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Effect of particle size distribution of polymer coated granules on the release profile of Lamotrigine sustained release matrix tablets

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ABSTRACT

The study was carried out to investigate the release profile of the Lamotrigine from the matrix tablets containing different particle size range of the coated granules. The polymer coated granules were prepared in Fluid bed processor using wurster technique. The granules obtained were separated for different particle size and were mixed in different ratio to formulate matrix tablets. The prepared tablets were evaluated for its hardness, weight variation, drug content, friability, swelling index and invitro dissolution studies. A kinetic model fitting studies were done to determine the type of release and release mechanism. The in vitro evaluation of each formulation is done to investigate the effect of particle size distribution of polymer coated granule on the release of the drug. The results indicated drastic changes in the release profile due to the difference in the particle size distribution The F5, which has the highest percentage of particles in the range of 600-800 microns has the highest release when compared to all the other batches. F3 which has the highest percentage of the particles in the range of 100 – 250 microns has the lowest release profile. The order of time taken for 90 % of the drug release can be written as F3 > F4 >F2>F1 >F5. Statistical studies like ANOVA and LSD were performed to find out the significance difference in the drug release. The goodness of fit using R^2 and MSC revealed that all the formulation exhibited zero order release from the matrix.

Key word: Lamotrigine, Hypromellose, Granules, Polymer coat.

INTRODUCTION

In the past few decades, different types of oral controlled release (CR) formulations have been developed to improve the clinical efficacy of drugs and patient compliance [1, 2]. These formulations are designed to deliver drugs at a predetermined rate over a wide range of conditions and durations of therapeutic treatment. Matrix-based systems in which the drug is

dispersed as a fine powder or granules in a matrix of polymeric and/or non-polymeric material are choices for CR applications, mainly because they are easy to manufacture [3]. Modifications in the release profiles are aimed at altering the onset, the rate of release from the dosage form or the site of release of the drug. Modifications can be performed on oral as well as non-oral dosage forms to control the drug release. For an oral dosage form, modification of drug release can be achieved via control of mechanisms that include diffusion, erosion, osmosis, etc. Most of the popular oral modified release dosage forms are matrix and coated systems. They are therefore invariably multi-unit dosage forms consisting of particles of different size. The Multiunit dosage form mentioned here is the polymer coated granules. During the particle coating, variation in the size of the particle causes the production of granules with different degree of polymer coat. Hence the different particle size in the matrix system would give different release which would help the formulation scientist to choose the best release profile required for the product. Lamotrigine is taken as a model drug. Lamotrigine is an antiepileptic drug (AED) indicated as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients ≥13 years of age. The dose of the drug available in the market for the extended release products are 25mg, 50mg, 100 mg, 200 mg and 300 mg. The half life of the drug is 25±10 hrs.

MATERIALS AND METHODS

Materials

Lamotrigine were received as a gift sample from Alembic Limited, India .Eudragit L 100 55 purchased from Evonik, India , Hypromellose from(Colorcon, India) ,Triethylcitrate ,Dibasic calcium phosphate & Microcrystalline cellulose Magnesium stearate were obtained from commercial sources.

Preparation of polymer coated Lamotrigine granules:

Lamotrigine and hypromellose were mixed thoroughly using a proper blender in the ratio (10:1). Then the mixture was granulated using Eduragit L 100 55 (20%) dissolved in Isopropyl alcohol in a fluid bed processor [1, 2, 3] Triethyl citrate(2%) was also added to the granulating fluid which would act as a plasticizer. Once the coating solution has been consumed, the granules were removed from the fluid bed processor and sifted through # 20 ASTM. Then the complete granules were separated in to three parts based on the particle size using the ASTM sieves. The fraction obtained were labeled as, A – 30: ASTM retained (600 – 800 micron), B- 60: ASTM retained (250- 600 micron) C – 60 : ASTM passed (100 – 250 microns)

Table 1. Composition of the granules

S.No	Ingredients	Mg/tab
1	Lamotrigine	50
2	Hypromellose	5
3	Eudragit L 100 55	20
4	Triethyl citrate	2
5	Isopropyl alcohol	q.s.
	Total weight of the granules	77

Formulation of Tablets

The prepared granules were mixed in different ratios [Table 2]. All the batches were mixed with the extra granular material like Dibasic calcium phosphate, Microcrystalline cellulose, Hypromellose and Magnesium stearate as mentioned in the [Table 2] in the blender for 10 min and transferred to closed containers and labeled as batch numbers I, II, III, IV, V. All the batches were compressed in the 16 station compression machine (Cadmach) using 9.0 mm circular, normal concave punches.

Table 2. Composition of the Formulations

Ingredients (mg)	FI	FII	FIII	FIV	FV
A-30 (Fraction)	15.4	23.1	30.8	30.8	38.5
B-60 (Fraction)	53.9	46.2	30.8	38.5	30.8
C -60(Fraction)	7.7	7.7	15.4	7.7	7.7
DCP (A-Tab)	91	91	91	91	91
Avicel PH 101	76	76	76	76	76
Hypromellose K 15 M CR	50	50	50	50	50
Magnesium stearate	6	6	6	6	6

Pre formulation studies

The prepared blend of all the batches were evaluated for Angle of repose, tapped density, Bulk density, Carr's index, Hausner ratio using conventional methods.

Compatibility studies

The physical compatibility of lamotrigine with the polymer is done with the help of DSC analysis.

Tablet analysis:

Physical Parameters

Diameter and thickness of the tablets from different batches was measured by screw gauge at different places and average was calculated.

Weight variation

20 tablets were weighed individually and average weight was calculated and the maximum percentage deviation was calculated. The result was compared with US pharmacopoeia.

Friability test

Friability of the tablets was determined by Roche's friabilator at 25 rpm for 100 rotations.

The results obtained were compared with US pharmacopoeia. The Pharmacopoeial limits of friability test for a tablet is not more than 1%.

Hardness test

The resistance of tablets to shipping or breaking under the conditions of storage , transportation , and handling before the uses depends on its hardness .the hardness of the tablets of each batch was measured by Pfizer hardness tester in terms of kg/cm^2.

Drug content

Drug content was determined according to IP using spectrophotometer at 245 nm (Model Spectronic 21D, Bausch and Lomb, USA)

Swelling index

Three tablets from each formulation were placed in empty baskets and the total weight of basket with tablet noted (W1). The tablets containing baskets were fixed to a six-station dissolution apparatus. Baskets immersed in a 500 ml dissolution medium (phosphate buffer pH6.8), at 37^0C and at 75 rpm. At regular interval of one hour, the baskets were detached from the dissolution apparatus and blotted with tissue paper to remove excess surface water. Then the weight of basket containing swollen tablet was taken and reported as (W2). The graph of swelling index Vs time was plotted for each formulation. [4,5,6]

$$\text{Swelling Index (SI)} = \frac{W_a - W_b}{W_b} \times 100$$

Where,

W_b - Dry weight of tablet.

W_a - Wet weight of swollen tablet

In vitro Dissolution test

Six units of each batch were analyzed for the dissolution profiles in dissolution apparatus using USP I apparatus (Basket).The dissolution medium used was 900 ml of 6.8 phosphate buffer. The release study was performed at a rotational speed of 75 RPM at 37 +/- 5 ^{0} C . 5 ml of the Samples were withdrawn from the dissolution vessel at selected time intervals with a pipette fitted with a cotton wool plug and Replaced with an equal volume of drug-free dissolution fluid. The samples were filtered through whatmann filter paper No 41 and appropriately diluted with phosphate buffer pH 6.8. The samples were analyzed for content of lamotrigine spectrophotometrically at 245 nm (Model Spectronic 21D, Bausch and Lomb, USA) against phosphate buffer 6.8 as blank. The amounts released were calculated and expressed as a percentage of the label claim. Time required for 10%, 50 % and 90% of drug release (t 10%, t 50 %, t 90% respectively) were also determined.

Drug Release Kinetics [6,7,8]

To analyze the mechanism of the drug release rate kinetics of the dosage form, the dissolution data obtained was fitted in to 1) Zero order kinetics 2) First order kinetics 3) Higuchi square root model, 4) Hixon crowell cube root model 5) Kosemeyer peppa's modelZero order equation:

$$Q_t = k_0.t \qquad [1]$$

Where Q_t is the percentage of drug released at time t and k_0 is the release rate constant.

First order equation:

$$\ln (100-Q_t) = \ln 100 - k_1.t \qquad [2]$$

Where k_1 is the release rate constant.

Higuchi's equation:

$$Q_t = k_H.t^{1/2} \qquad [3]$$

Where k_H is the Higuchi release rate constant.

Hixson-Crowell :

$$(100\text{-}Qt)\ 1/3 = 1001/3 - kHC.t \qquad [4]$$

Where kHC is the Hixson-Crowell rate constant.

Korsmeyer-Peppas:

$$Q_t/Q_\infty = k_{KP} . t^n \qquad [5]$$

Where Q_t/Q_∞ is the fraction of drug released at time t, k_{KP} a constant compromising the structural and geometric characteristics of the device, and *n*, the release exponent, which is indicative of the mechanism of drug release. The release mechanism of the drug from the dosage form was predicted by calculating the n value . value of n < 0.45 was for fickian release , 0.45-0.89 for non fickian anomalous diffusion , 0.89 for case II transport and > 0.89 is super case II.

The Criteria adopted for selecting the most appropriate model was based on the best goodness of fit by calculating regression coefficient(R^2). Goodness-of-fit was also evaluated using the Model Selection Criterion (MSC). MSC was determined by the following equation ,

$$MSC = In [\Sigma_{i=1}^{n} w_i (Yobs_j - \bar{Y}obs)^2 \Big/ In [\Sigma_{i=1}^{n} w_i (Yobs_j - Y cal_i)^2] - 2 p/n$$

Where $Yobs_i$ and $Ycal_i$ are observed and calculated values of the i-th point, respectively, and w_i is the weight that applies to the i-th point, n is number of points and p is number of parameters.

Statistical analysis

The difference in the release for the different formulation was done by ANOVA at 5 % significance level and multiple comparison was done by LSD analysis using Microsoft 2007 excel package [9,10,11]

RESULTS AND DISCUSSION

The present study was carried out to investigate the release profile of the Lamotrigine from the matrix tablets containing different particle size range of the drug coated granules. Granules of the lamotrigine were prepared with Hypromellose and Eudragit L 100 55 using Triethyl citrate and Isopropyl alcohol in a fluid bed dryer. The formula is provided in the [Table 1]. The granules were separated in to three parts based on the particle size using the ASTM sieves. The fraction obtained were labeled as, A – 30 :ASTM retained (600 – 800 micron),B- 60: ASTM retained (250- 600 micron)C – 60 : ASTM passed (100 – 250 microns).Different formulations (F1-F5) were made by taking different ratios of this fractions (A,B,C) along with other excipients. The batch number I has the granules in the ratio of 20% of 600-800 microns, 70% of 250-600 microns and 10% of 100-250 microns. The batch number II has the granules in the ratio of 30% of 600-800 microns, 60% of 250-600 microns and 10% of 100-250 microns. The batch number III has the granules in the ratio of 40% of 600-800 microns, 40% of 250-600 microns and 20% of

100-250 microns. The batch number IV has the granules in the ratio of 40% of 600-800 microns, 50% of 250-600 microns and 10% of 100-250 microns. The batch number V has the granules in the ratio of 50% of 600-800 microns, 40% of 250-600 microns and 10% of 100-250 microns. the ratios are shown in the [Table 2].

Blend and Tablet evaluations

The pre formulation studies conducted on the final blends containing different ratio of fractions (A, B and C) containing polymer coated granules like angle of repose , Carr's index, bulk density and tapered density showed good flow property and compressibility. The values are given in the Table .3. DSC studies shows that there was no interaction of lamotrigine with the polymer used [Fig 1 &2]. The prepared tablets in all formulations possessed good mechanical strength with sufficient hardness and the values obtained lies between 10-13 Kg/cm^2.Percent friability were less than1% in the all formulations and the values obtained lies between 0.1-0.15%.All the tablets from each formulation passed weight variation test, as the percentage weight variation was within the pharmacopoeial limits. The thickness was almost uniform in all formulations and the values obtained were between 4.30 – 4.50mm.In all the formulations the drug content was within the specified limit. Values are reported in the [Table 4].

Table 3. Blend evaluation

Properties	Formulations					
	FI	**F2**	**F3**	**F4**	**F5**	**Pure drug**
Angle of repose, degrees	22.16± 0.55	24.56±0.65	24.92±0.42	26.11±0.51	27.01±0.44	20.32±0.67
Bulk density, g/cm^3	0.56± 0.29	0.49± 0.63	0.52±0.24	0.42± 0.25	0.40± 0.36	0.59±0.78
Tapped density g/cm^3	0.57± 0.35	0.54± 0.42	0.53±0.12	0.51± 0.28	0.48± 0.19	0.58±0.24
%Compressibility	7.48± 0.13	8.37± 0.17	9.11±0.19	9.82± 0.23	14.43±0.3	7.01±0.45
Hausner ratio	1.01± 0.16	1.10± 0.17	1.19±0.54	1.21± 0.14	1.2± 0.14	1.01±0.24

Table 4. Tablet evaluation

Tests	Formulations				
	F1	**F2**	**F3**	**F4**	**F5**
Diameter(mm)	9.00	9.00	9.00	9.00	9.00
Thickness(mm)	4.30 – 4.50	4.30 – 4.50	4.30 – 4.50	4.30 – 4.50	4.30 – 4.50
Hardness(Kg/cm^2)	10 – 13	10 – 13	10 – 13	10 – 13	10 – 13
Friability (%)	0.1%	0.12%	0.15%	0.12%	0.14%
Drug Content (%)	99 ±1.5	100±0.98	98 ±1.2	99±0.75	100±2.46

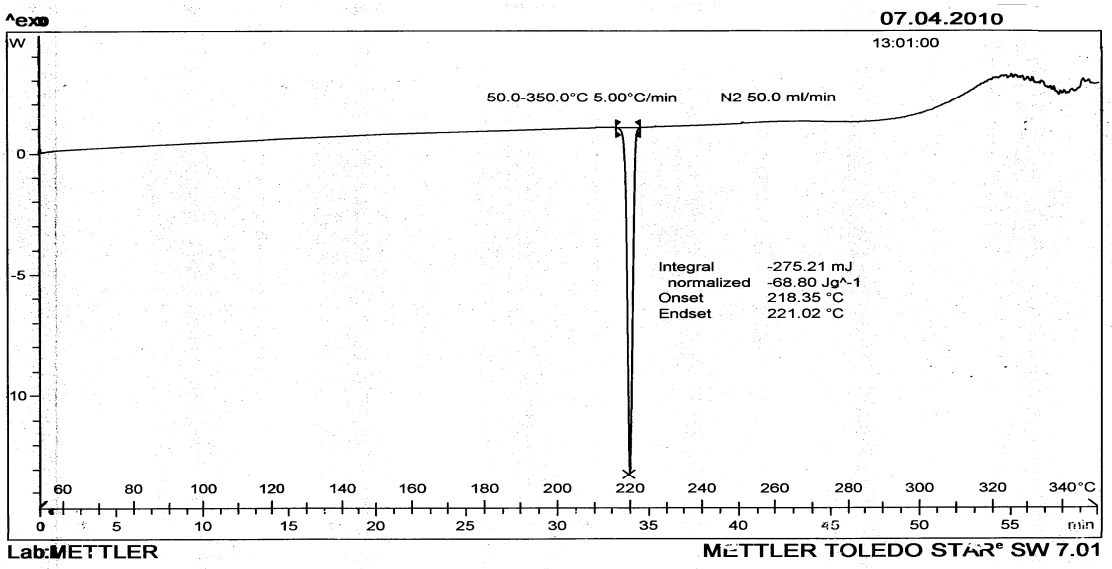

Figure 1 . DSC study of pure drug

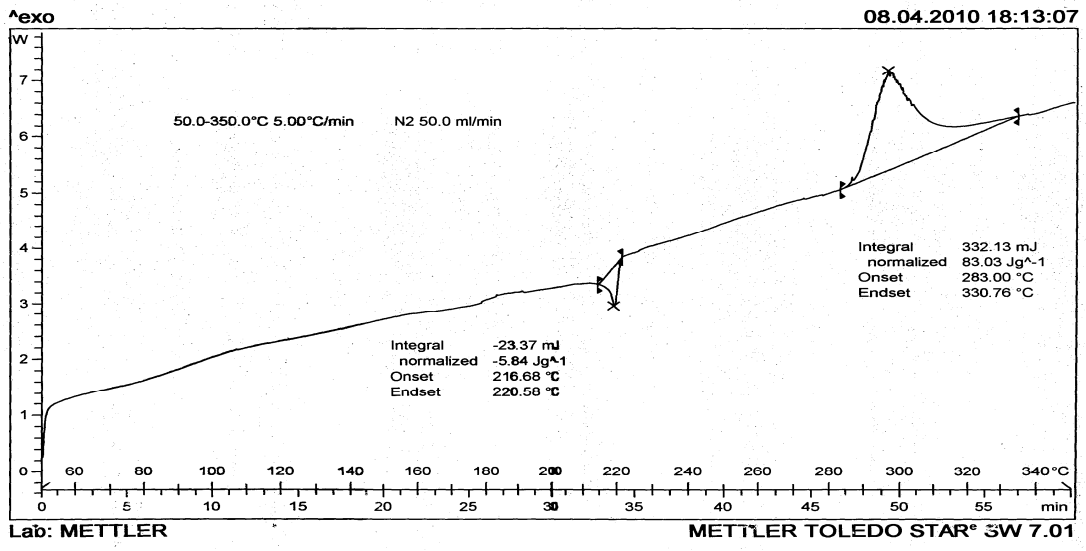

Figure 2 . DSC study of pure drug with Hypromellose K 15 M CR and Eudragit L 100

Swelling analysis

The swelling study conducted revealed the pattern of swelling and erosion happening in the formulation. The formulations F3 and F4 showed greater extend of swelling with no erosion up to 15 and 17 hours respectively. All other preparations swelled 6-10 hours and erosion starts there after. The pattern of swelling is shown in the [Figure 3].

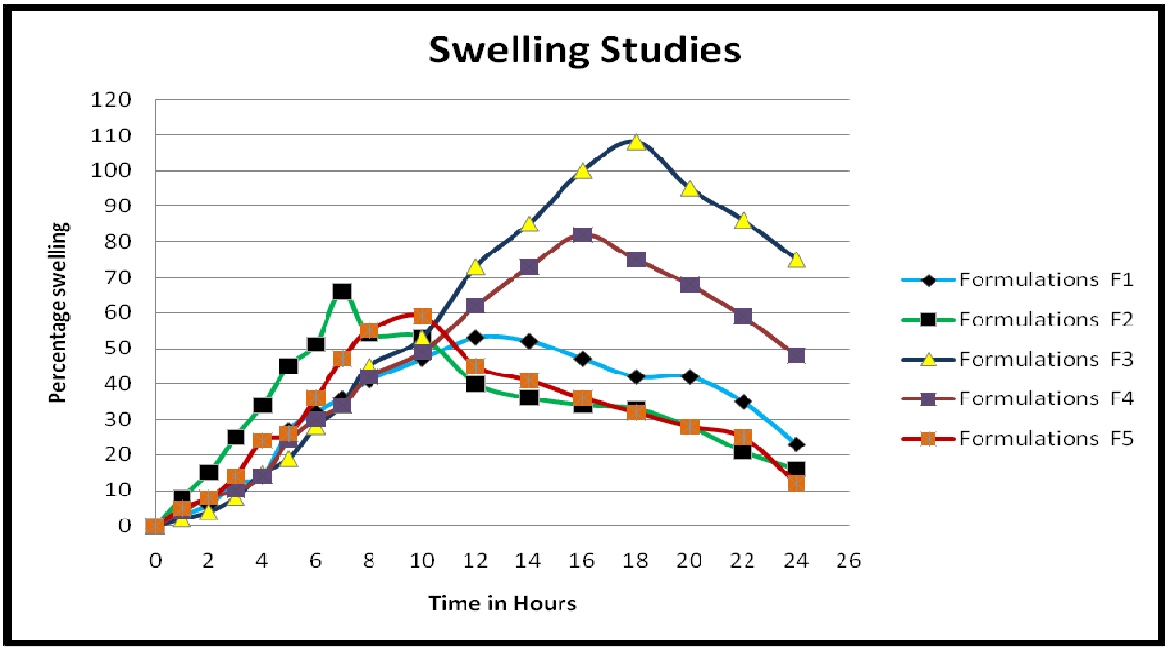

Figure 3 . Swelling studies of the formulations

F1 =*20% of 600-800 microns, 70% of 250-600 microns and 10% of 100-250 microns.*
F2 = 30% of 600-800 microns, 60% of 250-600 microns and 10% of 100-250 microns.
F3 = 40% of 600-800 microns, 40% of 250-600 microns and 20% of 100-250 microns.
F4 = 40% of 600-800 microns, 50% of 250-600 microns and 10% of 100-250 microns.
F5 = 50% of 600-800 microns, 40% of 250-600 microns and 10% of 100-250 microns.

In Vitro Dissolution

In vitro dissolution studies for all the fabricated tablets were carried out using USP basket method at 75 rpm in 900 ml of phosphate buffer pH 6.8 as dissolution media. All the formulations showed release of the drug more 20 hrs. The invitro analysis results showed that, changes in the release profile due to the difference in the particle size distribution [Fig 4].The batch number V, which has the highest percentage of particles in the range of 600-800 microns has the highest release when compared to all the other batches. While the batch number III which has the highest percentage of the particles in the range of 100 – 250 microns has the lowest release profile. The t 10% t 50% and t90% values showed that the formulation F5 showed lesser time for 90% drug release (<18 hrs) and F3 showed a greater extended time for the 90% release. The order of time taken for 90 % of the drug release can be written as F3 > F4 >F2>F1 >F5.

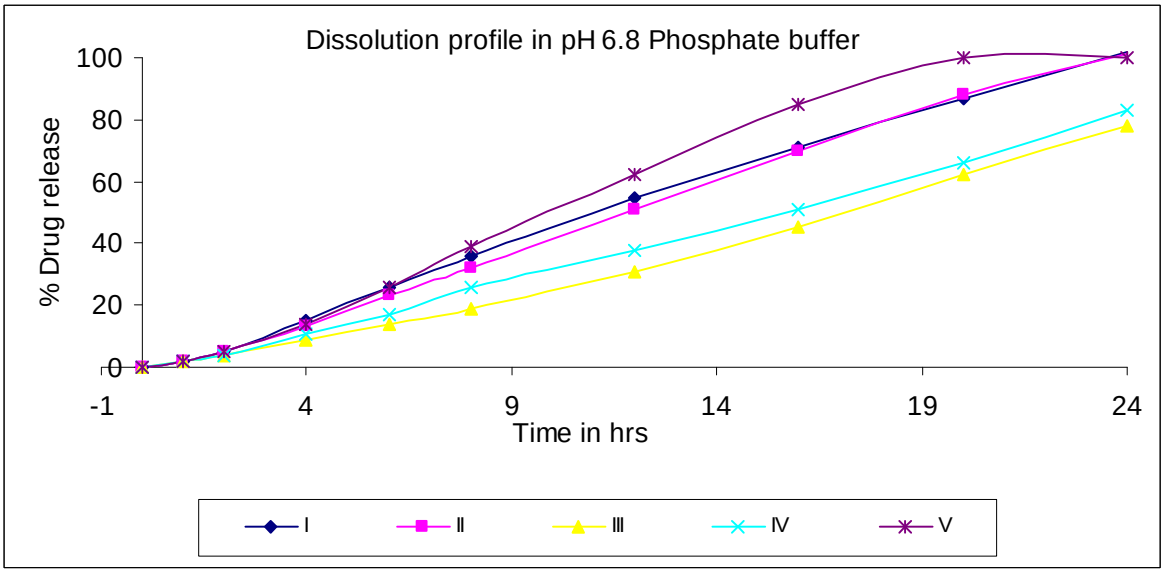

Figure 4 : Dissolution profile of the formulations

F1 =*20% of 600-800 microns, 70% of 250-600 microns and 10% of 100-250 microns.*
F2 = 30% of 600-800 microns, 60% of 250-600 microns and 10% of 100-250 microns.
F3 = 40% of 600-800 microns, 40% of 250-600 microns and 20% of 100-250 microns.
F4 = 40% of 600-800 microns, 50% of 250-600 microns and 10% of 100-250 microns.
F5 = 50% of 600-800 microns, 40% of 250-600 microns and 10% of 100-250 microns.

Table 5. Time for drug release

Formulations	Time for the drug release		
	$t_{10\ \%}$	$t_{50\ \%}$	$t_{90\ \%}$
F1	2.52	11.58	20.65
F2	3	11.9	20.95
F3	4.195	16.64	29.09
F4	3.54	15.16	26.78
F5	2.59	10.1	17.62

Kinetic Model Analysis

In order to describe the kinetics of the release process of drug in the five formulations various equations were used. The zero order model Eq. [1] describes the systems, where the drug release is independent of its concentration. The first order equation Eq. [2] describes the release from systems, where release rate is concentration dependent. According to Higuchi model Eq. [3], the drug release from matrix is directly proportional to a square root of time and is based on the Fickian diffusion. The Hixson-Crowell cube root law Eq. [4] describes the release from the systems, where it depends on the change in surface area and diameter of the particles or tablets with time and mainly applies in case of systems, which dissolute or erodes over time. A more comprehensive, but still very simple, semi-empirical equation to describe drug release mechanism from polymeric systems more precisely is the so-called Korsmeyer-Peppas power law, i.e. Eq. [5]. Thus, drug release data were fitted to these kinetic models to explain the drug release kinetics and mechanism from the matrices prepared .[Table -6] shows the data for the invitro drug release kinetic study of the formulations. Various constants K_o, K_1, K_H, K_{Hc} were determined Table 6. The best fit model was determined by comparing the r^2 values of all the

kinetic models. The r^2 values of the formulations F1- F5 ranges from 0.998- 0.955. All the formulations showed r^2 valve 0.998-0.992 for zero order model [Table 6].

MSC Analysis

The goodness of fit was also determined by MSC analysis. MSC Values were found to be larger for zero order kinetic models. Hence it can be concluded that the all the formulations followed a zero order pattern of release. The release mechanism is expected to be super case II as the n value of all the formulations was greater than one.

Table 6. Kinetic model analysis

Constants	Formulation				
	F1	F2	F3	F4	F5
K_0	4.473	4.689	3.46	3.537	5.913
r^2_0	0.996	0.997	0.992	0.997	0.998
K_1	0.042	0.049	0.045	0.041	0.061
r^2_1	0.954	0.931	0.965	0.939	0.928
K_H	14.68	28.51	23.65	24.32	32.64
r^2_H	0.989	0.991	0.959	0.978	0.98
K_{Hc}	0.117	0.127	0.108	0.103	0.16
r^2_{Hc}	0.955	0.969	0.991	0.975	0.967
n	1.34	1.295	1.141	1.189	1.412

Table 7. MSC values of the formulation for finding out the goodness to fit

MSC Value				
Formulation	Zero Order Model	First order Model	Higuchi Model	Hixson Crowell Model
F1	5.41	0.7	2.1	0.4
F2	5.09	0.3	1.3	1.4
F3	2.55	0.6	0.9	1.3
F4	3.54	0.3	1.2	1.2
F5	3.56	0.5	1.2	1.2

Statistical Analysis

The one way analysis of variance (ANOVA) performed at 5% of confidence interval by taking the amount dissolved at 12 hr .The results showed that the formulations are exceptionally different with a $P < 0.001$ [Table 8]. In order to find out the means which were exactly different a least square difference (LSD) was performed. From the LSD analysis it was found that except F1 & F2 the mean values were significantly different from each other at a probability of $P < 0.001$ [Table 9]. From the analysis it was clearly understood that by changing the ratio of the granules of different size there was a significant change in the dissolution.

Table 8. ANOVA at 5 % Significance level

Source of Variation	*SS*	*Df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	2487.7	4	621.925	157.4494	4.68E-12	3.055568
Within Groups	59.25	15	3.95			
Total	2546.95	19				

Table 9. LSD analysis

Differences	Value
F1 & F2	1.25
F2&F3	22.25
F1&F4	13.75
F1&F5	9.5
F2&F3	21
F2&F4	12.5
F2&F5	10.75
F3&F4	8.5
F3& F5	31.75
F4 & F5	23.25
LSD =	2.10

Now the question arises that, how the smaller particle size has the lowest release while the highest particles has the highest release which is a opposite phenomena of the relationship between particle size and the dissolution. Generally, the smaller particle size gives highest release when compared to the bigger particle size due to the increase in the surface area of the smaller particle size. Hence the increase in the surface area increases the solubility and the dissolution of the particles.

The process of granulation used is Fluid bed processor using Wurster technique. In this technique, the particles are coated by the means of bottom spray technique and mainly the coating takes place in the wurster chamber in uniform manner. All the particles are coated in the wurster chamber and dried in the drying chamber and recycled in to the wurster chamber and again gets coated and the cycle continues till the complete solution is sprayed. So all particles, irrespective of their sizes gets similar amount of polymer during the each cycle.
Larger particles surface area is bigger when compared to the smaller particle size granules. Hence the amount of the polymer required to cover the bigger particles would be higher. But in our Fluid bed process, all particles, irrespective of their sizes gets similar amount of polymer during the each cycle. Hence, the percentage buildup for the larger particles would be lesser when compared to the smaller particle size. So the larger particles dissolves faster when compared to the smaller particles due to the less amount of polymer and the smaller particles dissolves slower due to the high amount of polymer.

CONCLUSION

By using this technique, any desired release profile could be achieved by mixing different particle size of the granules. Hence this would give a formulator an advantage to use fluid bed processor for any kind of controlled release products.

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