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Original Article

Studies on controlled release formulations of a macrolide antibiotic drug: Influence of HPMC of different grades as matrix former

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ABSTRACT

In the present study, several combinations of different grades of hydroxy propyl methyl cellulose (HPMC) such as HPMC-K4M, HPMC-K15M, HPMC-K100M as hydrophilic polymers and hydrophobic polymer like ethyl cellulose(EC) are used to prepare the matrix tablets that resulted in desired and controlled drug release profile. Hydrophobic polymers provide several advantages including good stability at varying pH ranges and effectively retard the release of water soluble drug(s) along with hydrophilic polymers. Erythromycin ethylsuccinate is a model drug and having short half-life of 1.5 hours. Tablets containing 100 mg of drug were formulated by wet granulation. Pre-compression and post-compression parameters were evaluated for all the formulations, which are in the acceptable range. The dissolution data were fitted into zero-order, first-order, Higuchi and Korsemeyer–Peppas models to identify the pharmacokinetics and drug release mechanism. The optimized formulation (F5) prepared with EC: HPMC-K4M in the ratio 10 mg: 5 mg show 99.02% drug release in 24 hours, which is comparable with marketed sample. Kinetic results reveal that all formulations followed zero order. Hence, it can be concluded that the use of low viscous hydrophilic polymer can extend the release of drug up to 24 hours.

Key Words: Controlled release, HPMC, Ethyl cellulose, Matrix tablets, Release Kinetics.

INTRODUCTION

Erythromycin is produced by a strain of *Saccharopolyspora erythraea* and belongs to the macrolide group of antibiotics, mainly used in the treatment of infections caused by Gram-positive and some Gram-negative organisms. It is basic in nature and unstable in acidic media such as in gastric juice. It is therefore necessary to use structurally modified erythromycin derivatives or acid-resistant dosage forms in order to prevent gastric inactivation of the drug. Erythromycin ethyl succinate is an ester of erythromycin which is reported to be acid-stable due to its insolubility in acidic media and suitable for oral administration. Erythromycin ethyl succinate is known chemically as erythromycin-2'-(ethyl succinate); the molecular formula being $C_{43}H_{75}NO_{16}$ and the molecular weight is 862.06. The structural formula is in Figure 1. Due to its short biological half-life period of 1.5 hours and dosing frequency more than one per day; it becomes an ideal candidate for studies on its desirable or controlled drug release, patient compliance and cost–effectiveness.

In the present study, an attempt has been made to develop matrix tablet system with different grades and proportions of hydroxy propyl methyl cellulose (HPMC K4M, HPMC K15M and HPMC K100M), along with ethyl cellulose, in which HPMC as hydrophilic polymers and ethyl cellulose as hydrophobic polymer. Due to hydrophilic nature, HPMC polymers on contact with aqueous fluids get hydrated to form a viscous gel layer through which drug will be released by diffusion and/or by erosion of the matrix [1]. The drug release for extended duration; particularly for highly water soluble drug hydrophobic matrix system is suitable, along with a hydrophilic matrix because of the rapid diffusion of the dissolved drug though the hydrophilic network, for developing sustained release dosage forms. Therefore, the main objective of the study is that, the rate of diffusion of drug molecules influence by various viscosity grades of HPMC.

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MATERIALS AND METHODS

Materials: The chemicals used in the experiment were Erythromycin ethyl succinate, HPMC K4, HPMC K15, HPMC K100, Ethyl cellulose, Dibasic calcium phosphate, Magnesium stearate and Talc. All other ingredients used are of analytical grade.

Methods

Drug Excipients' Compatibility Studies

FT-IR Characterization Studies (physical compatibility studies): Infrared spectrum is taken for the drug (Figure-2) and drug-polymer mixtures (Figure-3). FT-IR studies are carried by KBr disk method using computer mediated Fourier Transformed Infrared Spectroscopy (FTIR) (Shimadzu Model). The characteristic FTIR bands of Erythromycin ethylsuccinate at 2973.37 cm^{-1} (alcohol stretch) and 3460.41 cm^{-1} (amine stretch) were observed.

Differential Scanning Calorimetry (DSC) (chemical compatibility studies): The chemical interaction between the drug and excipients have been studied using DSC apparatus, over a temperature range which will encompass any thermal changes due to both the drug and excipient. Basically, the thermal properties of a physical mixture are the sum of the thermal properties of individual components. This thermogram can be compared with those of the drug and the excipient alone (Figure 4 & Figure 5). Comparison of the DSC data shows changes in melting point, peak shape, area and/or the appearance of a transition.

Preparation of erythromycin ethyl succinate granules: Accurately weighed quantities of drug and excipients (except lubricant and glidant) blended properly and then passed through the 80# sieve. The wet damp mass is formed by slowly adding granulating liquid (as distilled water). The cohesive material was sieved through 22# and 44# mesh into granules of uniform size. The wet granules are dried at 50ºC for 2 hrs in a hot air oven (Universal Hot Air Oven) and then talc and magnesium stearate are added to lubricate [2-3].

Evaluation of granules:- The flow properties of granules were characterized in terms of angle of repose, Carr's index and Hausner's ratio. The bulk density and tapped density were determined using Bulk Density tester (Teknik Bulk Density Tester). The data summarized in Table 3.

Bulk Density: Bulk density is determined by Teknik Bulk Density Apparatus, by placing pre-sieved drug excipients blend in to a 100 ml graduated cylinder and measuring the volume and weight as it is, thus it is calculated using formula [4-5];

$$D_b = \frac{M}{V_b}$$

where, M =Weight of powder taken; V_b =Bulk volume

Tapped Density: Tapped density is determined by Teknik Bulk Density Apparatus, blend was filled in 100 ml graduated cylinder of tap density tester which operates for fixed number of taps until the powder bed volume reaches a minimum, thus is calculated using formula [5-6];

$$D_t = \frac{M}{V_t}$$

where, M =Weight of powder taken; V_t =tapped volume.

Angle of Repose: Angle of repose 'θ' is determined by using funnel method. Certain amount of tablet blend is poured from funnel that can be raised vertically until a maximum cone height 'h' is obtained. Diameter heap D, was measured. The angle of repose is calculated by formula (Table 1);

$$\theta = \tan^{-1}\frac{2h}{D}$$

Carr's Index: This is measured for the property of a powder to be compressed into a tablet; as such they are measured for relative importance of interparticulate interactions. Carr's index is calculated by following equation (Table 2) [5,7];

$$\text{Carr's Index (\%)} = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

where, ρ_t =tapped density; ρ_b =bulk density;

Hausner Ratio: Values less than 1.25 indicate good flow, whereas greater than 1.25 indicates poor flow. Hausner ratio is calculated by following equation [5];

$$\text{Hausner ratio} = \frac{\rho_t}{\rho_b}$$

where, ρ_t =tapped density and ρ_b =bulk density

Formulation of Tablets: The prepared granules of erythromycin ethyl succinate were compressed in 10 mm punches, Single tablet compression machine (Shakti). The formulae for batches F1 to F12 are shown in Table 4.

Evaluation of Tablet: The prepared matrix tablets were evaluated for thickness, hardness, friability, weight variation and drug content. The results are shown in Table 6.

Weight Variation: Twenty tablets are randomly selected from each batch and then individually weighed; calculated the average weight of twenty tablets. The requirements are met if the weights of not more than 2 of the tablets differ from the average weight by more than the percentage listed in the accompanying Table-5 [8-9].

Thickness: The thickness of the tablet is measured by using vernier calipers. Twenty tablets from each batch are randomly selected and thicknesses are measured. The mean and standard deviation (S.D) are calculated for precise readings [10].

Hardness: Hardness is measured using Monsanto hardness tester. For each batch five tablets are tested and calculated the mean and standard deviation for precision [11].

$$\%\text{Deviation} = \frac{\text{Tablet weight} - \text{Average weight}}{\text{Tablet weight}} \times 100$$

Friability: Twenty tablets are weighed and placed in the Roche Friabilator which is rotated at 25rpm for 4 minutes and then the tablets are removed; accurately weighed after dusting out any loose particles adhering the tablets. The percentage friability was calculated by [12]:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

where, w= weight of the tablet

Drug Content Uniformity: Twenty tablets of each type of formulation are weighed and crushed in mortar and powder equivalent to 100 mg of Erythromycin ethyl succinate is weighed and dissolved in 100 mL of 0.1N HCl. From the stock solution 1 mL sample is withdrawn and diluted to 10 mL with 0.1N HCl and then subsequent dilutions are prepared with 0.1N HCl. The absorbance is measured at wavelength 215nm using a Systronics Double Beam UV-Visible Spectrophotometer 2203.

In-Vitro Dissolution Study: The study is carried out using 0.1N HCl for initial 2 hours and then up to 24 hours with phosphate buffer 7.4 using the USP apparatus types II (paddle type) (Lab India Dissolution Test Apparatus DS 8000). The dissolution medium 900 mL maintained at temperature 37 ± 0.5 ºC, at a speed of 100 rpm. A 5 mL of aliquot was withdrawn from the dissolution apparatus at certain time intervals for 24 hours and immediately the samples were replaced with fresh dissolution medium. After filtration, the collected sample was diluted with suitable concentration with the corresponding dissolution medium. The absorbance was measured at 215 nm using a Systronic Double Beam Spectrophotometer 2203. The amount of the drug released was determined from the standard calibration curve of pure drug [13].

Kinetic Modeling of in-vitro Drug Release (Figure-6 to Figure-15): To study the release kinetics, the data obtained from *in-vitro* drug released studies of optimized formulation F5 was plotted in various kinetic models:

1. Zero order rate kinetics: Cumulative percentage of drug released vs. time
2. First order rate kinetics: Log cumulative percentage of drug remaining vs. time
3. Higuchi model: Cumulative percentage of drug released vs. square root of time
4. Korsmeyer Peppas model: Log cumulative percentage of drug released vs. log time

RESULTS

The FTIR spectral data of pure drug and drug-polymer mixture is interpreted in detail and the overlaid spectrum showed similar peaks. From FTIR characterization study, it is observed that there was no interaction between drug and excipients. Based on the physical compatibility result, the excipients were chosen for the formulation development. In DSC studies, drug peak showed at 115.18ºC in drug-polymer mixture whereas the pure drug showed an endothermic peak at 120.90°C.

The DSC thermograms of pure drug and drug-polymer mixture revealed that there were no polymer interactions or phase transformations occurred and the drug and excipients are chemically compatible with each other. The bulk density of granules was found to be between 0.365 and 0.394 gm/cc which indicates good packing capacity of granules. Carr's index was found to be between 12.23 and 14.53, showing good flow characteristics. Hausner's ratio ranged from 1.114 to 1.98 which indicates good flow ability. The angle of repose of all the formulations was within the range of 23°24′ to 25°63′, i.e. the granules of erythromycin ethyl succinate have good flow properties. The thickness ranged from 4.23 ± 0.03 mm to 4.45 ± 0.02 mm, and the hardness ranged from 5.22 ± 0.01 kg/cm^2 to 5.82 ± 0.01 kg/cm^2. The friability ranged from 0.32 ± 0.02 to 0.82 ± 0.02. The values of percentage weight variation ranged from 1.31 to 2.45. Drug content ranged from 91% to 96% indicating good content uniformity among the prepared formulations. Coefficient correlation values were found to be in the range 0.9242 to 0.9948, 0.7903 to 0.9829, 0.9379 to 0.9916 and 0.9588 to 0.9947 for zero-order, first-order, Huguchi model and Peppas

model respectively. The slopes were found in the range from 0.6670 to 1.0231 (in Table-7).

DISCUSSION

In the present work, matrix tablets of erythromycin ethyl succinate have been formulated by using ethyl cellulose and HPMC grade polymers in 2:1, 2:2, 1:1, and 1:2 proportions, to study the release of drug up to desired time in each formulation. From FTIR characterization and DSC studies, it is observed that there was no interaction between drug and excipients in the formulations. The matrix tablets so prepared by wet granulation method evaluated for their hardness and friability. More than 5.55±0.01 Kg/cm^2 hardness and below 1% friability indicated good physical strength of tablets.

Among all formulations, the optimized F5 formulation has 96% drug content indicated uniform distribution of drug and sustained good therapeutic activity. Kinetic results revealed that all formulations followed zero order kinetics, as zero order regression value (R^2) is more than first order value ie., 0.9699 > 0.9185. The calculated "n" values from power law equation for drug release profile of F5 is 0.7507 with a correlation coefficient 0.9712, suggesting that drug release mechanism from matrix tablets followed anomalous (non-fickian) diffusion mechanism [14].

CONCLUSION

The market for drug delivery system has come a long way and will continue to grow at an impressive rate. Today's drug delivery technologies enable the incorporation of drug molecules into a new delivery system, thus providing numerous therapeutic and commercial advantages. Matrix tablet drug delivery systems provide several advantages including greater flexibility and adaptability. The hydrophilic matrix of HPMC all grades alone could not control the drug release effectively for 24 hrs. It is evident from the results that the matrix tablets prepared from HPMC (low viscous polymer grade like HPMC K4M) along with ethyl cellulose a better system for once-daily controlled release matrix tablet of erythromycin ethylsuccinate. Formulation F5 exhibited satisfactory drug release in the initial hours and the total release pattern was very close to the theoretical release profile. So, F5 was the most successful, cost-effective and optimized formulation.

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Table-1: Angle of repose as an indication of powder flow [5].

Angle of repose (degrees)	Type of flow
<20	Excellent
20-30	Good
30-34	Passable
>40	Very poor

Table-2: Carr's index as an indicator of flow properties [5].

Carr's Index (%)	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Table-3: Pre-compression Evaluation Tests.

Formulation	Bulk Density (g/cc)	Tapped Density (g/cc)	Angle of Repose (°)	Carr's Index (%)	Hausner's Ratio
F1	0.384	0.441	25.41	12.92	1.148
F2	0.379	0.434	23.24	12.67	1.145
F3	0.394	0.461	24.32	14.53	1.170
F4	0.370	0.422	25.63	12.32	1.140
F5	0.369	0.428	24.21	12.18	1.149
F6	0.365	0.437	24.74	14.47	1.197

F7	0.372	0.428	25.62	13.08	1.150
F8	0.384	0.428	24.37	12.28	1.114
F9	0.370	0.422	23.38	12.32	1.140
F10	0.375	0.411	24.34	12.32	1.135
F11	0.380	0.421	25.12	12.23	1.142
F12	0.371	0.432	25.10	13.26	1.198

Table-4: Formulation of Erythromycin ethyl succinate Controlled Release Matrix Tablet.

Ingredients (mg/tablet)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Erythromycin ethylsuccinate	100	100	100	100	100	100	100	100	100	100	100	100
Ethyl cellulose	10	10	5	5	10	10	5	5	10	10	5	5
HPMC K4M	-	-	-	-	5	10	5	10	-	-	-	-
HPMC K15M	5	10	5	10	-	-	-	-	-	-	-	-
HPMC K100M	-	-	-	-	-	-	-	-	5	10	5	10
Dibasic Calcium Phosphate	173	168	178	173	173	168	178	173	173	168	178	173
Talc	6	6	6	6	6	6	6	6	6	6	6	6
Magnesium stearate	6	6	6	6	6	6	6	6	6	6	6	6
Distilled water (in mL)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight of the tablet	300	300	300	300	300	300	300	300	300	300	300	300

q.s=Quantity sufficient

Table-5: Weight variation tolerances for uncoated tablets [9].

Average weight of tablets(mg)	**Maximum percent deviation (%)**
130 or less	10
130-324	7.5
>324	5

Table-6: Post-compression Evaluation Data of Erythromycin ethyl succinate Matrix Tablets Prepared by Wet Granulation Method.

Formulations	**Hardness (kg/cm2)± S.D***	**Weight variation (%)**	**Friability (%) ± S.D***	**Thickness (mm) S.D***	**Drug content (%) ± S.D***
F1	5.22±0.01	1.93	0.32±0.02	4.23±0.03	92
F2	5.72±0.36	1.22	0.76±0.04	4.36±0.02	91
F3	5.82±0.01	1.71	0.82±0.02	4.35±0.01	92
F4	5.53±0.36	2.45	0.66±0.06	4.43±0.04	94
F5	5.55±0.35	1.31	0.42±0.03	4.35±0.03	96
F6	5.76±0.36	1.83	0.49±0.05	4.45±0.02	93
F7	5.68±0.33	2.15	0.66±0.01	4.35±0.01	91
F8	5.65±0.32	1.98	0.45±0.01	4.32±0.03	95
F9	5.52±0.36	1.76	0.59±0.05	4.29±0.05	94
F10	5.78±0.33	1.36	0.57±0.04	4.35±0.03	93
F11	5.54±0.32	1.46	0.45±0.03	4.32±0.01	92
F12	5.53±0.36	1.62	0.59±0.02	4.29±0.02	96

S.D=standard deviation, * Values are expressed as mean ± SD; n=3

Table- 7: Correlation Coefficient (R^2) Values in the Analysis of Release Data of the Pure Drug Matrix Tablets.

Formulation	R^2 Values				
	Zero order	First order	Higuchi	Peppas	'n' (slope)
F1	0.9728	0.9122	0.9889	0.9733	0.8637
F2	0.9615	0.9177	0.9869	0.9588	1.0231
F3	0.9667	0.9239	0.9907	0.9742	0.7878
F4	0.9354	0.9083	0.9784	0.9630	0.7832
F5	0.9699	0.9185	0.9905	0.9712	0.7507
F6	0.9583	0.9165	0.9879	0.9743	0.7539
F7	0.9809	0.9214	0.9894	0.9801	0.7196
F8	0.9242	0.7903	0.9757	0.9602	0.6670
F9	0.9941	0.9611	0.9643	0.9833	0.8747
F10	0.9638	0.9829	0.9916	0.9782	0.8768
F11	0.9851	0.9449	0.9379	0.9947	0.9942
F12	0.9948	0.9826	0.9757	0.9864	0.9764

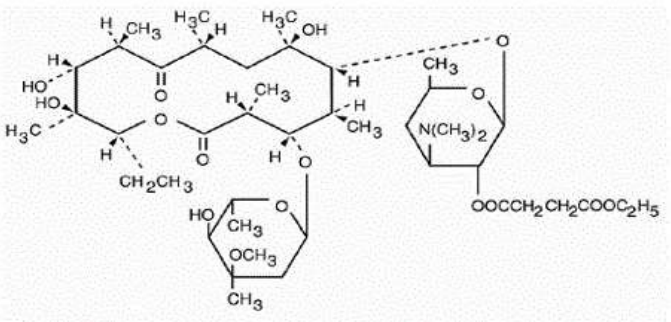

Figure-1: Erythromycin ethyl succinate.

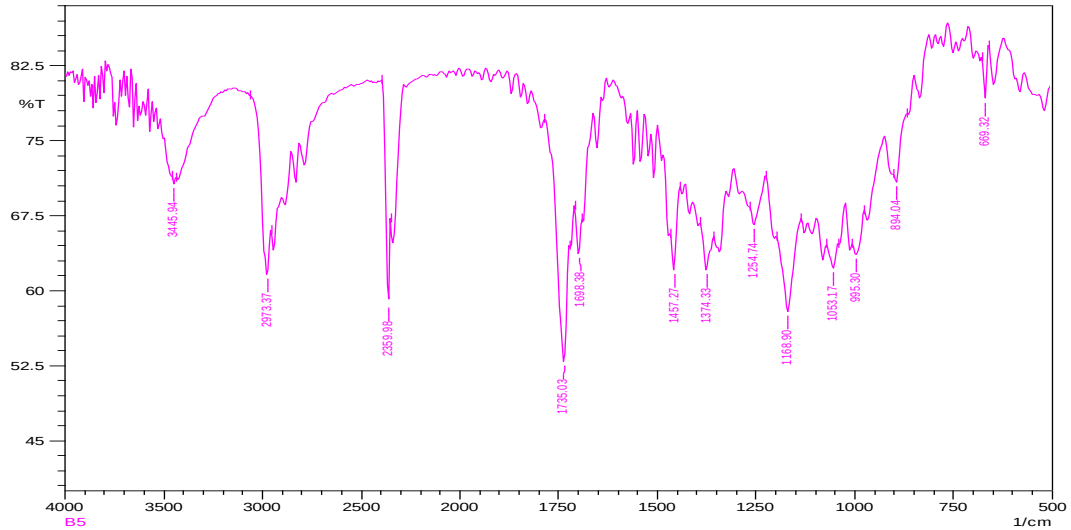

Figure-2: FTIR spectra of pure drug.

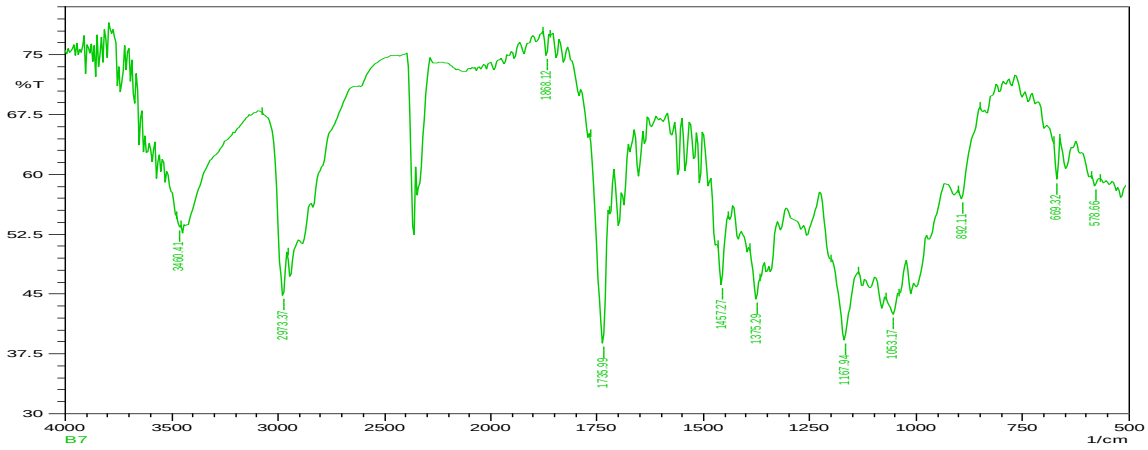

Figure-3: FTIR spectra of drug-polymer mixtures.

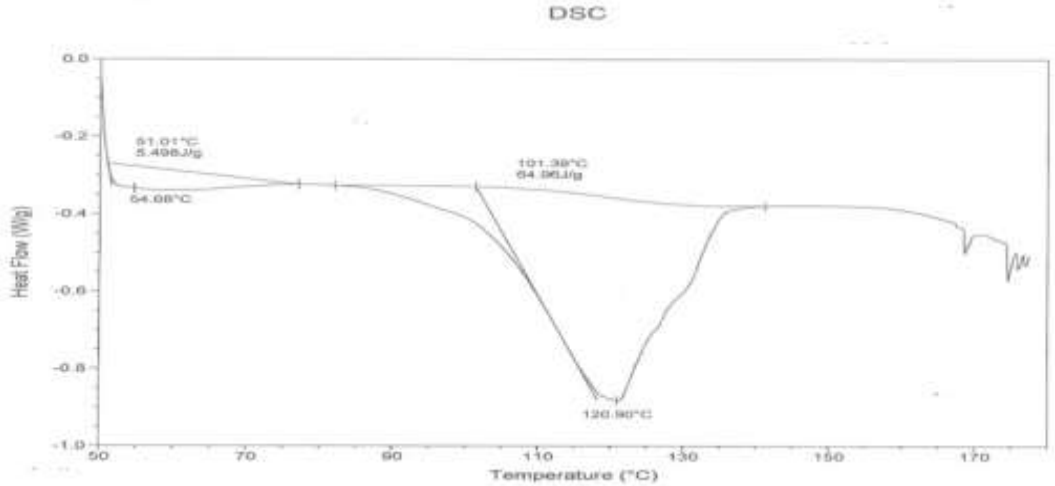

Figure-4: DSC Thermogram of pure drug.

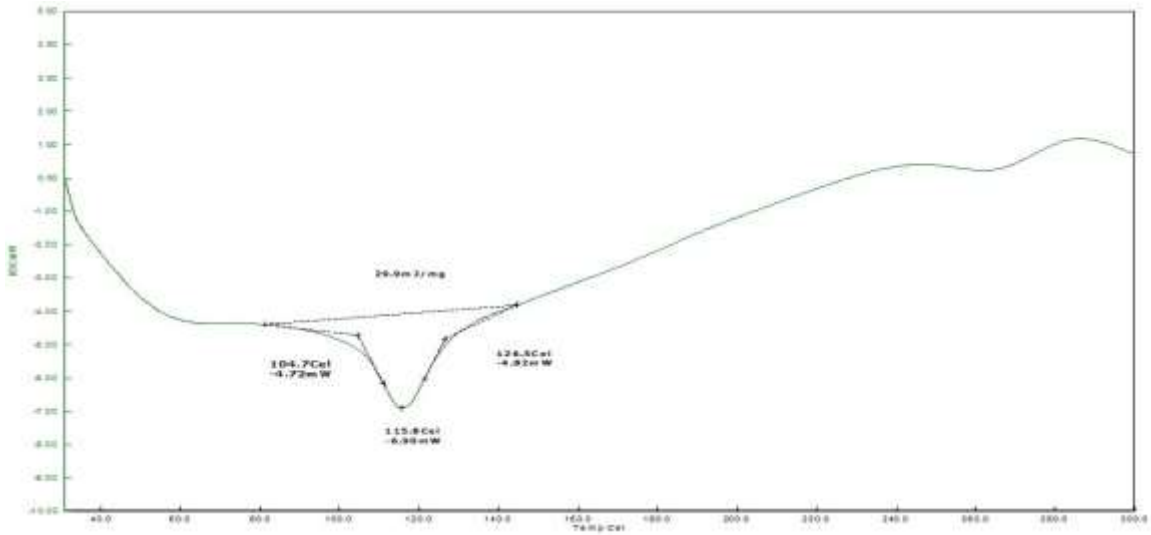

Figure-5: DSC Thermogram of pure drug with polymers

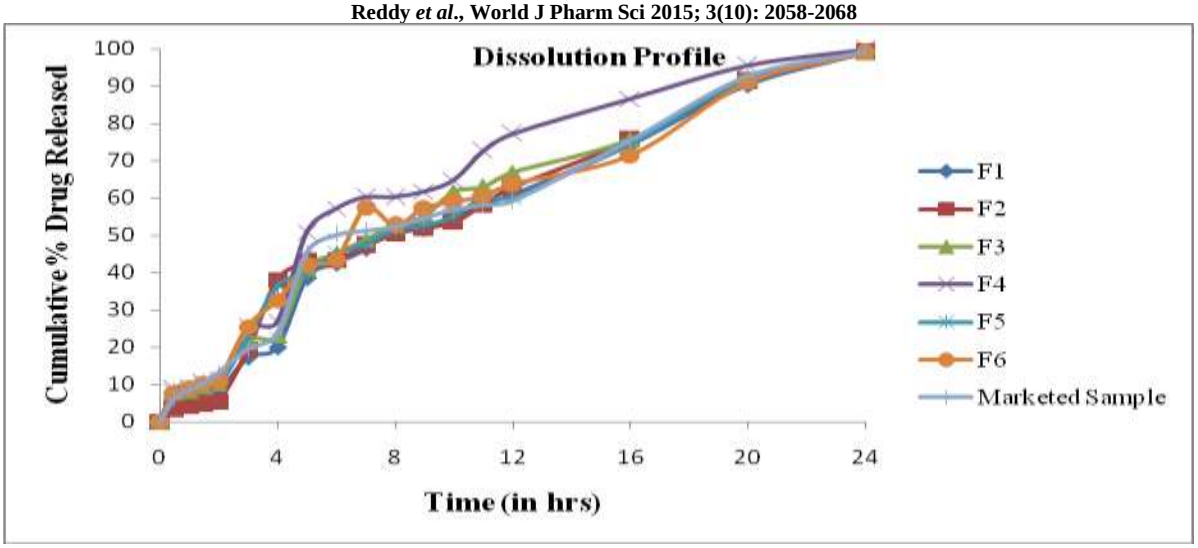

Figure-6: Dissolution profile for F1-F6 and comparison with marketed sample.

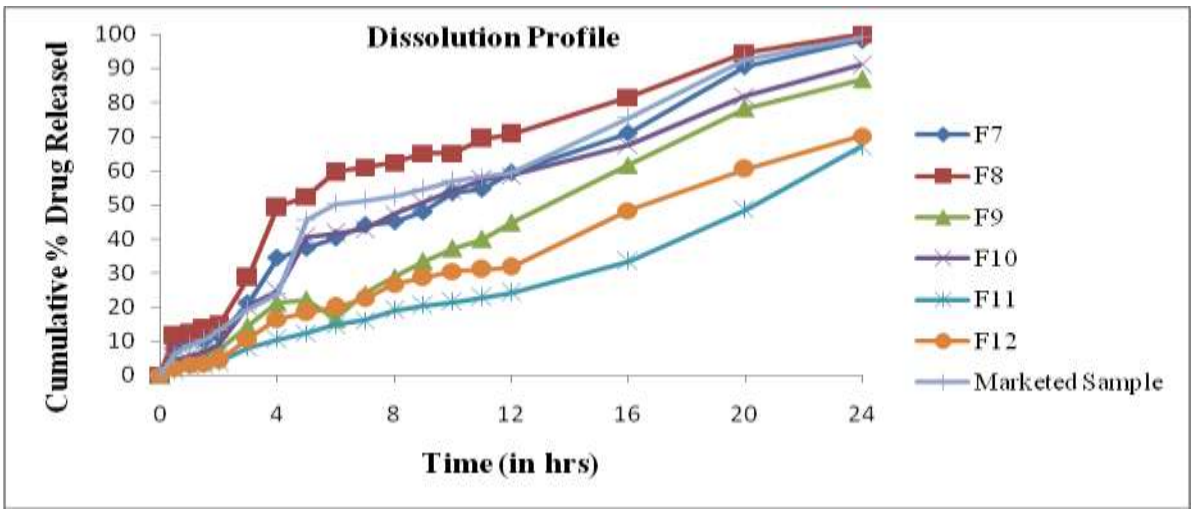

Figure-7: Dissolution profile for F7-F12 and comparison with marketed sample.

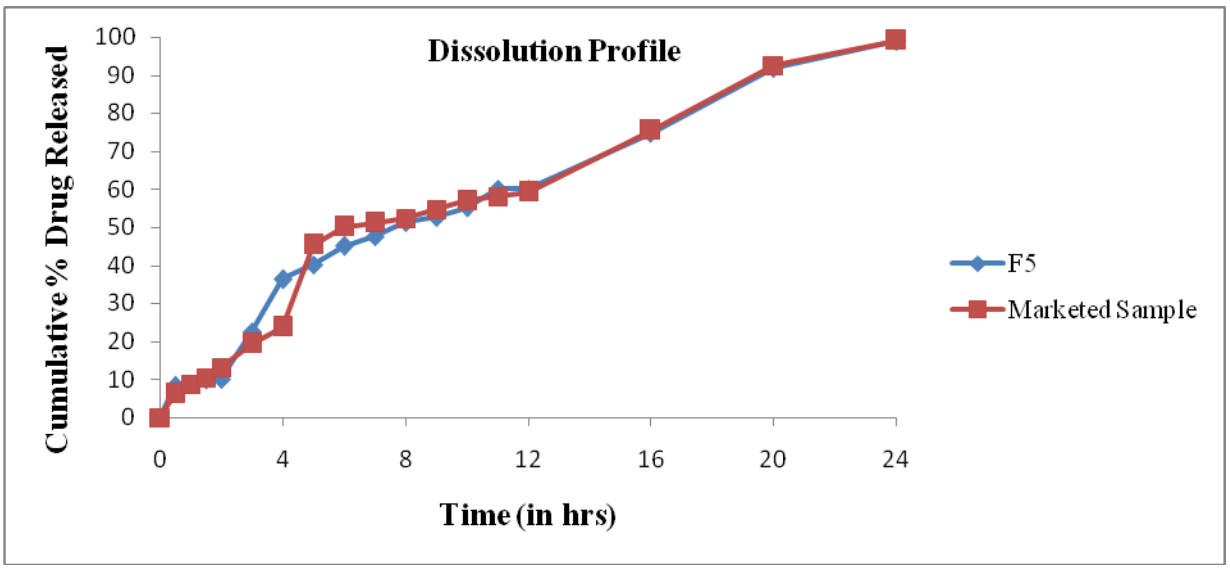

Figure-8: Dissolution profile for optimized Plot for F1-F6 and Comparison with marketed sample

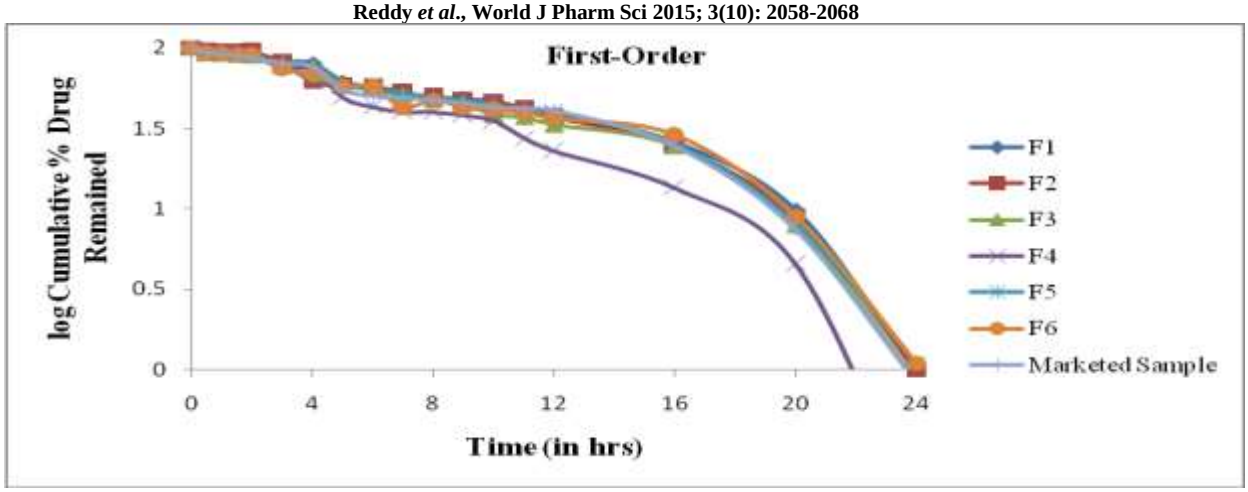

Figure-9: Time Vs log Cumulative % Drug Remained formulation F5 and comparison with marketed sample

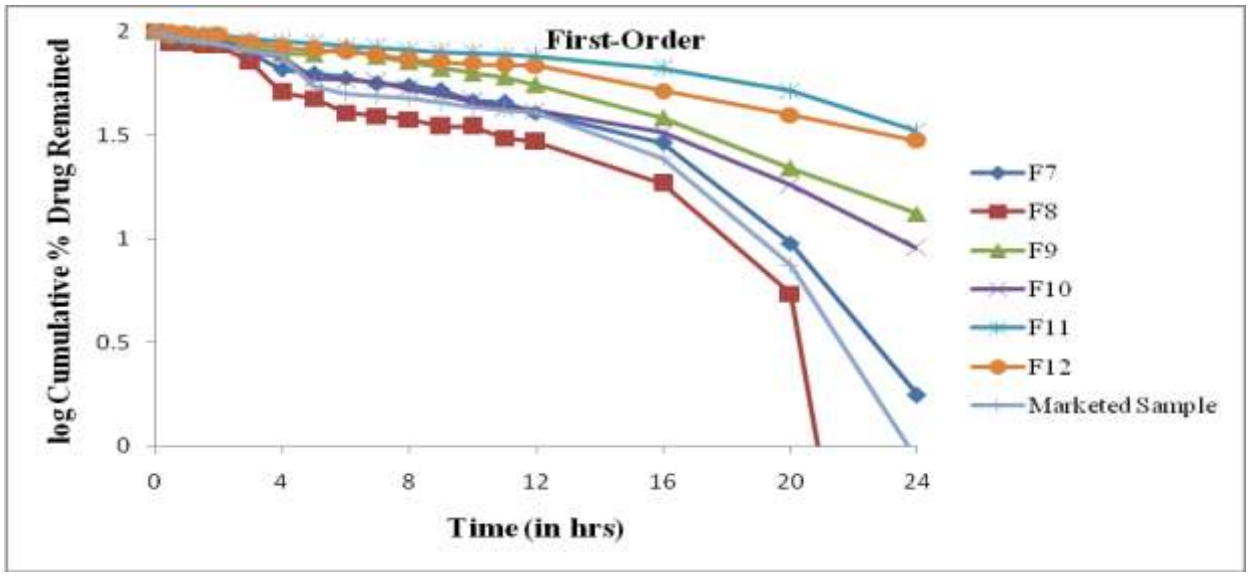

Figure-10: Time Vs log Cumulative % Drug remained Plot for F7-F12 and Comparison with Marketed sample.

Figure-11: Time Vs log Cumulative % Drug remained Plot for optimized formulation F5 and Comparison with marketed sample.

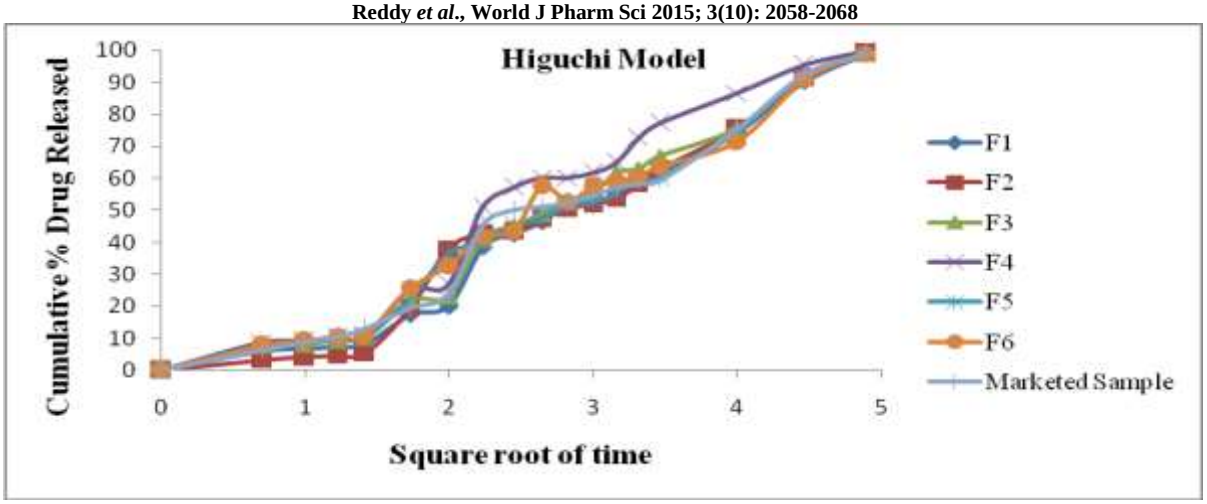

Figure-12: Square Root Time Vs Cumulative % Drug Released Plot for F1-F6 and Comparison with Marketed sample.

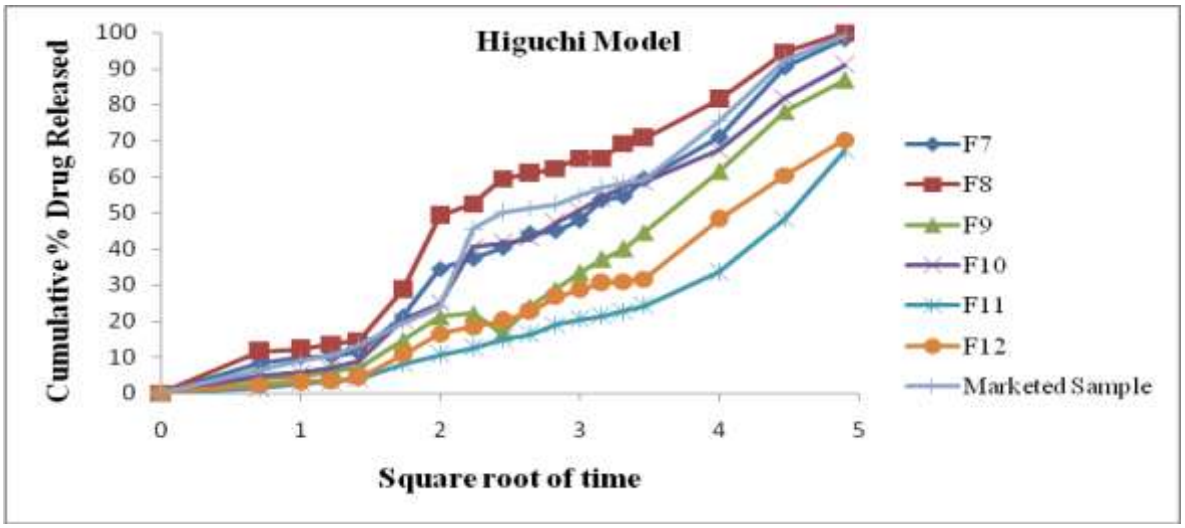

Figure-13: Square Root Time Vs Cumulative % Drug Released Plot for F7-F12 and Comparison with Marketed sample.

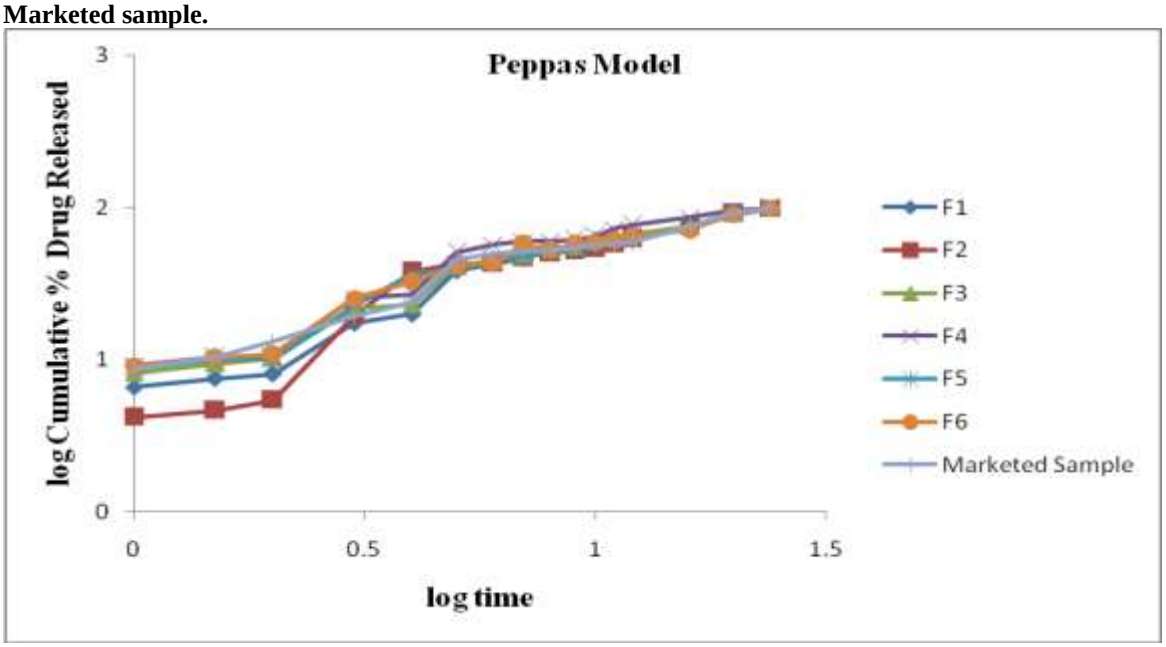

Figure-14: Log Time Vs. Log Cumulative % Drug Released plot for F1-F6 and comparison with Marketed sample.

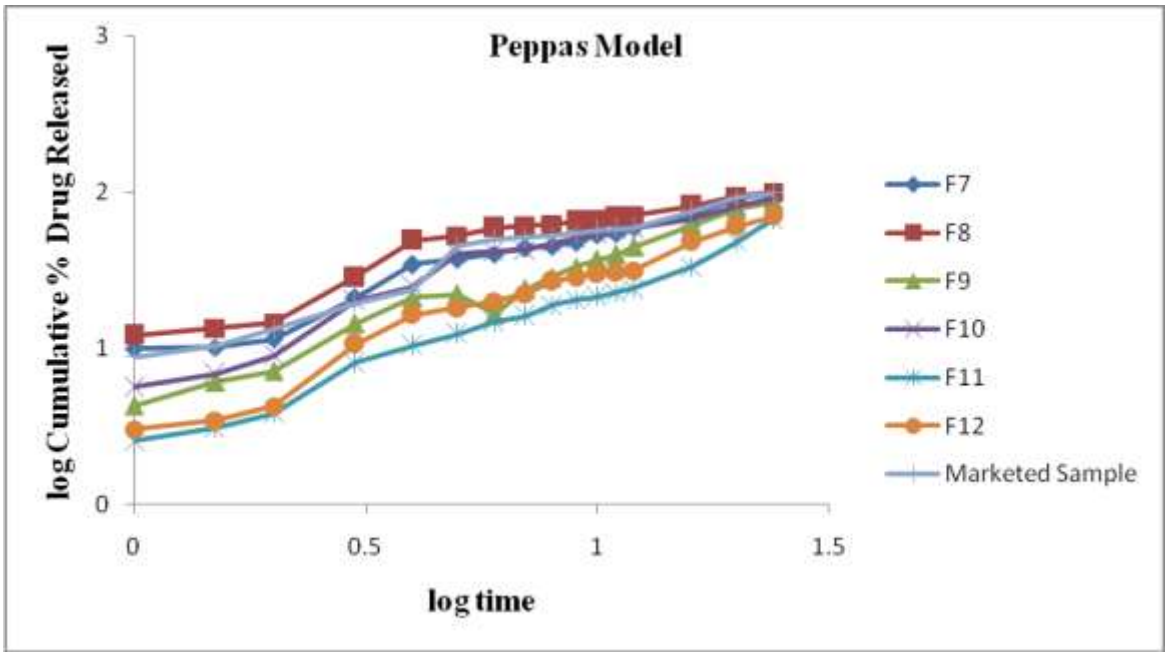

Figure-15: Log Time Vs. Log Cumulative % Drug Released plot for F7-F12 and comparison with Marketed sample

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