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Formulation and Evaluation of Rapimelt Tablet of Anti-Vertigo Drug (Lorazepam)

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Abstract : A. Rapimelt tablet of Lorazepam was prepared by direct compression method using Indion 414, Cross Carmellose Sodium and sodium starch glycolate as superdisintegrants with aim to get rapid onset of action, improve bioavailability and to give pleasant taste and better mouth feel. The tablets prepared were evaluated for various parameters like various density parameters, thickness, hardness, friability, disintegration time, wetting time and in-vitro dissolution time and were found to be within limits as per Indian Pharmacopoeia. FT-IR spectra of physical mixture of Lorazepam with Indion 414showedretention of basic peaks of Lorazepam. The developed formulation of Lorazepam batch F5 (10% Indion 414) showed good palatability and dispersed within 30 seconds as compared to Crosscarmellose Sodium batches F1-F3 and Sodium starch glycolate batches F6-F9.
Keywords : Rapimelt Drug Delivery System, Lorazepam, Anti-Vertigo, FTIR.

1. Introduction:

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. One important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Or dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. Rapimelt tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispersible tablets, rapimelts, porous tablets, quick dissolving etc. Rapimelt tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. Faster the drug into solution, quicker will be absorption and onset of clinical effect[1-3].+

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Present study deals with development and evaluation of rapimelt tablet of anti-vertigo drug (Lorazepam[4,5]) using different super disintegrants such as Crosscarmellose, sodium starch Glycolate and Indion 414 in various ratios to achieve rapid onset of action and improve bioavailability.

2. Materials and Methods:

2.1 Materials

Lorazepam was gift sample procured from Getz Pharma Research Pvt. Ltd., Mumbai. Crosscarmellose sodium, Sodium Starch Glycolate and Indion 414 were also procuredfrom Getz Pharma Research Pvt. Ltd., Mumbai. All other chemicals procured were of analytical grades.

2.2 Methods

2.2.1 Organoleptic Properties[2,3]

Organoleptic properties such as colour, taste, odour and melting point has been studied and summarized in Table 1.

2.2.2Lorazepam estimation by UV Spectrophotometer[3]:

2.2.2.1 Preparation of Stock solution

20 mg of Lorazepam was accurately weighed in a 20 ml volumetric flask then the volume was made up to 100 ml with distilled water. This was stock solution containing 200 µg/ml.

2.2.2.2 Determination of wavelength (λ_{max}) of Lorazepam[3]

The solution of 10µg/ml in distilled water was prepared and scanned in the range of 200-400 nm and wavelength maxima was determined by using Shimandzu U.V. Spectrophotometer.

2.2.2.3 Standard Calibration Curve of Lorazepam[2]

From stock solution, 10 ml was pipette out and transferred in to a 100 ml volumetric flask and volume was made up to 100 ml with distilled water which contained the concentration of 20 µg/ml. From this solution, aliquots equivalent to 2-12 µg (2, 4, 6, 8, 10 and 12 ml) were pipetted out in to a series of 10 ml volumetric flask and volume was made up to 10 ml with distilled water. The absorbance of these solutions was measured against distilled water as blank at 224 nm using UV-Visible double beam spectrophotometer. Then a calibration curve was plotted taking concentration in µg/ml on X-axis and absorbance on Y-axis and was summarized in Table 2 and Figure 1.

2.2.3 Drug Excipient Compatibility Study using Fourier Transform Infrared Spectroscopy[3-5]

The samples were crushed with KBr to make pellets under hydraulic pressure of 10 tons, and then the FTIR spectra were recorded between 400 and 4000 cm^{-1}. It was used to study the interactions between the drug and polymer. The drug and polymer must be compatible with one another to produce a stable product. Drug and polymer interactions were studied by using FTIR. IR spectral analysis of pure Lorazepam (Figure 2A) and mixture of Loraepam with Indion 414 (Figure 2B) were carried out.

2.2.4 Evaluation of powder parameters (Pre-Formulation)[6]:

Bulk density, Bulk Density, Compressibility index, Hausner ratio and Angle of repose of powder were evaluated according to the procedure given in Indian Pharmacopoeia and results were summarized in Table 3.

2.2.5 Preparation of Rapimelt tablets by direct compression method[6]:

The Rapimel tablets prepared by superdisintegrant addition method. The superdisintegrant (Cross Carmellose Sodium, Indion 414 and Sodium Starch glycolate) were used to formulate the tablets. The tablets

were formulated employing direct compression method according to the formula given in Table No. 14 using 8 mm biconcave punches. It is the process by which tablets are compressed directly from mixtures of the drug and excipients without preliminary treatment such as granulation.

Lorazepam (2mg), super disintegrants in different ratios (Table 4) and excipients were blended using mortar and pestle. The drug and the disintegrants were sieved through mesh #120 before blending. The mixture was evaluated for angle of repose, bulk density and compressibility. The mixture was mixed with 1% magnesium stearate as a lubricant. The granules were then compressed by using Fluidpackmultistation rotary tablet machine using 8 mm punch. The hardness was adjusted to 2-5 kg/cm^2.

2.2.6 Evaluation of RapimeltTablets[2,3]:

The tablets were compressed using 8 mm diameter, round, biconcave punches on a Fluidpackmultistation rotary tablet machine. The tablet weight was kept 200 mg and hardness between 2 – 5 kg/cm^2. Other parameters like taste and colour, size, thickness, shape, hardness, friability, weight variation, wetting time were carried out as shown in Table 5.

2.2.6.1In-Vitro disintegration test[6]:

Wire Basket Type Disintegration Apparatus:

The disintegration taster consists of 6 glass tubes that was 3 inch long and 10-mesh screen at the bottom, one tablet was placed in each tube and basket was placed in 1 liter beaker of simulated gastric fluid at $37^0C \pm 2^0C$. The basket assembly containing the tablet up and down through distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute as shown in Table 5.

2.2.6.2In-Vitro drug release study[6]

The development of dissolution methods for Fast dissolving tablet is comparable to the approach taken for conventional tablets, and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent Fast dissolving tablet. Other media such as 0.1N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for Fast dissolving tablet much in the same way as their ordinary tablet counter parts.

The USP 2 Paddle apparatus is used for this purpose which is the most suitable and common choice for orally-disintegrating tablets, with a paddle speed of 50 rpm commonly used. Typically the dissolution of Fast dissolving tablet is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to obtain a profile. The USP 1 Basket apparatus may have certain applications but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles. Results were shown in Table 6 & Figure 3.

2.2.6.3 Mechanism of Release from Matrix tablets[6]:

Data obtained after applying all suitable mathematical models we can conclude that the optimized formulations selected are proposed to explain the mechanism of release of drug from formulation. Results were shown in Table 7 & Figures 4 – 7.

3. Results And Discussion

3.1 Organoleptic Properties:

The test was performed as per procedure given in material and method, showed its purity and is illustrated in following table.

Table 1: Tests and Observations

Tests	Observations	IP Specifications
Description	White powder	Complies
Taste	Tasteless	Complies
Odour	Odourless	Complies
Melting point	192^0C-194^0C	Complies

3.2 Determination of wavelength (λ_{max}) of Lorazepam

The solution of 10µg/ml in distilled waterwas prepared and scanned in the range of 200-400 nm and wavelength maxima was determined by using Shimandzu U.V. Spectrophotometer shown and was found to be 224 nm.

3.3 Preparation of Standard Calibration curve of Lorazepam

Table 2 Standard Calibration curve of Lorazepam

Concentration (µg\ml)	Absorbance	± S.D.
0	0	0.00
15	0.225	± 0.036
30	0.285	± 0.012
45	0.341	± 0.01
60	0.401	± 0.034
75	0.438	± 0.049
90	0.523	± 0.084

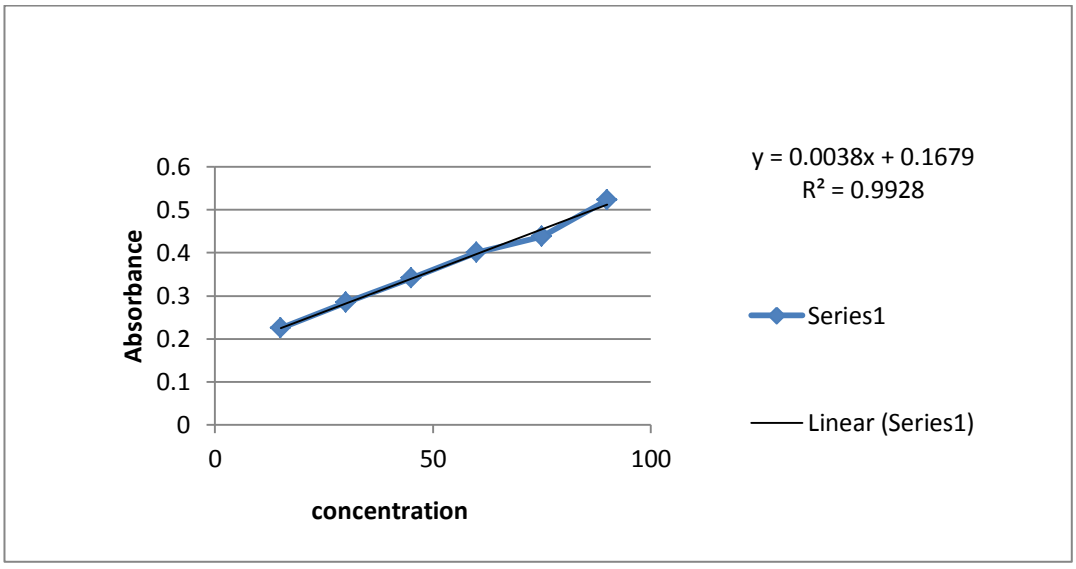
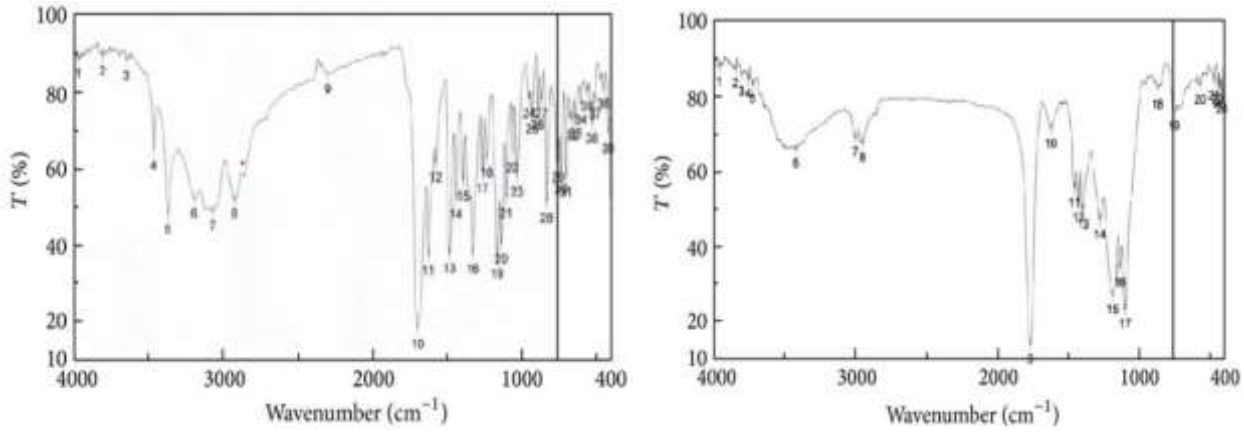


Fig. 1: Standard Calibration curve of Lorazepam

3.4 Drug Excipient Compatibility Study using Fourier Transform Infrared Spectroscopy

The interaction studies of drug with polymers suggest no incompatibility as retention of basic characteristics Lorazepamas shown in FTIR of drug and excipients. The typical FTIR curves were shown in Figure 2.



[A] **[B]**

Fig. 2: FTIR of [A] Lorazepam, [B] Physical mixture of Lorazepam with Indion 414

3.5 Evaluation of powder parameters (Pre-Formulation):

Batches F1-F9 were evaluated and found to passes for various batches according to the procedure given in Indian Pharmacopoeia and summarized in Table 3.

Table 3: Preformulation studies of various batches

Batches	Angle of repose (θ) ±SD	Bulk density (g/ml) ±SD	Tapped density (g/ml) ±SD	Compressibility Index (%)±SD	Hausner's ratio±SD
F1	$29^0$12'	0.55	0.73	23.60	1.32
F2	$30^0$56'	0.59	0.79	25.22	1.34
F3	$32^0$70'	0.58	0.78	23.61	1.34
F4	$30^0$33'	0.53	0.70	20.03	1.32
F5	$29^0$81'	0.57	0.71	19.42	1.25
F6	$32^0$76'	0.52	0.67	21.57	1.29
F7	$35^0$64'	0.54	0.69	20.38	1.28
F8	$28^0$91'	0.58	0.69	18.93	1.19
F9	$31^0$03'	0.54	0.66	21.32	1.22

3.6 Preparation of Rapimelts tablets:

Rapimelts tablets of Lorazepam were prepared by direct compression method as shown in Table 4.

Table 4: Formulation of Rapimelt tablets (200 mg)

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lorazepam	2	2	2	2	2	2	2	2	2
MCC (PH-102)	120	120	120	120	120	120	120	120	120
Crosscarmellose sodium	10 (5%)	20 (10%)	30 (15%)	-	-	-	-	-	-
Indion 414	-	-	-	10 (5%)	20 (10%)	30 (15%)	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	-	10 (5%)	20 (10%)	30 (15%)
Povidone	1	1	1	1	1	1	1	1	1
Pearlitol SD200	63	53	43	63	53	43	63	53	43
Aspartame	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talcum powder	2	2	2	2	2	2	2	2	2
Mg. Stearate	2	2	2	2	2	2	2	2	2

3.7 Evaluation of Tablet (Post-Formulation):

Evaluation of tablets of batches F1 to F9 were carried out and found thickness in range of 2.56 to 2.64 mm; Hardness 3.0 to 4.8kg/cm^2; Friability around 1.03%; Wetting time 29 to 52 Seconds; Disintegration time 9 to 22 Seconds while drug content from 96.7 % w/v to 98.9 % w/v, which is maximum in F5 batch and illustrated in Table 5.

Table 5: Physical evaluation of formulated tablet batches

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)/± SD	2.64	2.61	2.63	2.56	2.56	2.58	2.62	2.64	2.61
Hardness (kg/cm^2)/± SD	4.6	4.2	4.0	4.5	4.0	4.0	4.8	4.5	3.0
Friability (%w/w)/± SD	0.26	0.72	1.16	0.14	0.34	0.37	0.57	0.42	1.03
Wetting time (sec)/± SD	52	46	43	48	34	29	49	40	37
Disintegration time(sec)/± SD	22	12	10	20	10	09	17	10	09
Drug content (%w/v)/± SD	96.7	98.3	98.7	97.3	98.9	98.2	98.1	97.9	98.4

3.8In-Vitro disintegration test

Disintegration time of different formulation are shown in Table 5 and found to be less than 30 seconds. Among the 9 formulations F2, F5 and F8 showed 12 sec, 10 sec and 10 sec respectively by basket method. Thus the formulation F2, F5 and F8 containing 10 % superdisintegrant such as Cross Carmellose Sodium, Indion 414 and Sodium Starch Glycolate showed faster disintegration compared to 5 % and 15 % superdisintegrants.

3.9 In-vitro drug release studies:

In vitro dissolution of various formulations at different time interval is reported (Figure3A, 3B & 3C) and Table 6. Formulation with 10% Crosscarmellose Sodium, Indion 414 and sodium starch glycolate showed maximum dissolution rates with 94.47%, 99.86% and 98.41% respectively of the drug released in 8 minutes. Formulation with 10% Indion 414 released 99.86% of the drug in 8 minutes as compared to formulation containing 10% Cross Carmellose Sodium and sodium starch glycolate. Formulation with 10% Indion 414 was superior compared to other superdisintegrants.

Table 6: Comparative study of % drug release from Fast dissolving tablet of batches F1-F9

Time	% Drug release from batches								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
30	7.38	17.08	16.15	28.15	24.92	32.31	7.38	9.23	36.92
60	65.6	75.88	59.26	62.62	84.28	86.67	76.69	85.95	86.26
90	75.2	85.49	83.45	68.39	87.06	87.63	78.47	86.90	87.21
120	76.0	86.89	84.37	70.98	88.47	89.05	79.79	87.86	88.16
180	76.8	88.29	87.13	74.98	92.66	90.01	82.97	92.50	92.81
240	79.4	89.25	88.08	79.02	93.72	93.28	87.09	93.49	94.73
300	80.4	91.11	89.48	80.32	94.65	94.27	89.41	94.44	95.73
360	88.6	92.54	90.88	83.02	96.11	95.72	90.35	95.49	96.74
420	89.4	93.50	91.83	87.11	97.57	98.10	92.21	97.41	98.21
480	91.4	94.47	92.77	91.75	99.86	99.57	94.55	98.41	99.04

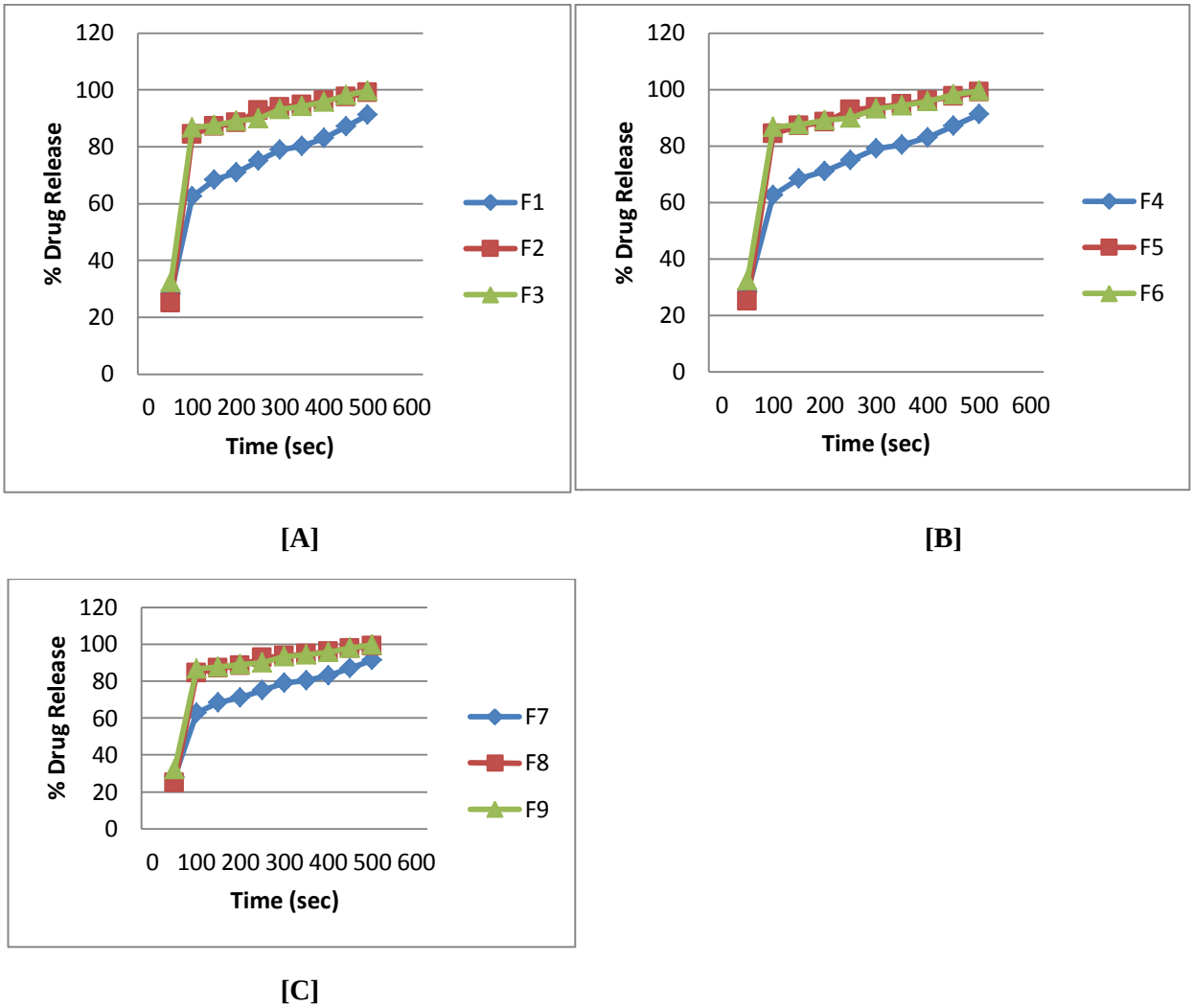


Figure 3:Comparative study of % Drug release from Fast dissolving tablet of batches [A] F1 – F3, [B] F4 – F6 & [C] F7 – F9.

3.9 Mechanism of Release from Matrix tablets:

The best fitted model for the optimized formulation of F5 batch was found to be Higuchi model. Higuchi model show the maximum release of drug having R value 0.996 shown in Table 7 and Figures 4 - 7.

Table 7: Drug release kinetic study of optimized batch

MODELS		**F_5 (Lorazepam)**
Korsmeyer- peppas	n	0.986
Zero order	R	0.978
First order	R	0.845
Higuchi model	R	0.996
Best fit model		Higuchi

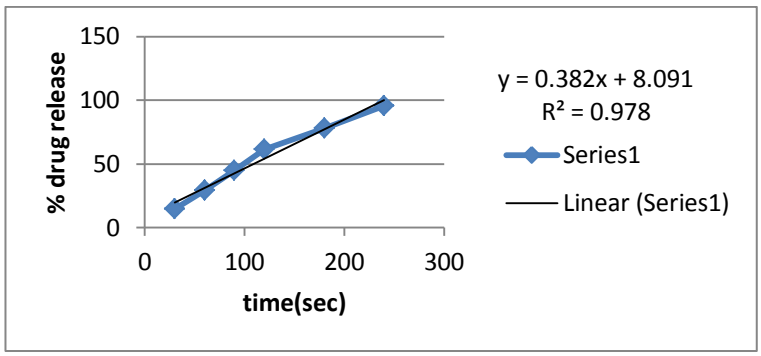


Figure 4: Curve fitting data of the release rate profile of zero order.

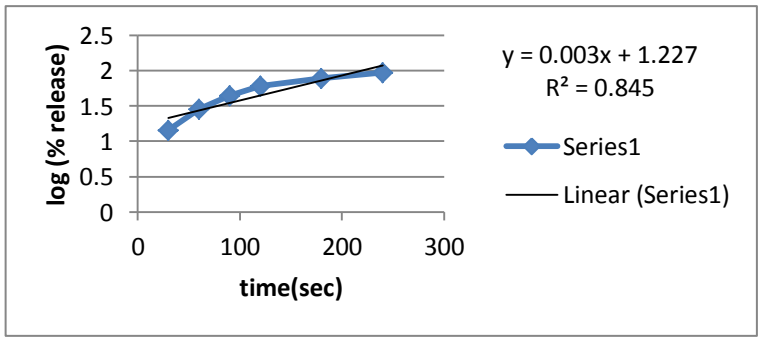


Figure 5: Curve fitting data of the release rate profile of first order.

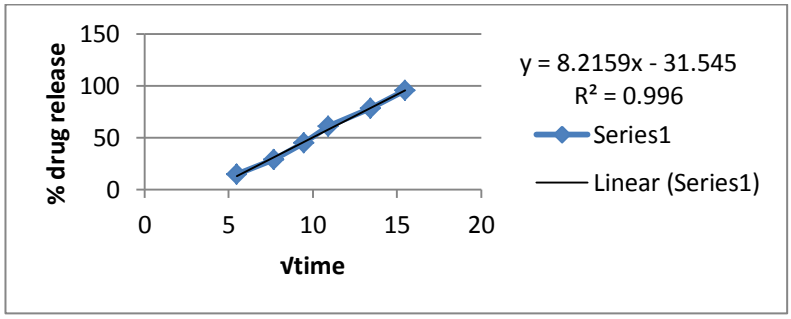


Figure 6 Curve fitting data of the release rate profile of Higuchi model

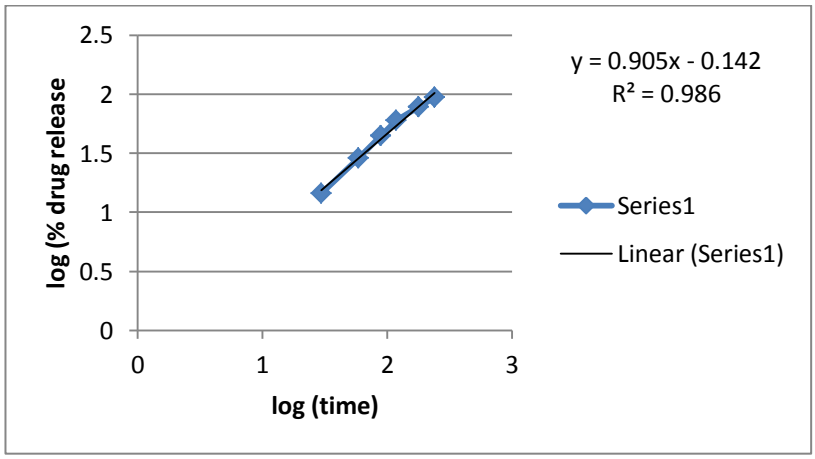


Figure 7: Curve fitting data of the release rate profile of Korsmeyer-peppas

4. Conclusion

In present study Lorazepam Rapimelt tablet prepared using different types and concentrations of superdisintegrant by direct compression method which was confirmed by various characterization and evaluation studies.

Indion 414 as superdisintegrant gives better result as compared to crosscarmellose sodium and Sodium starch glycolate. Prepared tablets disintegrate within 30 sec having better mouth feel.

5. Acknowledgement:

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