 3459 cm^{-1}. Numbers of C-H peaks are also observed between 2900 to 3000 cm^{-1}. C-O peak is also observed at 1086 cm^{-1}. The ethyl cellulose exhibited expected peaks for the carboxylate residue and carboxylate carbonyl groups. The strong absorption peak is absorbed at 3400 cm^{-1} and another peak at 1700 cm^{-1} corresponding to the carboxylate and carbonyl residues. When formulation F-3 is prepared by taking drug along with HPMC (E 15), HPC (M) and ethyl cellulose all the peaks corresponding to the four constituents were found to be present in its higher spectra indicating that none of the functional groups of either drug or polymers have undergone any chemical reaction. All functional groups are intact. Hence, it is a confirmation that no chemical reactions have taken place amongst any of the four constituents in the formulation.

DSC studies: To study the thermal stability of the drug it is subjected for DSC **(Figure 3)** studies in the range of 30^0C to 250^0C. During the process of study it is observed that the drug starts melting at 138.64^0C within the range of less than 1^0C i.e. at 138.84^0C. It melts completely indicating that the drug has got thermally stability upto 139 to 140^0C. Same drug along with HPMC (E 15), HPC (M) and ethyl cellulose in formulation F-3 when it subjected for DSC studies, it give rise to wider degree of onset of melting process and finished at 172^Oc suggesting that the formulated batch is a mixture of drug and polymers but not pure reaction product. If it is in the purer form of the product it would have given sharp melting as the drug has done.

Micromeritic properties: Granules of all the formulations were subjected for various pre-compressional evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio. Results of all the pre-compressional parameters performed on granules for formulations shown in **Table 2.**

The angle of repose was found to be ranging from 21º.33' to 26º.57' for the granules of all the formulations. Compressibility index was found to be ranging from 14.28 to 16.52 % for the granules of all the formulations. The results of Hausner's ratio were found to be in range between 1.16-1.19. The results of angle of repose (<30) indicates good flow properties of the powder. This was further supported by lower compressibility index values. Generally compressibility values up to 15% results in good to excellent flow properties.

Evaluation of prepared tablets: The results of physical evaluation of tablets were given in **Table 3**. The tablets of different batches were found uniform with respect to hardness within the range of 3.14 ±0.80 to 3.37±0.25 kg/cm^2. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In weight variation test, the pharmacopoeial limit for percentage deviation for tablets of more than 250 mg is ±5% and all the formulations were found to comply with the specifications given in I.P. for weight variation test. Good uniformity in drug content was found among the formulations, and percentage of drug content was more than 95%. All the tablet formulations showed acceptable pharmaco technical properties.

In - vitro drug release study: The release profile of Montelukast sodium from different batches of formulated matrix tablets were illustrated in **Table 4** and plotted in **Figure 4**. Based on the results of in-vitro dissolution testing it was known that all the formulations shown the drug release for a period of 12 hours. It is due to the reason that used concentrations of polymers have increased the viscosities of formulations which lead to the sustained-release of drug. But the formulation F-3 shown maximum amount of drug release i.e. 98.92 % for a period of 12 hours in a sustained-manner and hence was considered as the best formulation. It was also found to be optimum for stability studies.

Drug release study: The kinetic data of all the formulations are shown in **Table 5** and graphical representation in **Figures 4-7.** When the data were plotted according to zero-order equation, the formulations showed correlation coefficient values between 0.8097-0.9301. But when the data were plotted according to the first order equation, the formulations showed significantly higher correlation coefficient vales than the zero-order plots i.e. from 0.9636 to 0.9967. Hence, the results revealed that all the formulations (F-1 to F-4) release the drug by first-order kinetics. Higuchi's model was applied to the in-*vitro* release data, linearity was obtained with high 'r' value indicating that drug release from the sustained-release tablets through diffusion. The *in-vitro* release data was further fitted to Krosmeyer-Peppas model which is generally used to analyze the release mechanism when more than one type of release phenomenon is operational. Good linearity was observed with high 'r' values. The value of release exponent 'n' is an indicative of release mechanism. The value of 'n' obtained for all the formulations

ranged from 1.17 to 1.34 suggesting probable release by super case-II transport.

Stability studies: The results of accelerated stability studies shown in **Table 6** carried out according to ICH guidelines indicated that the tablets did not show any physical changes (color change, friability and hardness), assay and dissolution characteristics during the study period.

CONCLUSION

The study was undertaken with the aim to Formulation and evaluation of Montelukast sodium sustained-release matrix tablets using various concentrations of polymers. From the above results and discussion, it is concluded that the formulation of sustained release tablet of Montelukast sodium containing HPMC (E15), HPC (M), ethylcellulose and microcrystalline cellulose which are taken as ideal or optimized formulation for 12 hours release fulfills all the requirement of sustained release tablet. From the kinetic studies it was known that all the formulations released at first-order rate and were even found to be optimum for stability studies.

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Table 1: Composition of sustained release matrix tablets

Ingredients	F 1	F 2	F 3	F 4
Montelukast	10 mg	10 mg	10 mg	10 mg
HPMC E15	10 mg	15 mg	5 mg	20 mg
HPC (M)	10 mg	5 mg	15 mg	5 mg
Ethyl cellulose	30 mg	30 mg	30 mg	25 mg
Microcrystalline cellulose	38 mg	38 mg	38 mg	38 mg
Magnesium stearate	1mg	1mg	1mg	1mg
Talc	1 mg	1 mg	1 mg	1 mg
Total	100 mg	100 mg	100 mg	100 mg

Table 2: Results of physical evaluation of Pre-compression Blend

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	22º.45'	0.214	0.251	14.74	1.17
F2	21º.33'	0.308	0.364	15.38	1.18
F3	24º.36'	0.276	0.322	14.28	1.16
F4	26º.57'	0.288	0.345	14.52	1.19

Table 3: Evaluation of Sustained release matrix tablets of Montelukast sodium

Formulation	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability	Drug Content (%)
F1	1.50 ± 0.44	3.22 ± 0.17	3.75 ±1.25	0.36 ± 0.12	98.25 ± 1.37
F2	1.50 ± 0.31	3.37 ± 0.25	4.05+1.40	0.39 ± 0.09	95.28 ± 0.8
F3	1.58 ± 0.40	3.14 ± 0.80	3.4+1.35	0.43 ± 0.06	99.12 ± 2.47
F4	1.66 ± 0.55	3.20 ± 0.20	3.25+1.45	0.12 ± 0.08	101.22 ± 0.88

Table 4: Data of In-Vitro Drug Release Studies of sustained-release matrix tablets of Montelukast sodium

Time	F1	F2	F3	F4
1	16.21908	20.51237	21.94346	11.44876
2	24.09011	31.96113	46.98763	24.80565
3	36.96996	40.07067	58.91343	40.78622
4	52.23498	50.08834	74.89399	57.48233
6	64.39929	67.97703	86.81979	73.70141
8	68.45406	76.5636	92.30565	81.09541
10	73.93993	83.9576	96.59894	90.15901
12	81.57244	90.15901	99.46113	94.4523

Table 5: Kinetic Values Obtained from Different Plots of Formulations F-1 to F-4

Formulations	Zero order (R)	First order (R)	Higuchi's (R)	Peppa's	
				(R)	(N)
F-1	0.9000	0.9796	0.9706	0.6592	1.20
F-2	0.9301	0.9967	0.9897	0.6217	1.17
F-3	0.8097	0.9636	0.9545	0.5802	1.19
F-4	0.9152	0.9926	0.9598	0.7309	1.34

Table 6: Summary of physical properties of F-3 before and after accelerated stability studies

Parameter	Before stability studies (Initial)	After stability studies		
		After 1 month	After 2 months	After 3 months
Thickness (mm)	3.4+1.35	3.4+1.12	3.3+1.28	3.3+1.20
Hardness (kg/cm^2)	3.14 ± 0.80	3.14 ± 0.64	3.14 ± 0.56	3.14 ± 0.08
Friability (%)	0.43 ± 0.06	0.43 ± 0.05	0.43 ± 0.03	0.43 ± 0.03
Drug content (%)	99.12 ± 2.47	99.12 ± 2.39	99.12 ± 1.12	99.12 ± 0.80
In-vitro release study (at the end of 12 hours)	99.46	99.42	99.08	99.00
Number of trials (n) = 5				

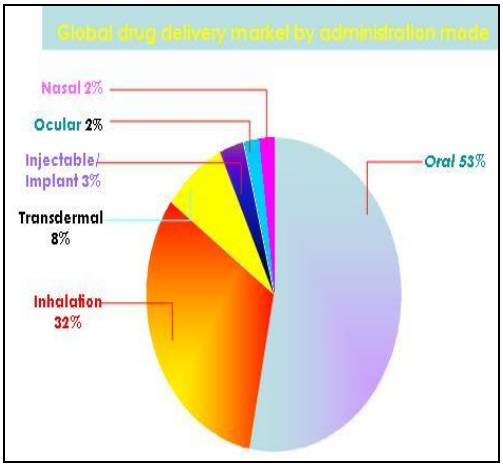

Figure 1: Global drug delivery market by administration mode

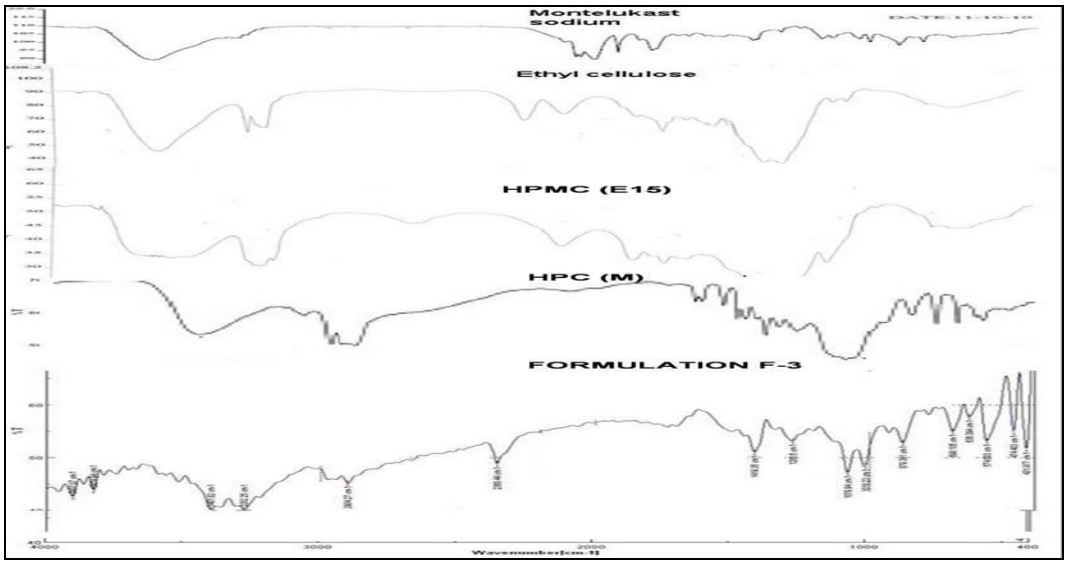

Figure 2: IR spectra of a) Pure drug Montelukast sodium b) Ethyl cellulose c) HPMC (E15) d) HPC (M) e) Formulation (F-3).

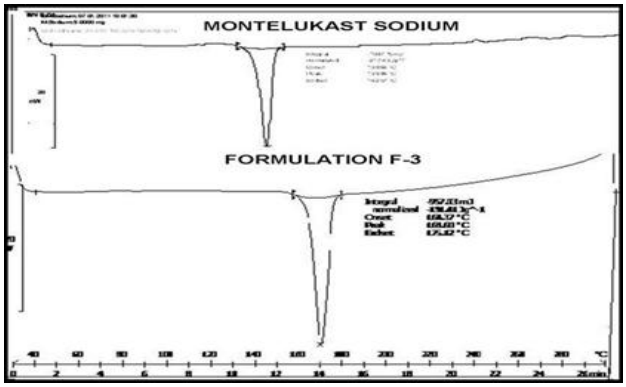

Figure 3: DSC spectra of a) Pure drug Montelukast sodium b) Formulation (F-3).

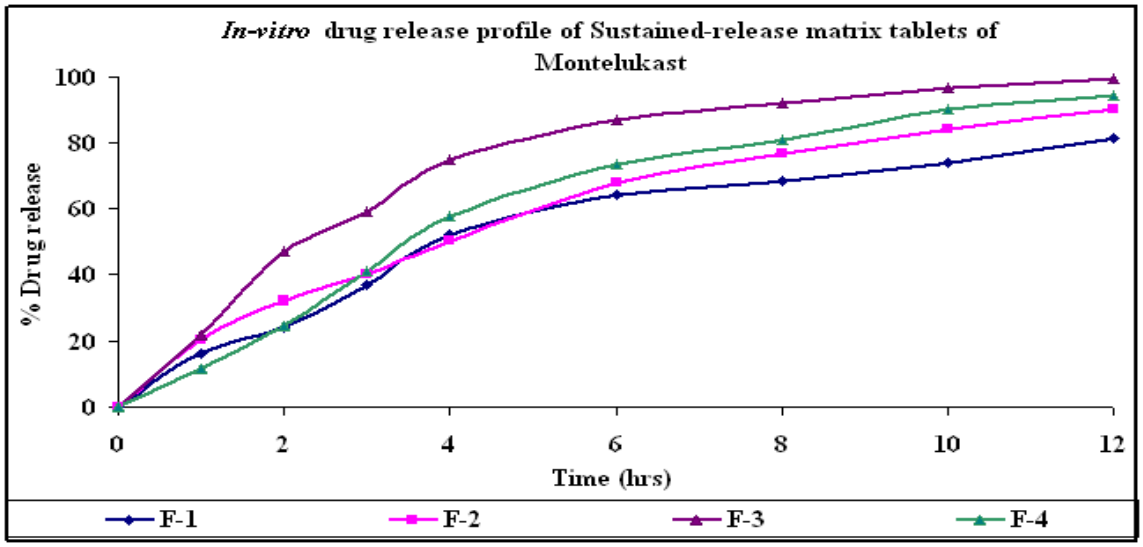

Figure 4: *In-vitro* drug release profile of Sustained-release matrix tablets of Montelukast sodium

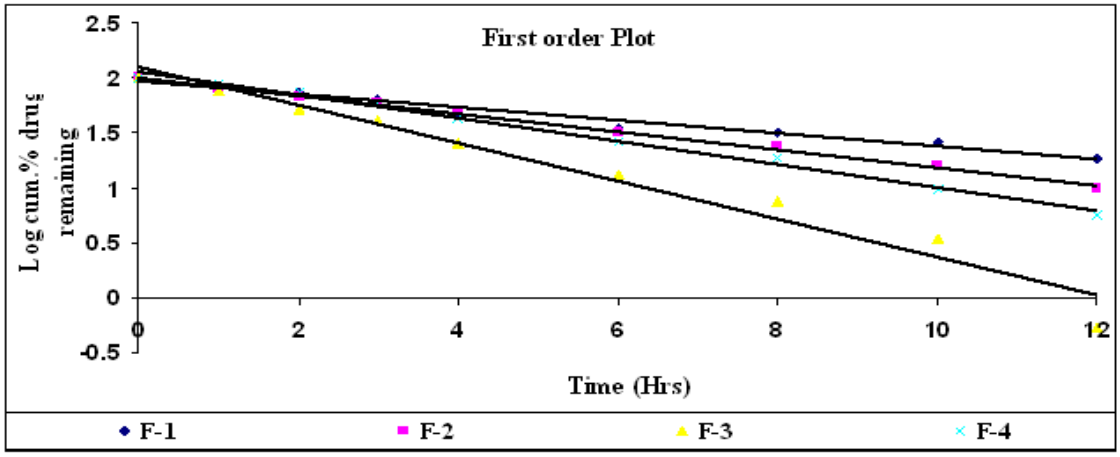

Figure 5: First order release plots

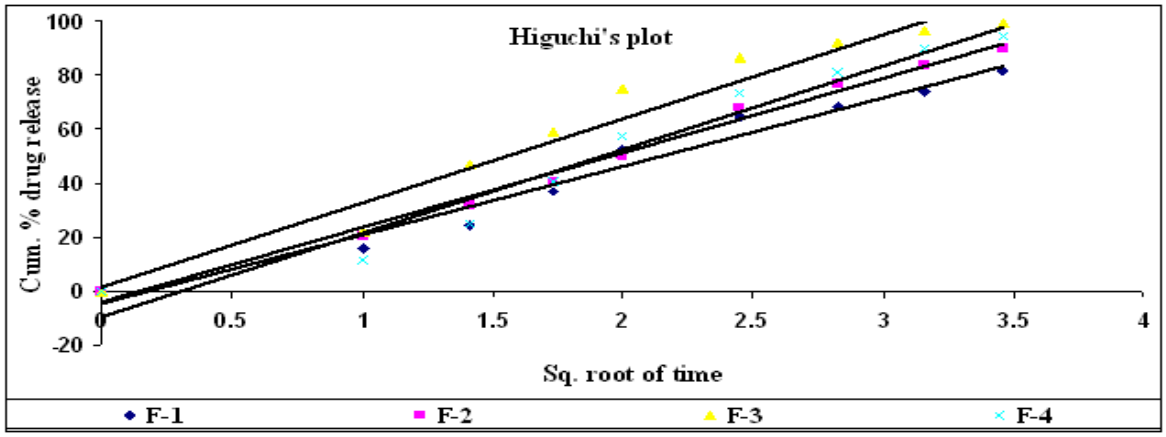

Figure 6: Higuchi plots

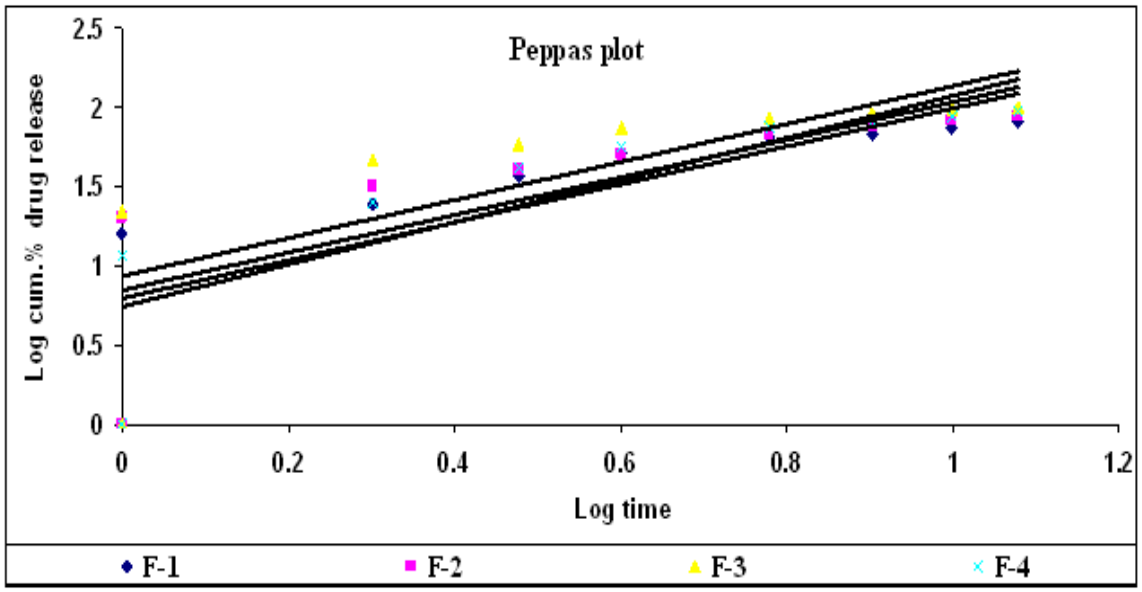

Figure 7: Korsmeyer-Peppa's plots

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