INTERNATIONAL RESEARCH JOURNAL OF PHARMACY **ISSN 2230 – 8407**
Available online http://www.irjponline.com
Research Article

FORMULATION AND EVALUATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF STAVUDINE

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Article Received on: 02/01/11 Revised on: 09/02/11 Approved for publication: 18/02/11

ABSTRACT
The present study was designed to formulate and evaluate hydro dynamically balanced Floating Drug Delivery Systems as controlled release modules, which prolongs the release rate of the drugs. Stavudine is an anti- retroviral, reverse transcriptase inhibitor (Nucleoside). Stavudine triphosphate inhibits the HIV reverse transcriptase by competing with natural substrate, thymidine triphosphate. It also causes termination of DNA synthesis by incorporating into it. Formulation of Stavudine as gastro retentive drug delivery systems (GRDDS) is especially advantageous over other prolonged type drug delivery systems and conventional tablets because the drug is having absorption window in the duodenum and jejunum level and having relatively short half life. Stavudine was taken as the model drug to optimized formulations was prepared. The floating ability of lipoidal fatty polymers Gelucire 13/01, Gelucire 43/ 01 is compared over various polymers like HPMC, HPMC K4M, Ethocel, Sodium carboxy methyl cellulose. The drug: polymer ratios used to prepare the different formulations were 1:0.5 and 1:1. Blend of all the formulations are prepared by melt granulation technique. All the tablets were subjected for dissolution study using USP dissolution apparatus (USP XXIII paddle method) and data were analyzed at 265nm. The drug release of Stavudine from all the formulations followed zero order kinetics. According to the dissolution profiles of formulations drug retardation was enhanced in 1:1 Drug: Polymer proportion than 1:0.5 proportions. Of all the formulations in which Gelucire 13/01 is used as a floating polymer, has retarded the drug successfully upto 12 hours.

KEYWORDS: Stavudine, Gelucire 13/01, Gelucire 43/ 01, Ethocel, HPMC K_4M.

INTRODUCTION

Oral route has been the most popular and successfully used route for controlled delivery of drugs over an extended period of time. Design and development of oral controlled release dosage form for a given drug involves the optimizations of the dosage form characteristics relative to G.I. environment[1]. Design of controlled delivery system involves optimization of dosage form characteristics within the inherent constraints of the G.I. physiology[2].Dosage forms with a prolonged gastric residence and controlled drug delivery are called as Gastro Retentive Drug Delivery System (GRDDS) [3] which extended the period of time over which the drug may be released in comparison to Controlled drug delivery systems. Since the majority of drugs are preferentially absorbed in the upper part of the small intestine[4] and the relatively brief GET in humans, normally averages 2-3h through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the drug delivery system leading to diminished efficacy of the administered dose.

Thus, control placement of a drug delivery system in a specific region of the GI tract offers numerous advantages especially,

- For drugs exhibiting absorption window
- Or drugs with stability problem

These considerations have led to the development of oral controlled release dosage forms possessing gastric retention capabilities.

Various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract includes floating drug dosage systems (FDDS)[5] swelling or expanding systems[6], mucoadhesive systems[6], modified-shape systems, high-density system[7]and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used. But the dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems (GRDDS). The present work was undertaken on Stavudine, an analogue of thymidine with less half life of 1.2 – 1.6 hrs, so as to design a low density gastro retentive dosage forms that can reside for a prolonged period of time with in the body there by offering better pharmacological action.

MATERIALS AND METHODS

Stavudine was a gift sample from Dr.Reddy Laboratories; HYD. Gelucire 43/01 was a gift sample from Gattefosse Pvt Ltd, France. HPMC and HPMC K_4M (Methocel) was purchased from ISP Hongkong Ltd, Hyderabad. Ethyl Cellulose (Ethocel) was a gift sample from Arubindo Pharma Ltd, Hyderabad.

Preparation of floating granules

Floating granules containing Stavudine were prepared using the melt granulation technique. The drug: lipid ratios used to prepare the different formulations were 1:0.5, 1:1.Stavudine was taken as the model drug to optimize the release and floating characteristics of the formulations and the final optimized formulations were prepared. All the polymers except Gelucire 43/01 were weighed accordingly, dissolved in limited extent of suitable solvent and heated to their melting point. To the melt the drug was added, cooled to room temperature. In case of Gelucire 43/01, the lipid was melted at 50^{o}C, and the drug or drug and additives mixture was added, mixed well, and cooled to room temperature. The mass was passed through a 510 µm sieve to obtain uniform- sized granules. The level of polymer(S) was optimized to obtain a formulation that would afford to release more than 95 % of the drug in 12 hours, which will have potential as twice daily dosage form. Different formulations named as F1, F2, F3, F4, F5, F6, F7, F8, F9 and F10 were prepared. **(Table 2)**

Formulation and development

Dose Calculation

Immediate Release Loading Dose

Pure Stavudine in the dose of 25 mg per tablet was used as an immediate release loading dose in case of matrix tablets.

Sustained Release Dose

The maintenance dose was calculated by applying the following equation

$$Dt = Dose \frac{(1+ 0.693 \text{ X } t)}{t½}$$

Where

Dt = Total dose of the formulation
Dose = Dose of the immediate release part.
t = Duration in hours till which the sustained release was desired.
t½ = Half life of the drug.

Evaluation

Drug content and Percentage Yield

Ten milligrams of floating granules were added to 10 ml of distilled water, heated to 60^{o}C to 70^{o}C, and allowed to cool to room temperature.The lipid was solidified and the drug solution was filtered through Whatman No. 1 paper.The sample was analyzed for drug content by UV Spectrophotometry (Cyberlab) atλ_{max} 265 nm for Stavudine after suitable dilutions.Percentage yield of the formulations were calculated.

Floating characteristics

***In Vitro* Evaluation Of Floating Ability**

Fifty unit granules were placed in 900ml of distilled water and USP simulated gastric fluid (pH 1.2) in a vessel maintained at 37^{o}C±0.2^{o}C and stirred at 50 and 100 rpm in USP type II dissolution test apparatus (Lab India). The percentage of floating granules upto 6 hours was determined and the floating times were measured by visual observation.

***In vitro* release studies (USP XXIII, 1995)**

USP XXIII Paddle type dissolution apparatus was used. The dissolution fluid was 900ml of 0.1N hydrochloric acid, a speed of 75 rpm and a temperature 37±0.5^{0}C were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted and assayed for Stavudine by measuring absorbance at 265 nm using UV Spectrophotometer[8].

RESULTS AND DISCUSSION

According to the dissolution profiles of formulations, drug retardation was enhanced in 1:1 Drug: Polymer proportion than 1:0.5 proportions. Of all the formulations F10 in which Gelucire 13/01 is used as a floating polymer, has retarded the drug successfully up to 12 hours. It was found that granules of formulation F10 were found to be in tact and floated successfully for 12 hours. F10 formulation was selected as the optimized formulation for further studies as it has shown good floating for12 hours and the drug release of more than 95 % in 12 hours during the in vitro dissolution studies

CONCLUSION

According to the dissolution profiles of formulations, drug retardation was enhanced in 1:1 Drug: Polymer proportion than 1:0.5 proportions. Of all the formulations F10 in which Gelucire 13/01 is used as a floating polymer, has retarded the drug successfully up to 12 hours and it has shown good floating for12 hours and the drug release of more than 95 % in 12 hours during the in vitro dissolution studies.

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Table 1: Standard plot of stavudine

S.No	Concentration µg/ml	Absorbance at 265 nm ± S.D
1	0	0 ± 0
2	5	0.1231 ± 0.0036
3	10	0.2602 ±0.0047
4	15	0.4018 ± 0.0015
5	20	0.5168 ± 0.0074
6	25	0.6533 ± 0.0114
7	30	0.7925 ± 0.0024
8	35	0.8825 ± 0.0048

Table 2: Composition of formulations F1 to F10

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	[Drug: Polymer-1:0.5]					[Drug: Polymer-1:1]				
Stavudine	100	100	100	100	100	100	100	100	100	100
HPMC	50	--	--	--	--	100	--	--	--	--
HPMC K_4M	--	50	--	--	--	--	100	--	--	--
Ethocel	--	--	50	--	--	--	--	100	--	--
Sodium CMC	--	--	--	50	--	--	--	--	100	--
Gelucire 43/01	--	--	--	--	50	--	--	--	--	--
Gelucire 13/01										100

Table 3: Cumulative percent drug release of formulations F1 to F5.

Time (Hrs)	F1	F2	F3	F4	F5	MARKET FORMULATION
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
0.5	19.92 ± 0.20	16.57 ± 0.64	19.54 ± 0.24	33.41 ± 0.53	7.22±0.67	80.40 ± 0.73
1	22.47 ± 0.24	27.32 ± 0.15	29.62 ± 0.27	48.57 ± 0.52	9.13±0.58	89.31 ± 0.42
1.5	30.42 ± 0.21	39.56 ± 0.19	41.32 ± 1.14	67.61 ± 1.98	20.63±3.2	94.90 ± 0.68
2	41.12 ± 0.11	50.25 ± 0.12	59.67 ± 0.78	71.32 ± 2.35	40.42±0.34	100.00 ±0.35
3	58.36 ± 0.10	65.32 ± 0.4	73.32 ± 0.3	90.56 ± 1.6	56.39± 0.22	
4	70.52 ± 0.69	80.36 ± 0.2	89.56± 0.34	100.00± 0.57	68.69±1.64	
5	81.32 ± 0.19	92.63± 0.25	100.00 ± 0.88		78.19±2.64	
6	90.65 ± 0.25	100.00 ± 0.21			83.32±0.25	
8	100.00 ± 0.39				93.43±0.86	
10					100.00±0.77	

*Average value of 3 determinations.

Table 4: Cumulative percent drug release of tablet formulations F6 to F10.

Time (Hrs)	F6	F7	F8	F9	F10	MARKET FORMULATION
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
0.5	8.47 ± 0.10	9.79 ± 0.64	11.70 ± 0.24	24.36 ± 0.53	7.21±0.67	80.40 ± 0.73
1	10.38 ± 0.14	16.83 ± 0.15	20.00 ± 0.27	38.42 ± 0.52	11.56±0.58	89.31 ± 0.42
1.5	15.47 ± 0.31	28.31 ± 0.19	32.15 ± 1.14	53.67 ± 1.98	20.63±3.2	94.90 ± 0.68
2	19.92 ± 0.01	36.67 ± 0.12	41.15 ± 0.78	69.23 ± 2.35	28.93±0.34	100.00 ±0.35
3	34.56 ± 0.20	48.18 ± 0.4	53.88 ± 0.3	85.42 ± 1.6	41.06± 0.22	
4	45.39 ± 0.79	57.78 ± 0.2	82.20± 0.34	90.11± 0.57	51.28±1.64	
5	63.85 ± 0.29	79.34± 0.25	96.06 ± 0.88	100.00± 0.14	66.61±2.64	
6	73.39 ± 0.15	94.98 ± 0.21	100.00± 0.25		71.08±0.25	
8	90.58 ± 0.39	100.00± 0.39			87.04±0.86	
10	100.00± 0.19				97.26±0.77	
12					100± 0.16	

*Average value of 3 determinations

Table 5: Buoyancy time of the tablet formulations

Batches	F6	F7	F8	F9	F10
Duration of floating (Hrs)	8	7.5	6	3	12

Table 6: Analysis of The Release Data

FORMULATION	CORRELATION COEFFICIENT [r] VALUE				n' VALUE IN PAPPAS EQUATION
	Zero Order	First Order	Higuchi Equation	Erosion Equation	
F6	0.969	0.942	0.990	0.970	0.4
F7	0.973	0.963	0.995	0.978	0.3
F8	0.981	0.959	0.987	0.972	0.35
F9	0.979	0.951	0.981	0.989	0.4
F10	0.991	0.962	0.986	0.993	0.45

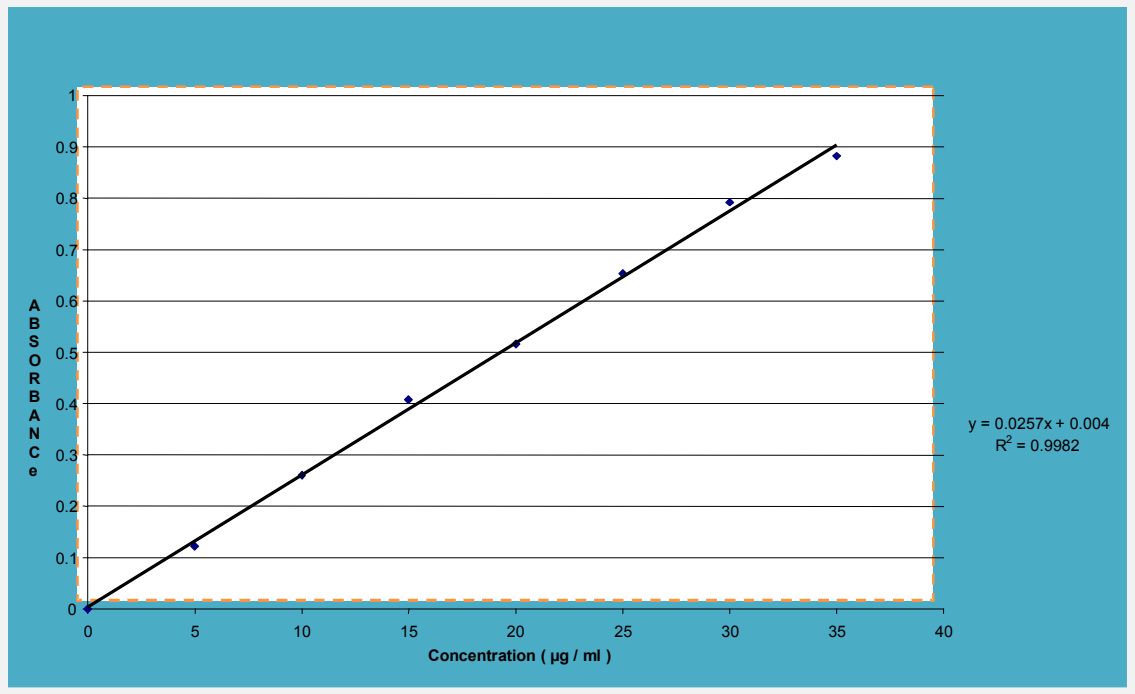

Fig .1: Calibration of stavudine

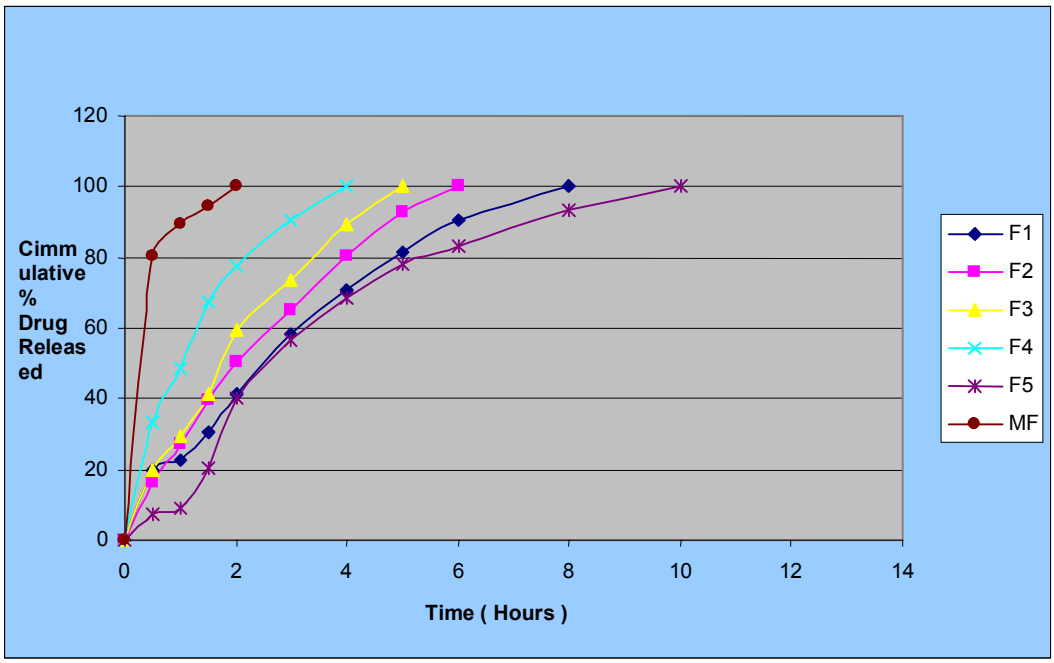

Fig.2: Comparitive Dissolution Profiles of Formulations F1 - F5

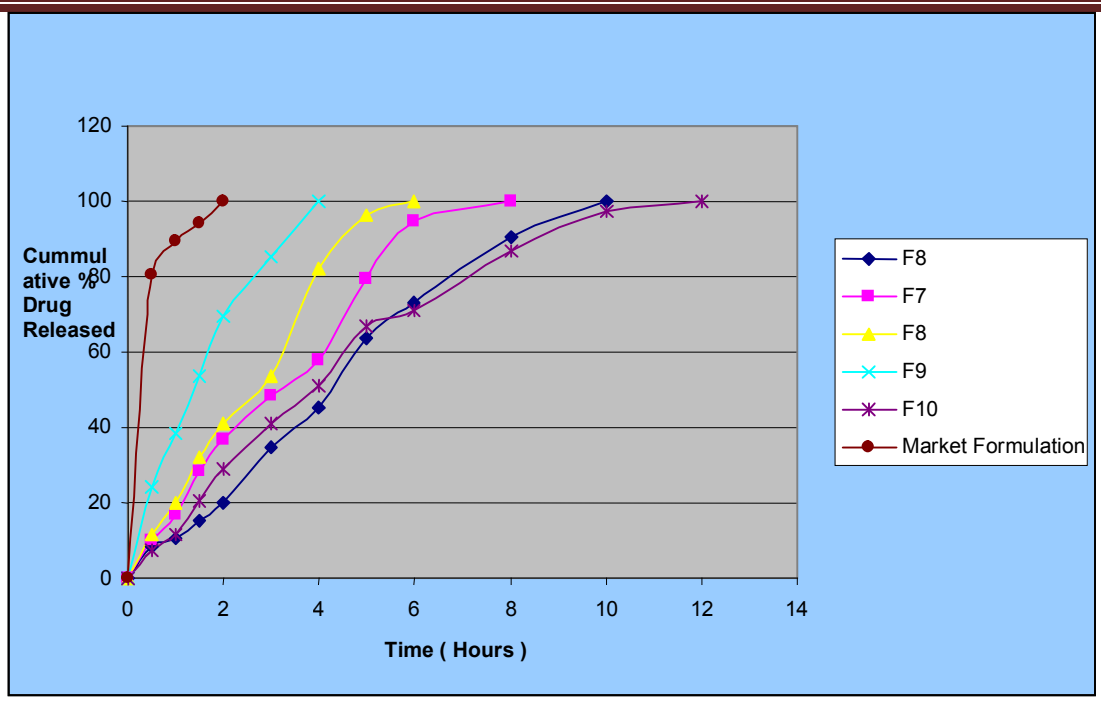

Fig.3: Comparative Dissolution Profiles of Formulations F6 to F10

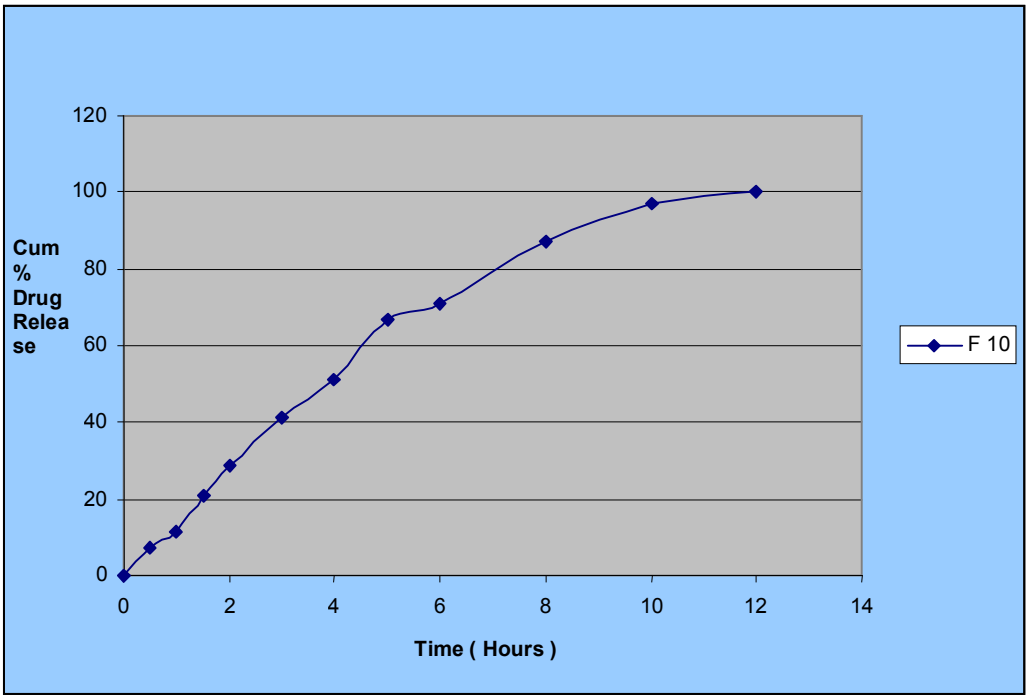

Fig.4: Release profile of F 10 formulation.

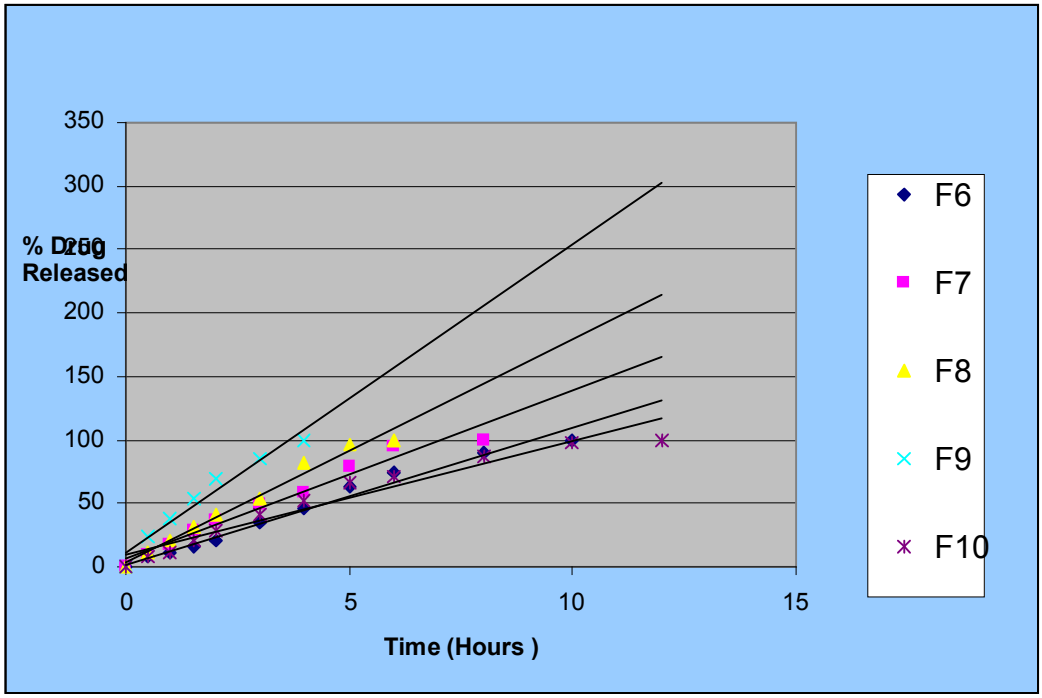

Fig.5 Zero Order Plot F6-F10 Formulations

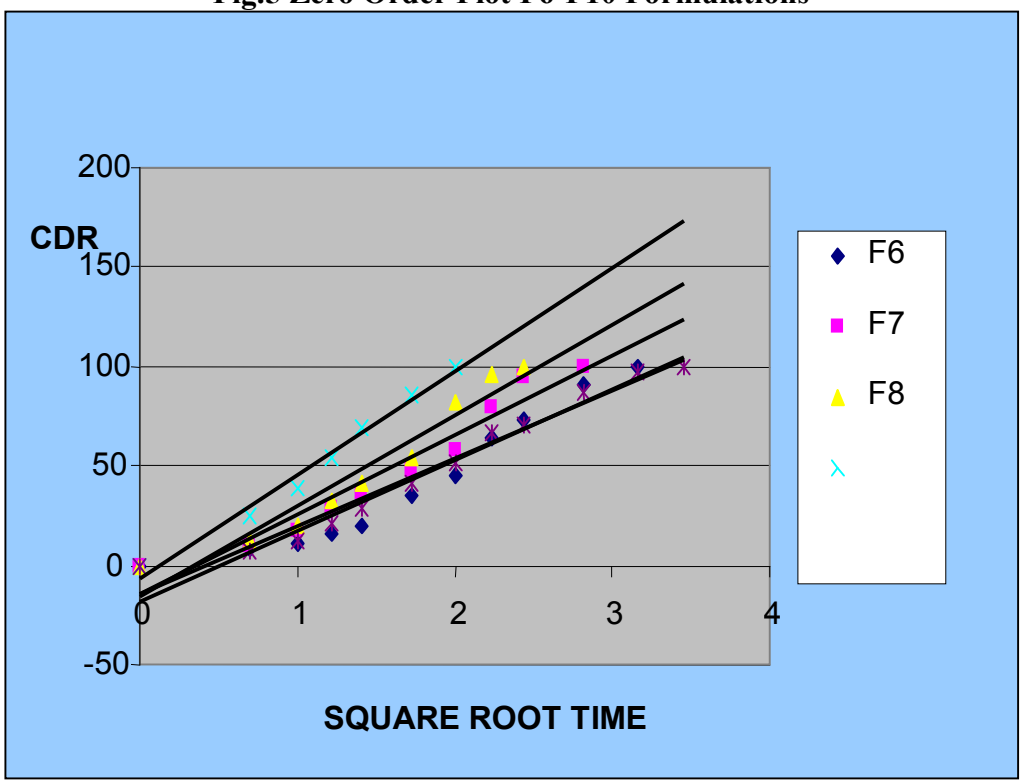

Fig.6: Higuchian Plot- For Formulations F6-F10

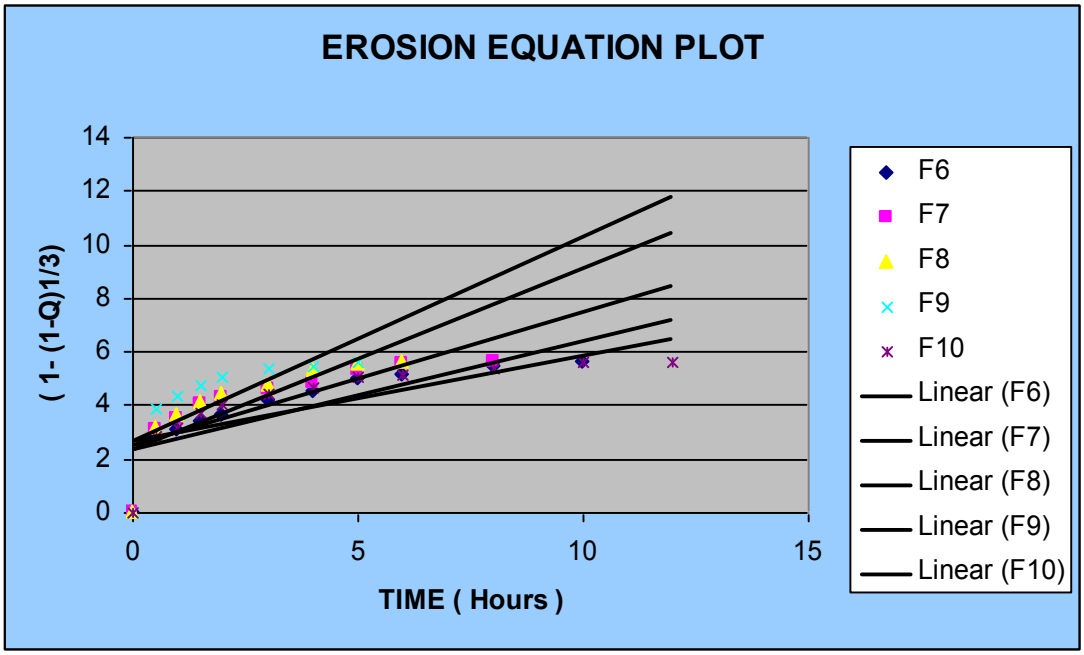

Fig.7: Erosion Equation Plot For Formulations F6-F10

Source of support: Nil, Conflict of interest: None Declared