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FORMULATION AND CHARACTERIZATION OF MONTELUKAST SODIUM MATRIX TABLET

G. N. V. Rama Raju[1*], A. Sambasiva Rao[2], Nansri Saha[1], K. Mamatha[1], Chandrasekhara Rao. Baru[1]

1. SSJ College of Pharmacy, N Pally, Gandipet, Hyderabad-500075.
2. Principal, Sri Indu Institute of Pharmacy,Ibrahimpatnam, Hyderabad, India.

Abstract

Montelukast sodium is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene receptor. Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD 4 in Asthmatics. Doses as low as 5 mg cause substantial blockage of LTD 4 -induced bronchoconstriction. Montelukast biological half life is 2.5 to 5.5 hrs, thereby decreasing bioavailability up to 64%. So in order to improve the bioavailability and efficacy we have designed matrix release tablets. The prepared matrix tablets found to have good pre-compression and post compression parameters. The swelling performance, release rate features and the in vitro dissolution study. The drug release kinetics from optimized F-5 formulation showed zero order release. The study concludes to retard the release of Montelukast from the tablets.

Keywords: *Montelukast sodium, HPMC, matrix tablets, sustained release*

Corresponding Author:

G. N. V. Rama Raju
Department of pharmaceutics,
SSJ College of Pharmacy, V N Pally,
Gandipet, Hyderabad-500075,
Telangana, India.

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INTRODUCTION:

In most patients, the condition worsens at night with acute exacerbation being most common. Chronotherapeutics 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. 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). It is a variable exacerbation of the underlying asthma conditions associated with increases in symptoms, need for medication, airway responsiveness, and/or worsening of lung function. Generally a reduction in peak flow or forced expiratory volume in one second of at least 20% is implicit in this definition. Approximately two-thirds of asthmatics suffer from night time symptoms. In a large study involving 8,000 asthmatics it is observed that 70% awakened one night per week, 64% awakened 3 nights per week and 39% had their sleep disturbed on a nightly basis. The patients who self-characterized their asthma as mild, 26% has nightly awakenings and 53% of asthma deaths occurred during the night time hours. 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 [1, 2].The Montelukast sodium is a leukotrine receptor antagonist (LTRA) used for the maintenance treatment of asthma, chronic asthma attacks and to relive symptoms of seasonal allergies [3]. The main drawback of conventional Montelukast formulation is that it undergoes hepatic first pass metabolism. Thus, it shows plasma or biological half- life 2.5 to 5.5 hrs4, thereby decreasing bioavailability upto 64%5. The present work describes such delivery system, which will improve the biological half-life as well as bioavailability of Montelukast. This makes Montelukast sodium a candidate for incorporation in sustained release dosage form and was used as a model drug. The purpose of this study was to develop a Montelukast sodium matrix tablets (MMT) dosage form using a dry granulation method to be administered in the evening hours to achieve an elevated Montelukast sodium level overnight when the risk of asthma was found to be maximum. Our MMT comprises controlled-release tablets (CRT) in a tablet prepared with HPMC, a water soluble polymer, SODIUM ALGINATE and carbopol .

MATERIALS AND METHODS:

Materials:

Montelukast sodium was obtained as gift sample from Divis laborataries Ltd, india. HPMC, Sodium alginate and Carbopol were received as gift samples from Colorcon, goa. All other chemicals/Solvents were procured from market are of analytical grade.

Preparation of Montelukast Sodium Matrix Tablets:

Matrix tablets of Montelukast sodium were prepared by dry granulation method. The compositions of the ingredients are shown in the Table 1. Dry granulation is a process of using a all the ingredients were mixed together in different ratios with HPMC,sodium alginate and carbopol. The lubricated granules were compressed into tablets weighing 200 mg using 9.0 mm round punches in a rotary tablet press.

Table 1: Compositions of Montlukast Sodium Matrix Tablets

Ingredients	Mg/tablet					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Drug	**20**	**20**	**20**	**20**	**20**	**20**
HPMC k4m	**75**	**-**	**25**	**100**	**-**	**25**
Sodium alginate	**-**	**75**	**-**	**-**	**100**	**-**
Carbopol	**25**	**25**	**75**	**25**	**25**	**100**
MCC	**72**	**86**	**86**	**47**	**47**	**47**
Talc	**3**	**3**	**3**	**3**	**3**	**3**
Magnesium stearate	**5**	**5**	**5**	**5**	**5**	**5**
Total	**200**	**200**	**200**	**200**	**200**	**200**

Pre Compressional parameters [4]:

Angle of Repose

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

The angle of repose (θ) was calculated using the following formula.

tan θ = h/r or θ = tan -1 (h/r)

Bulk Density

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

Bulk Density = M/ Vo

Where M= mass of the powder; V_0=bulk volume of the powder

Tapped Density

A known quantity of powder was transferred to a graduated cylinder and volume V0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed.

Tap density = M / V_r

Where M = mass of the powder,

V_r = final tapping volume of the powder.

Compressibility Index and Hausner's Ratio

Basic methods for the determination of compressibility index and Hausner's ratio:

While there are some variations in the method of determining the compressibility index and Hausner's ratio, the basic procedure is to measure the unsettled apparent volume,(V_O), and the final tapped volume, (V_f), of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner's ratio are calculated as follows:

Compressibility index = 100 × Vo-V_f/Vo

Hausner's ratio = Vo/V_f

Where, V_o = apparent volume, V_f= final tapped volume Alternatively, the compressibility index and Hausner's ratio may be calculated using measured values of bulk density and tapped density as follows:

Compressibility index = 100 × tapped density / bulk density

Hausner's ratio = tapped density / bulk density

Drug-Excipients Compatibility Study [5]

Fourier Transformation Infra-Red (FT-IR) Analysis:

Fourier-transform infrared (FTIR) spectra of the Drug and polymer were obtained on Alpha Booker FTIR (Tokyo, Japan). The spectra were scanned over the wave number range of 4200 to 400 cm^{-1}

Post Compressional Parameters of Matrix Tablets:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include hardness, thickness, friability, weight variation and invitro-dissolution characters.

Hardness [6]

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester. The tablets from each batch were used for hardness studies and results are expressed in Kg/cm^2.

Thickness [7]

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value. Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier caliper. It was determined.

Friability [8]

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Weight Variation Test [9]

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests.. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Content Uniformity Test [10]

The content uniformity test is used to ensure that

every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets and all capsules intended for oral administration where the range of size of the dosage form available include 50mg or smaller sizes.

Dissolution [11]

In vitro dissolution for matrix tablets were done initially in 0.1N HCL for 2hrs and next in 6.8 phosphate buffer for 10hrs. In vitro drug release studies of the prepared matrix tablets were conducted for a period of 14 hours using an eight station USP XXII type 2 apparatus (DBK instruments, India) at 37± 0.5 ºC, paddle speed was 50± 1 rpm. The dissolution medium used in each flask was 900 ml of buffer media pH – 6.8 Phosphate buffer at every 1 hour interval samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant and maintain sink conditions. After filtration and appropriate dilution, the sample solutions were analyzed at 285 nm by using double beam U.V/visible spectrophotometer (ELICO SL 244) and dissolution medium as blank. Experiments were performed in triplicates. The amount of drug present in the samples was calculated with the help of calibration curve constructed from reference standard. Dissolution data of matrix tablets are reported in following table 4.

Drug Release Kinetics [12,13,14]

Zero-Order Model:

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation

Qt = Q0 + K0t

Where Qt is the amount of drug dissolved in time *t,* Q0 is the initial amount of drug in the solution (most times, Q0 = 0) and

K0 is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released versus time.

First Order Model:

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

Release behavior generally follows the following first order equation: **Log C= Log C_o-kt/2.303**

Where C is the amount of drug dissolved at time t,

C

A graph of log cumulative of % drug remaining vs time yields a straight line.

Higuchi Model:

The first example of a mathematical model aimed to describe drug release from a system was proposed by Higuchi in 1961. Initially conceived for planar systems, it was then extended to different geometrics and porous systems. This model is based on the hypothesis that initial drug concentration in the is much higher than drug solubility.

Drug diffusion takes place only in one dimension (edge effect must be negligible);

Drug particles are much smaller than system thickness; swelling and dissolution are negligible; drug diffusivity is constant; and Perfect sink conditions are always attained in the release environment.

The data obtained were plotted as cumulative percentage drug release versus square root of time.

Korsmeyer-Peppas Model:

It derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model,

$Mt / M\infty = Kt^n$

Where Mt / M∞ is a fraction of drug released at time t,

k is the release rate constant and n is the release exponent.

The n value is used to characterize different release for cylindrical shaped matrices. In this model, the value of *n* characterizes the release mechanism of drug.

RESULTS AND DISCUSSIONS:

Powder prepared for direct compression method was evaluated by measuring the parameters such as; bulk density, angle of repose, Hausner's factor, compressibility index and drug content. Angle of repose: The results of angle of repose (<30) indicate good flow properties and the values for prepared formulations ranges from 16 to 22. Hausner's factor: The values of Hausner's factor are under satisfactory range. Compressibility index: The values up to 15% result in good to excellent flow properties and values for all formulation ranges from 4.44 to 11.62%. All these results obtained indicate that the granules possessed satisfactory flow properties, compressibility, and uniform drug content. The results for all the formulations were shown in Table 2.

Post Compressional parameters: Thickness Test reveals that all the formulations showed uniform thickness. Weight Variation Test: It was carried out as per official method and the average percentage deviation of all the formulation was found to be within the limit (as per Pharmacopoeial standard the deviation should not be more than 7.5% for tablet having weight 250 mg). All formulations showed values within ranges. Content Uniformity was also carried out as per official method and it was found that all batches shows good content uniformity. It was found that all batches shows

percent drug content more than 95 percent. Hardness Test states that all the formulations were found in the range 4.2 to 4.8 kg/cm^2. Friability Test measure of tablet hardness was the friability, compressed tablets that lose less than 1 % of their weight are generally considered acceptable. For all formulation tried here the weight loss was <1 % hence acceptable. Drug Content values for all the formulations were in the ranges from 95.20 to 98.90%. The results for all the formulations were shown in Table 3. Swelling Factor: The swelling characteristics of matrix tablets were studied and the results are shown in table 4.

From the spectra of Montelukast sodium, combination of Montelukast sodium with excipient, it was observed that all characteristic peaks of Montelukast sodium were present in the combination spectrum, thus indicating compatibility of the drug and excipient. IR spectra are shown in Figure 1&2.

All the 6 formulation of prepared matrix tablets of Montelukast sodium were subjected to *in vitro* release studies, these studies were carried out using dissolution medium, (pH 1.2 and Phosphate buffer pH 6.8).by using USP-2 (paddle type) dissolution apparatus. The results were evaluated for 14 hours.

As per the results of dissolution study formulations F1, F2, F3, F4, F5 and F6 showed 95.10%,96.58%,93.56%, 95.11%, 98.90% and 92.80% release respectively over a period of 14 hours results shown in table no 5 and figure 3 .

Release was found to follow; Zero order, and Higuchi kinetics. The mechanism of release is swelling and erosion that is by non-Fickian kinetics (anomalous transportation) for all the batches of formulations shown in table 6 and figures 4-7.

CONCLUSION:

In the present study, Montelukast sodium matrix tablets were prepared using polymers like Hydroxy propyl methyl cellulose, sodium alginate, and Carbopol. From this study it can be concluded that Montelukast sodium matrix tablets prepared by sodium alginate (i.e. F5) showed good release rate than the tablets prepared by using other polymers. The formulation F5 was considered optimum because it showed negligible drug release in acidic medium and drug release in the phosphate buffer (pH6.8) was found to be almost complete.

Table 2: Values of pre-compressive parameters of prepared formulations

FORMULATION CODE	Angle of Repose	Bulk density (g/ml)	Tapped Density (g/ml)	Hausner Factor	Carr's Index %
F1	20.09 ±0.010	0.4509±0.002	0.4803±0.006	1.066 ±0.011	6.252 ±1.051
F2	18.32 ±0.015	0.4426 ±0.001	0.4743 ±0.003	1.068 ±0.024	6.388 ±0.882
F3	19.50 ±0.017	0.3817 ±0.004	0.4368 ±0.005	1.131 ±0.045	11.620 ±0.08
F4	17.35 ±0.030	0.4218 ±0.003	0.4570 ±0.002	1.071 ±0.031	6.664 ±0.095
F5	19.29 ±0.039	0.4371 ±0.005	0.4501 ±0.006	1.046 ±0.026	4.442 ±0.069
F6	19.86 ±0.041	0.4462 ±0.008	0.471 ±0.004	1.068 ±0.019	6.387 ±0.108

Table 3: Physical characteristics of prepared matrix tablets

FORMULATION CODE	Thickness (mm)	Hardness (kg/cm^2)	Weight variation	Friability	Drug content %
F1	3.10 ±0.10	4.5 ±0.20	1.1 ±0.102	0.096 ±0.012	98.1±0.70
F2	3.05 ±0.22	4.2 ±0.35	1.4±0.148	0.081 ±0.042	95.2±0.66
F3	2.96 ±0.29	4.8 ±0.22	1.5 ±0.192	0.075 ±0.065	95.8±0.79
F4	2.98 ±0.41	4.9 ±0.45	1.03±0.167	0.065 ±0.047	97.7±1.15
F5	3.14 ±0.58	4.9 ±0.50	1.8 ±0.182	0.095 ±0.028	98.8±1.55
F6	3.12 ±0.64	4.8 ±0.60	1.79 ±0.196	0.091 ±0.068	98.9±0.98

Table 4: Swelling indices of matrix tablets in Phosphate buffer pH 6.8

FORMULATION CODE	Initial weight (mg)	Final weight (mg)	Swelling index (%)
F1	195.20	204.21	95.58
F2	210.10	218.62	96.10
F3	205.51	212.98	96.49
F4	208.20	213.60	97.47
F5	200.80	205.65	97.64
F6	205.56	210.45	97.67

Fig 1: FTIR spectrum of Montelukast sodium

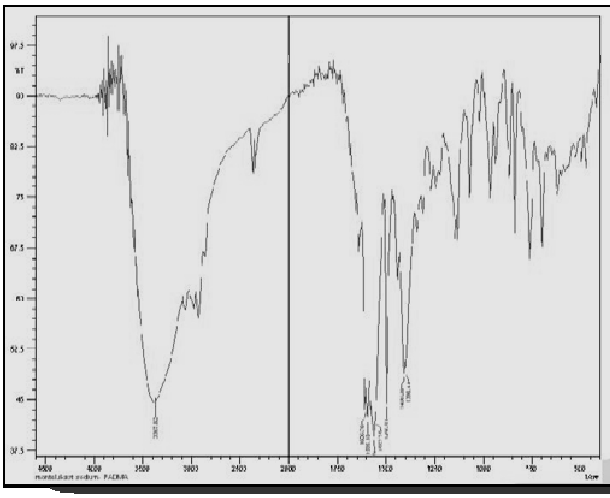

Fig 2: FTIR spectra of optimized formulation F5

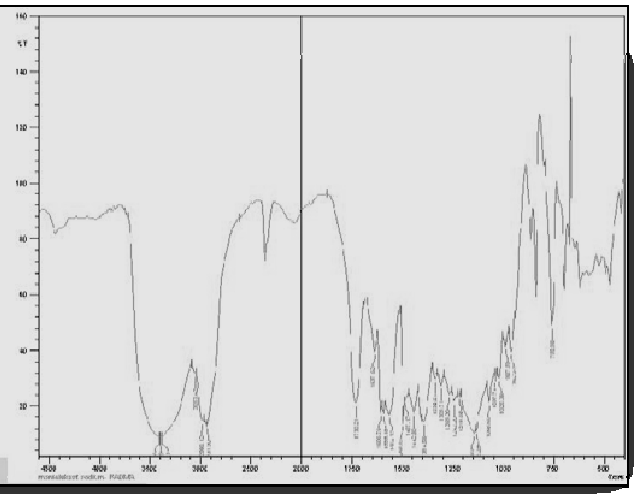

Table 5: In-vitro Dissolution study parameters for Montelukast sodium matrix tablets

Time in hours	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	4.50± 0.858	3.02± 1.20	3±1.45	4.5± 1.22	4.95± 1.31	1.5± 0.98
2	9± 1.55	4.5± 1.62	6± 1.22	9.30±0.68	9.75± 1.34	5.25± 1.12
3	15.10± 1.27	6.75±1.34	9.76± 1.41	15.01± 1.08	18.01±1.21	9.01± 1.06
4	24.03± 1.21	12.83± 1.54	19.52± 1.37	20.78± 1.31	26.28± 1.20	18.01± 0.84
5	28.55± 1.45	29.39± 1.57	29.29± 1.06	27.05± 0.78	36.81± 1.26	24.03± 1.16
6	30.09± 1.44	32.31± 1.40	33.07± 0.96	33.08± 1.29	45.10± 1.28	30.06± 1.27
7	37.62± 1.62	39.09± 1.51	36.85± 1.88	42.11± 1.67	52.65± 1.42	38.34± 1.44
8	45.16± 1.22	46.64± 1.40	45.14± 1.09	45.16± 1.26	54.20± 0.82	42.13± 1.65
9	52.71± 1.23	54.19± 1.98	51.19± 1.79	57.21± 1.20	58.76± 1.98	51.18± 1.29
10	60.27± 1.29	61.75± 1.21	57.25± 1.27	60.27± 1.89	63.33± 1.96	58.73± 1.21
11	69.34± 1.44	72.31± 1.66	66.31± 1.56	72.34± 1.41	75.40± 1.07	67.80± 1.27
12	78.41± 1.55	81.39± 1.47	73.14± 1.77	82.92± 1.37	82.96± 1.96	75.37± 1.20
13	87.50± 1.84	90.48± 1.67	82.97± 0.77	88.26± 1.61	92.80± 1.20	86.70± 1.33
14	95.10± 1.33	96.58± 0.99	93.56± 1.23	95.11± 1.27	98.90± 1.11	92.80± 1.87

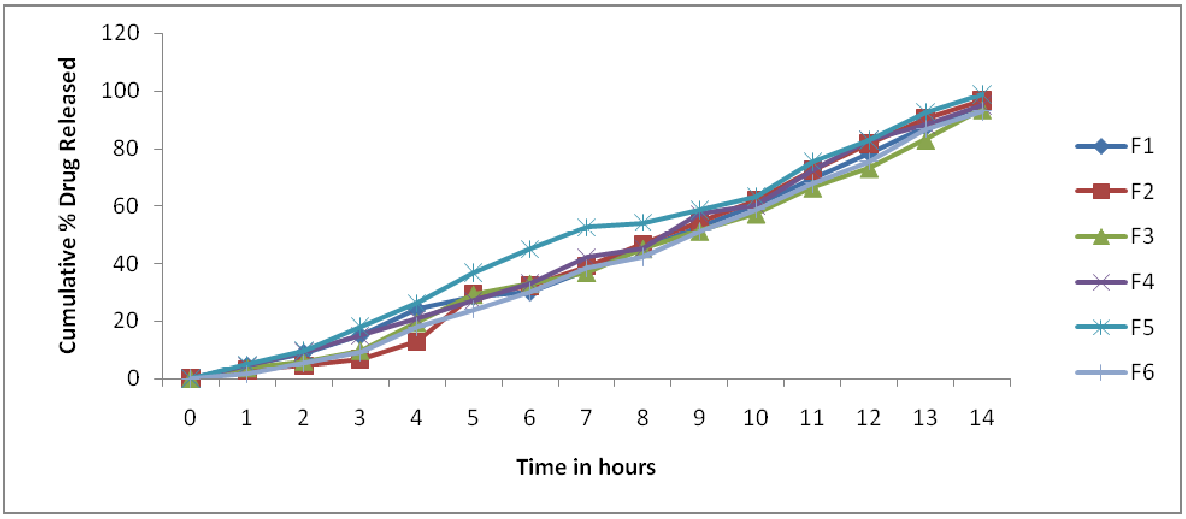

Fig 3: In-vitro cumulative % release of drug from matrix tablets

Table 6: Coefficient of Determinations for Prepared Matrix Tablets

FORMULATION CODE	Coefficient of Determination (R^2)			
	Zero order	First order	Higuchi square root	Peppas
F1	0.986	0.793	0.871	0.994
F2	0.982	0.786	0.852	0.969
F3	0.987	0.804	0.871	0.990
F4	0.989	0.820	0.875	0.997
F5	0.991	0.711	0.914	0.990
F6	0.986	0.826	0.857	0.993

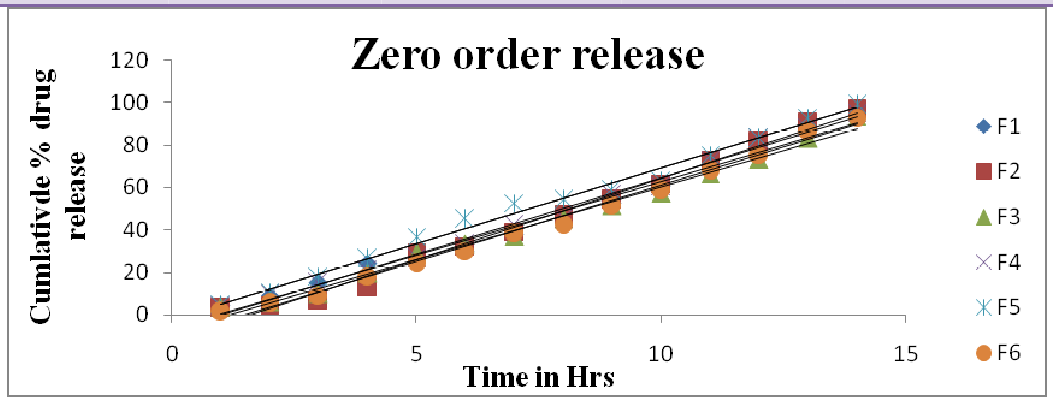

Fig 4: Zero Order Release of All Formulations

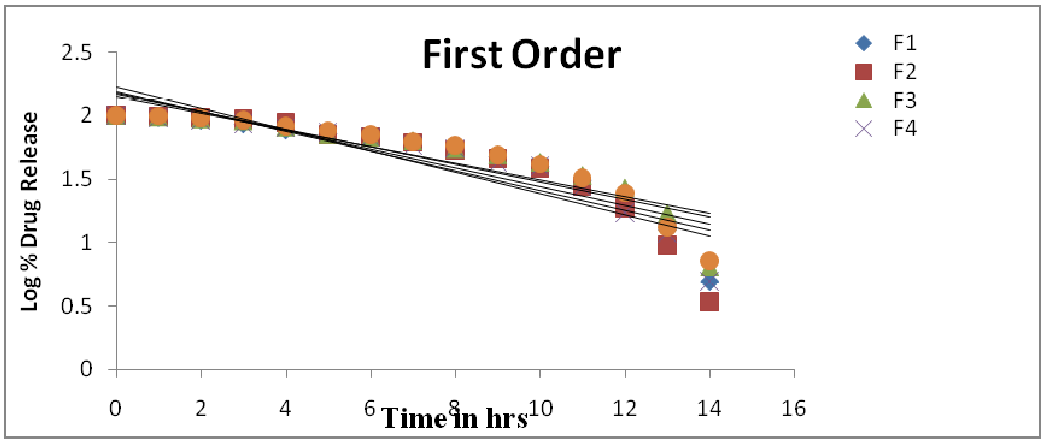

Fig 5: First Order Release of All Formulations

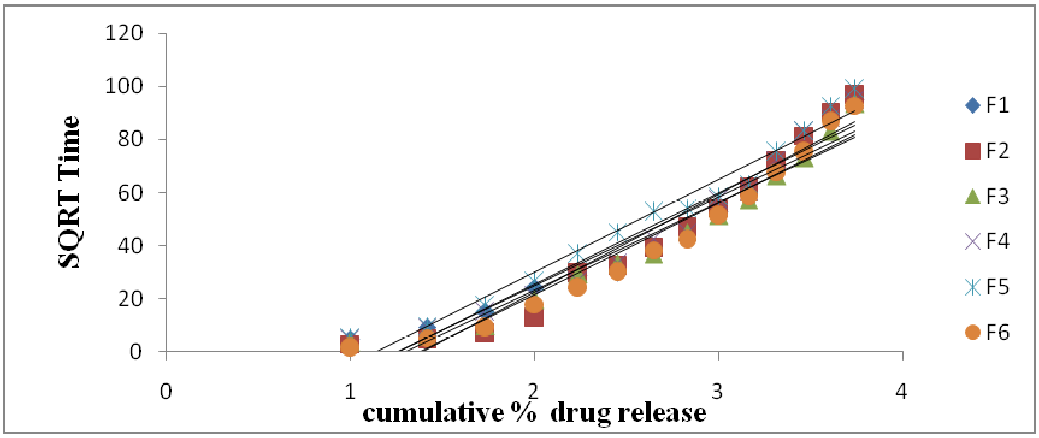

Fig 6: Higuchi model for all formulations

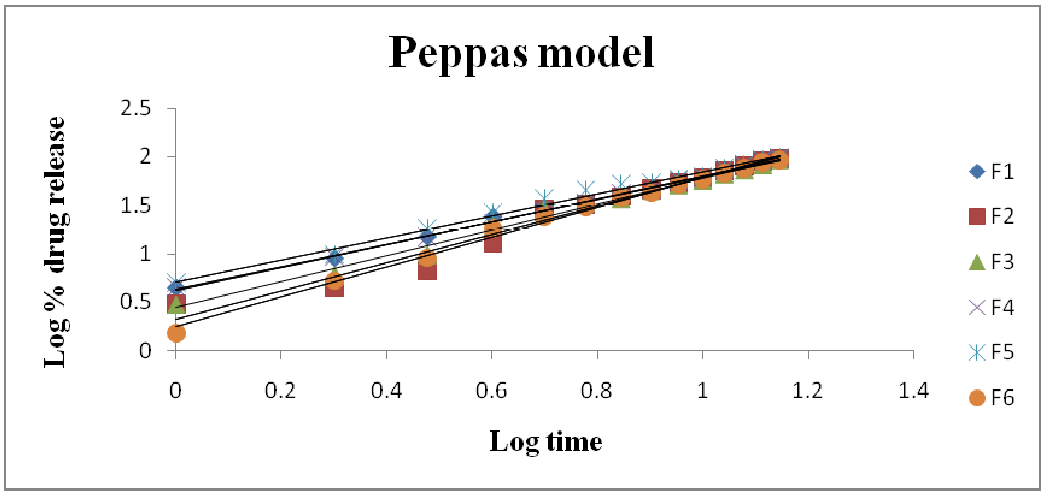

Fig 7: peppas model for all formulations

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