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Formulation and Evaluation of Topical Gel to Treat Clinical Mastitis

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ABSTRACT:
The primary aim of this study was to develop sustained-release matrix tablets of Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor used in managing cardiovascular diseases associated with type 2 diabetes. The study focuses on optimizing the release profile of Sotagliflozin by employing various controlled drug delivery systems (CDDS) utilizing different polymer matrices. The formulation included synthetic polymers (HPMC) and natural polymers (sodium alginate and guar gum) in varying concentrations. The matrices were prepared using non-aqueous wet granulation and evaluated for their physicochemical properties, including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. Post-compression evaluations included tablet weight, hardness, friability, and drug content. Dissolution studies were conducted using USP Type II apparatus in 0.1N HCl and 6.8 phosphate buffer, and the release kinetics were analyzed using various models (Zero-order, First-order, Higuchi, and Peppas). Results indicated that the combination of HPMC with sodium alginate and guar gum (F9 formulation) provided the most effective controlled release profile, demonstrating superior performance in maintaining sustained drug levels over 12 hours. The study concludes that combining synthetic and natural polymers enhances the controlled release characteristics of Sotagliflozin tablets, optimizing therapeutic efficacy and patient compliance.

Keywords: Sotagliflozin, Controlled Drug Delivery Systems (CDDS), Sustained-release, HPMC, Sodium Alginate, Guar Gum, Matrix Tablets, Dissolution Kinetics, Drug Release Profiles.

I. INTRODUCTION

The goal of drug therapy is to maintain effective and non-toxic drug levels over time through appropriate dosage regimens. Drug delivery systems must address spatial placement, targeting, and temporal control of drug release. Traditional therapy often requires frequent dosing, leading to fluctuating blood levels and noncompliance, which sustained-release systems aim to resolve. Controlled Drug Delivery Systems (CDDS) help sustain therapeutic levels, enhance patient compliance, and target specific sites. CDDS include rate pre-programmed systems (e.g., polymer membranes, matrix systems), activation modulated systems (e.g., osmotic, pH-sensitive systems), feedback-regulated systems(1) (e.g., bioresponsive systems), and site targeting systems (e.g., liposomes, nanoparticles). Benefits include optimized therapy, improved compliance, reduced side effects, and less frequent dosing, while drawbacks involve high costs, dose dumping risks, and limited flexibility. Future trends involve responsive systems for precise delivery based on blood levels and targeted sites. Matrix systems control drug release by balancing diffusion and erosion.

Sotagliflozin (Inpefa) is a cardiovascular agent used to reduce the risk of heart attack, stroke, or heart failure in adults with type 2 diabetes, kidney disease, and heart disease. With the molecular formula $C_{24}H_{26}ClNO_5S$ and a weight of 466.99 g/mol, it acts as a dual SGLT1 and SGLT2 inhibitor to promote sodium and glucose elimination through the kidneys. Contraindications include allergies, type I diabetes, pancreatic disorders, heavy alcohol use, and certain infections. Side effects range from serious issues like stomach pain and difficulty breathing to common problems such as urination pain and low blood sugar. Sotagliflozin is available by prescription only. Its formulation incorporates excipients such as hydroxypropyl cellulose (HPC-L), ethyl cellulose, and sodium alginate as hydrophilic polymers; sodium bicarbonate, citric acid, and calcium carbonate as gas-forming agents;

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polypropylene foam powder and polyvinyl alcohol (PVA) as matrix-forming polymers; and calcium silicate, povidone, and microcrystalline cellulose.

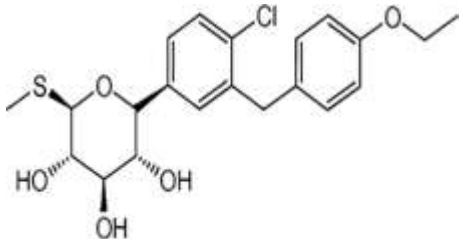

Figure 1: Structure of Sotagliflozin

II. MATERIALS & METHOD :

2.1 Materials

The ingredients used in the formulation include Sotagliflozin, which is supplied by Qualychrome. The remaining ingredients are sourced from SD Fine Chemicals, Mumbai, including HPMC K 100M, sodium alginate, guar gum, Avicel PH102 (microcrystalline cellulose), Aerosol, and magnesium stearate.

The equipment used in the formulation and testing processes includes an electronic weighing balance by Scale-Tec, a Roche Friabilator from Electrolab, Mumbai, and a Dtc-00r laboratory oven. Tablet compression is performed using a CMD (Cadmach) compression machine, while tablet hardness is tested with a Pfizer Hardness Tester from Mumbai. The UV analysis is conducted using a Labindia UV 3000+, and dissolution testing is performed with an Electrolab TDT-08L dissolution apparatus. Measurements are taken with CD-6"Cs vernier calipers.

2.2 Method

I. Analytical Method Development

Preparation of Standard Calibration Curve for Sotagliflozin:

1.Reagents

0.1N Hydrochloric acid Buffer Solution
6.8 Buffer Solution

2. Method of preparation of 0.1n Hcl and 6.8 buffer solutions

Preparation of 0.1 N HCl Solution:

Dilute 8.5 mL of concentrated hydrochloric acid to 1000 mL with distilled water.

Preparation of 6.8 pH Phosphate Buffer Solution:

Dissolve 27.22 g of monobasic potassium phosphate in 1000 mL of water. Prepare 0.2 M sodium hydroxide by dissolving 8 g in 1000 mL of water. Mix 50 mL of the potassium phosphate solution with 22.4 mL of the sodium hydroxide solution, then dilute to 200 mL with water.

3. Principle:

For Sotagliflozin standard solutions, 100 mg of the drug was dissolved in methanol to create a first stock solution. This was diluted with either 0.1 N HCl or 6.8 buffer to prepare the second stock solution. Various concentrations (2 µg/ml to 10 µg/ml) were prepared from this second stock and analyzed at 271 nm for 0.1 N HCl and 270 nm for 6.8 buffer, with blanks prepared using the respective buffers without the drug.

Preparation of matrix tablets by non aqueous wet granulation method:

Matrix tablets were prepared by blending Sotagliflozin, polymers, and diluent, granulating with isopropyl alcohol, and drying. The granules were sifted, lubricated with Aerosil-200 and magnesium stearate, and compressed into tablets weighing 500 mg with a hardness of 5-6 kg/cm².

TABLE 1: Sotagliflozin formulation table for f1 –f6 formulations

Sno	Ingredients	F1 30% HPMC	F2 45 % HPMC	F3 30% GG	F4 45 % GG	F5 30% SA	F6 45% SA
INTRAGRANULAR							
	Sotagliflozin	100	100	100	100	100	100
	HPMC K100M	15	30	--	--	--	--
	Sodium Alginate	--	--	--	--	15	30
	Guar gum	--	--	15	30	--	--
	Avicel PH 102	75	60	75	60	75	60

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Extra granular							
	Aerosil	5	5	5	5	5	5
	Mg Stearate	5	5	5	5	5	5
	Total	200	200	200	200	200	200

TABLE 2: Sotagliflozin formulation table for f7 – f9 formulations

Sno	Ingredients	Qty per Tablet (mg)			Purpose
		F7 HPMC+SA	F8 HPMC+GG	F9 HPMC+SA+GG	
Intragranular					
1	Sotagliflozin	100	100	100	API
2	HPMC K100M	30	30	30	Synthetic CR Polymer
3	Sodium Alginate	20	--	20	Natural CR Polymer
4	Guar gum	--	20	20	Natural CR Polymer
5	Avicel PH 102	40	40	40	diluent
Extragranular					
6	Aerosil	5	5	5	glidant
7	Mg Stearate	5	5	5	lubricant
	Total	200	200	200	

EVALUATION OF TABLETS

The formulated tablets were evaluated for the following Pre, post compression quality control studies & In vitro Buoyancy studies and dissolution studies

A) Pre Compression studies:

The angle of repose is the maximum angle between the surface of a powder pile and the horizontal plane, determined using the funnel method. An accurately weighed powder blend is poured through a funnel, which is adjusted so its tip just touches the apex of the pile. The diameter of the resulting powder cone is measured, and the angle of repose is calculated using the formula $q = \tan^{-1} \left(\frac{h}{r}\right)$, where h is the height and r is the radius of the cone. This measurement characterizes the flow properties of solids and reflects inter-particulate friction or resistance to particle movement.

TABLE 3 : ANGLE OF REPOSE LIMITS

Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

2. Density:

a) Bulk density (BD):

Bulk density is the mass of powder divided by its bulk volume. Weigh 25 g of granules (passed through a 22# sieve) and transfer to a 100 ml graduated cylinder, level the powder, and calculate.

Bulk density = weight of powder / Bulk volume.

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$$D_b = \frac{M}{V_0}$$

b) Tapped density (TD): Tapped density (TD) is the mass of powder divided by its tapped volume. Weigh 25 g of granules (passed through a 22# sieve), place in a 100 ml graduated cylinder, and tap until the volume stabilizes, then calculate using Tapped density = Weigh of powder / Tapped volume

Dt = (M) / (V_f).

3. Carr's Index:
Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below:

$$\textbf{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

4. Hausner's Ratio:
Hausner's Ratio is a number that is correlated to the flow ability of a powder.

$$\textbf{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

TABLE 5: COMPRESSIBILITY INDEX LIMITS

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Post Compression Studies:
1.General Appearance: Tablets were evaluated for shape, color, texture, and odor.
2. Average Weight/Weight Variation: Weigh 20 tablets collectively and individually. Calculate average weight and compare individual weights to ensure no more than 7.5% deviation for 300 mg tablets, or 15% deviation for others.
3. Thickness: Measured using Vernier calipers (n=3).
4. Hardness Test : Measured with the Monsanto hardness tester (n=3) to assess force required for tablet fracture.
5.Friability Test: Weigh 20 tablets before and after rotating in the Friabilator at 25 rpm for 4 min. The weight loss should be between 0.5% and 1.0%. %Friability = [(W1 - W2)/W1] × 100.
6.Assay Procedure: Powder 20 tablets, extract with 0.1N HCl, dilute, and analyze. Calculate assay using the formula: assay = (test absorbance/standard absorbance) × (standard concentration/sample concentration) × (purity of drug/100) × 100.

Dissolution parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCl and 6.8 phosphate buffer
Volume	900 ml
Speed	100 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	1,2,4,6,8,10 and 12hr
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	271 nm

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TABLE 6: Drug release kinetics mechanism

Diffusion exponent(n)	Mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous(Non- Fickian) diffusion
0.89	Case II transport
n > 0.89	Super Case II transport

III. RESULTS AND DICUSSION

1. Construction of Standard calibration curve of Sotagliflozin in 0.1N HCl:

The absorbance of the solution was measured at 225 nm using a UV spectrometer with 0.1N HCl as a blank. A graph of absorbance versus concentration showed compliance with Beer's law within the 2 to 10 µg/ml range.

Table 7: Standard Calibration graph values of Sotagliflozin in 0.1N Hcl at λ_{Max} = 225 nm

Conc.(µg / ml)	Absorbance at λ_{Max} = 225 nm
0	0
2	0.218
4	0.413
6	0.621
8	0.81
10	0.988

Standard plot of Sotagliflozin plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown fig No.3

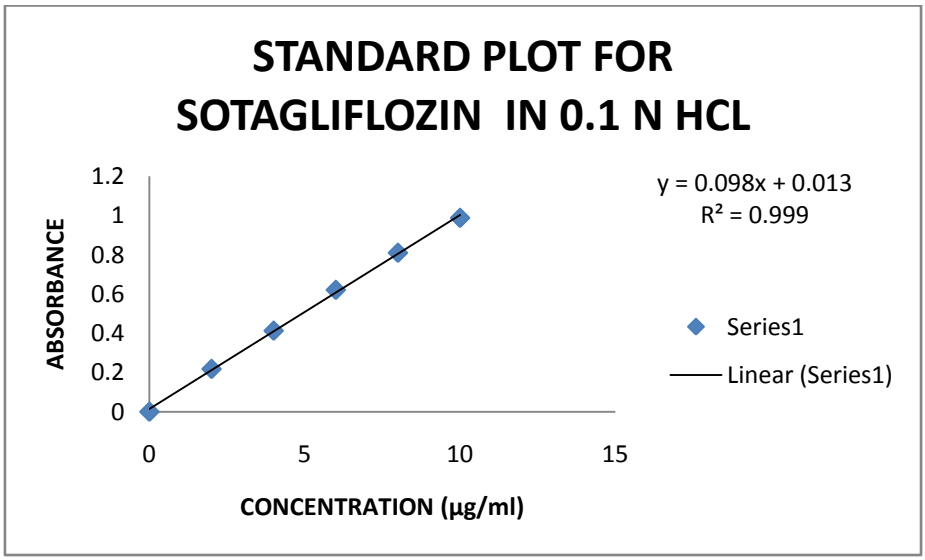

Figure 2: Standard calibration curve of Sotagliflozin in 0.1N Hcl at λ_{Max} = 225 nm

2.Construction of Standard calibration curve of Sotagliflozin in 6.8 phosphate buffer:

The absorbance of the solution was measured at 225 nm using a UV spectrometer with 6.8 phosphate buffer as a blank. The graph of absorbance versus concentration, as shown in Table 11, confirmed compliance with Beer's law in the 2 to 10 µg/ml range.

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Table 8: Standard Calibration graph values of Sotagliflozin 6.8 phosphate buffer at λ_{Max} = 225 nm

Conc.(µg / ml)	Absorbance at λ_{Max} = 225 nm
0	0
2	0.191
4	0.372
6	0.558
8	0.744
10	0.948

Standard plot of Sotagliflozin plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown fig No.3

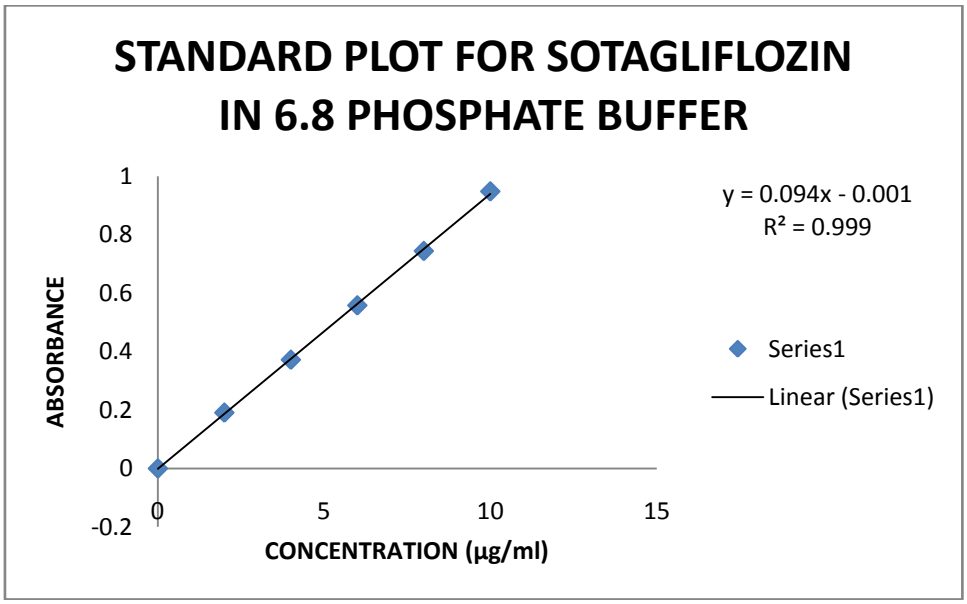

Figure 3: Standard calibration curve of Sotagliflozin in 6.8 phosphate buffer at λ_{Max} = 225 nm

Evaluation of Tablets:

A) Pre Compression studies:

Table:9: Pre compression studies of Sotagliflozin CR tablets *n=3

Formulation Code	Pre compression studies*,*n=3				
	Angle of repose (^{o})	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index (%)	Hausner's Ratio
F1	22.17±0.15	0.515±0.015	0.522±0.008	13.15±1.04	1.10±0.07
F2	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11
F3	25.71±0.13	0.505±0.005	0.527±0.015	14.26±0.65	1.15±0.31
F4	23.31±0.13	0.522±0.023	0.519±0.022	12.36±0.26	1.09±0.23
F5	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11
F6	25.71±0.13	0.505±0.005	0.527±0.015	14.26±0.65	1.15±0.31
F7	23.31±0.13	0.522±0.023	0.519±0.022	12.36±0.26	1.09±0.23
F8	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11
F9	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11

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B) Post compression studies:

Table10 : Post compression studies of Sotagliflozin CR tablets

Formulation Code	Post compression studies				
	Avg. Wt (mg) (n=20)	Thickness (mm) (n=3)	Hardness (kp) (n=3)	*%Friability	%Drug content (n=3)
F1	500.4±0.6	5.82±0.34	5.9±0.26	0.59	99.98±0.18
F2	502.2±0.4	5.91±0.23	6.2±0.25	0.68	100.21±0.20
F3	499.6±0.4	5.84±0.1	6.3±0.21	0.58	99.67±0.12
F4	498.0±0.3	5.88±0.1	5.9±0.23	0.59	100.32±0.14
F5	499.6±0.4	5.84±0.1	6.3±0.21	0.58	99.67±0.12
F6	502.2±0.4	5.91±0.23	6.2±0.25	0.68	100.21±0.20
F7	500.4±0.6	5.82±0.34	5.9±0.26	0.59	99.98±0.18
F8	502.2±0.4	5.91±0.23	6.2±0.25	0.68	100.21±0.20
F9	499.6±0.4	5.84±0.1	6.3±0.21	0.58	99.67±0.12

INVITRO DISSOLUTION STUDIES:

Dissolution profile:

Table11 : Dissolution profile

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCL AND 6.8 sodium phosphate buffer
Volume	900 ml
Speed	100rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	1,2,4,6,8,10 and 12hr
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	271 nm

Table12: In-vitroDissolution results of Formulation trails of Sotaglifliozin

time(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
	30% HPMC	45 % HPMC	30% GG	45 % GG	30% SA	45% SA	HPMC +SA	HPMC+GG	HPMC+SA+GG
0	0	0	0	0	0	0	0	0	0
1	29.52	24.6	38.32	32.52	35.5	30.32	16.54	17.38	9.52
2	43.51	28.9	52.25	48.57	45.32	42.54	25.28	27.38	25.6
4	67.32	40.32	78.35	72.32	69.55	64.54	34.24	36.57	38.52
6	84.54	65	91.32	89.54	89.32	87.24	58.58	51.22	50.32
8	92.32	87.32	96.55	95.32	96.47	93.23	78.32	82.34	62.58
10	99.54	94.45	99.21	98.34	99.54	99.21	88.54	92.35	81.35
12	99.54	98.34	99.21	98.34	99.54	99.21	99.58	99.32	99.35

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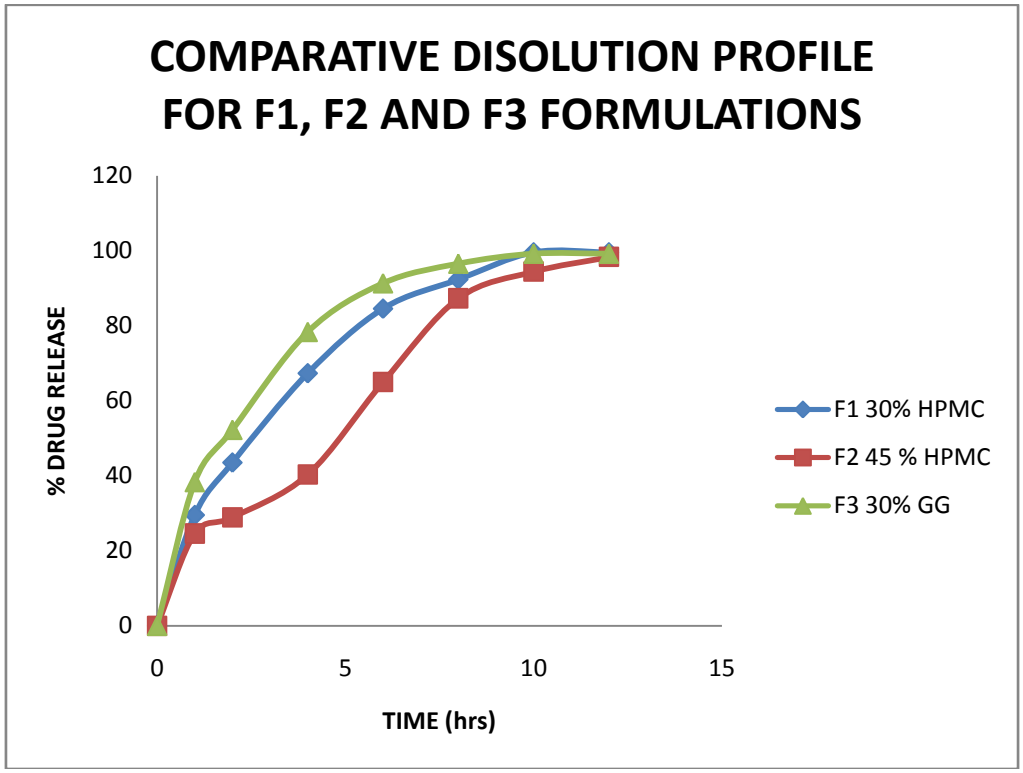

Figure 4: comparative dissolutionF1, F2 and F3 formulations of Sotagliflozin

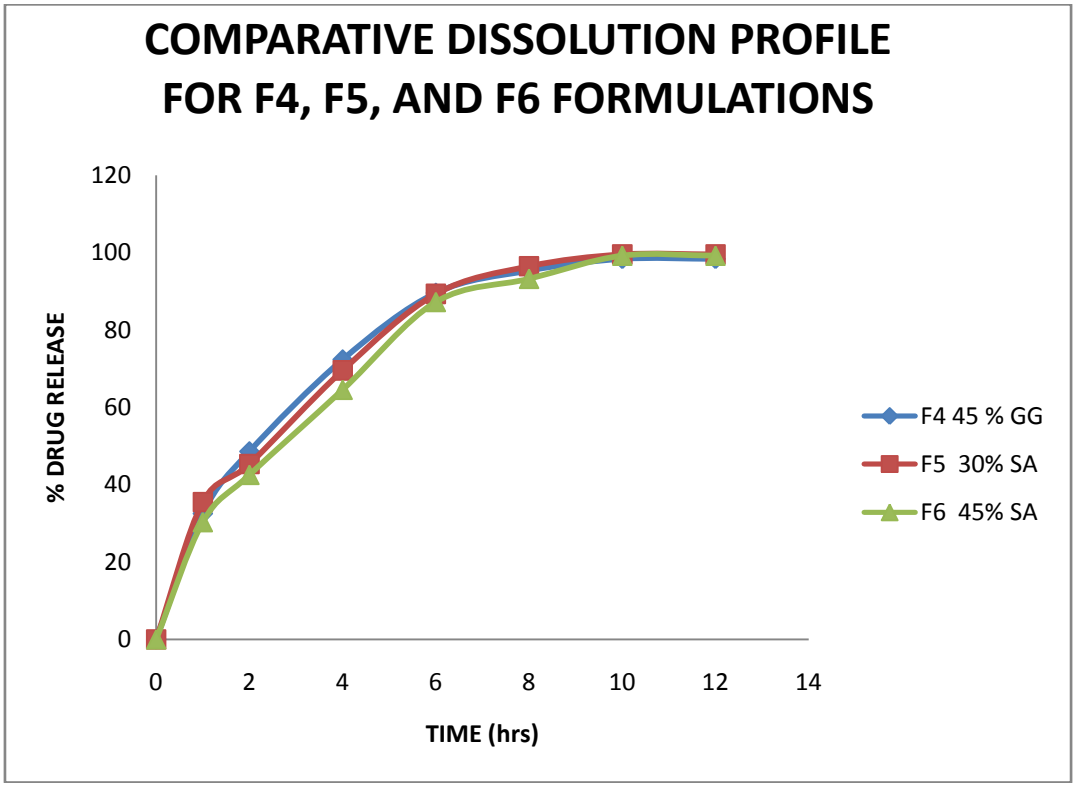

Figure 5: comparative dissolutionF4, F5 and F6 formulations of Sotagliflozin

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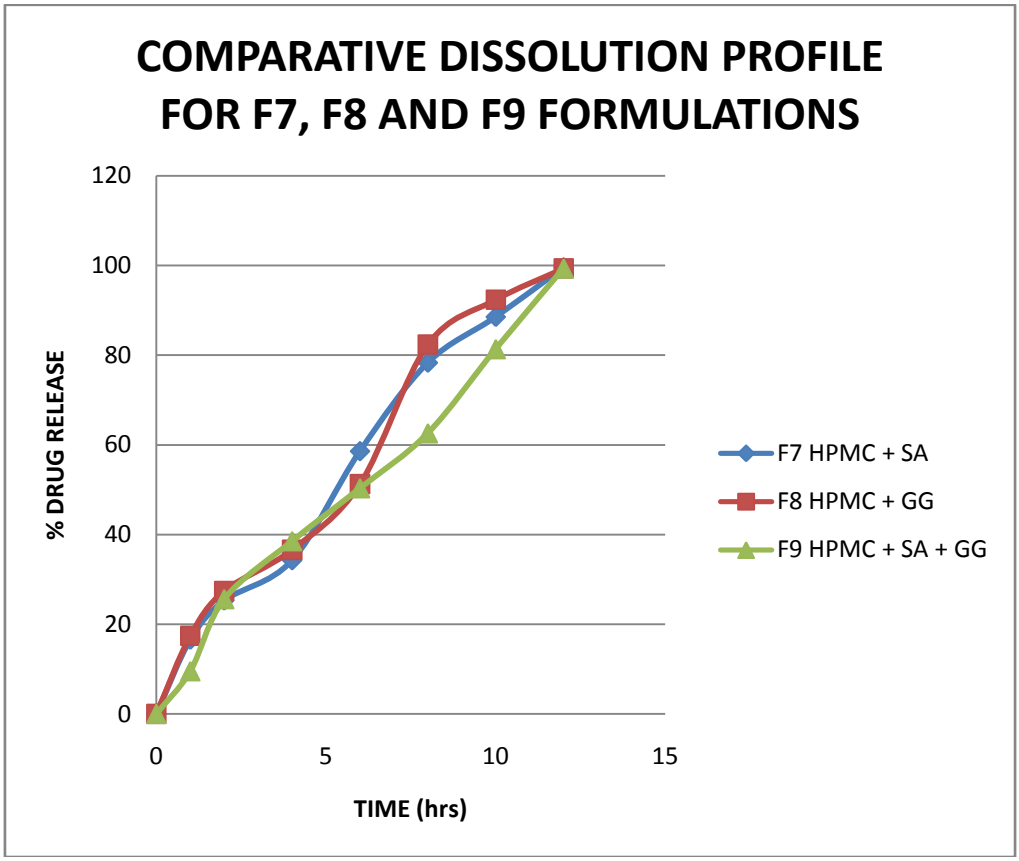

Figure 6: comparative dissolutionF7, F8 and F9 formulations of Sotagliflozin

Table14: R^2 value and n result table

Formulation code	R square value				
	Zero order	First order	Higuchi plot	Peppas plot	n value
F1	0.929	0.961	0.990	0.980	0.513
F2	0.977	0.965	0.979	0.948	0.624
F3	0.880	0.990	0.974	0.958	0.404
F4	0.901	0.991	0.981	0.963	0.464
F5	0.911	0.980	0.984	0.97	0.455
F6	0.928	0.976	0.988	0.977	0.511
F7	0.991	0.872	0.973	0.976	0.750
F8	0.987	0.909	0.967	0.969	0.723
F9	0.994	0.829	0.969	0.976	0.869

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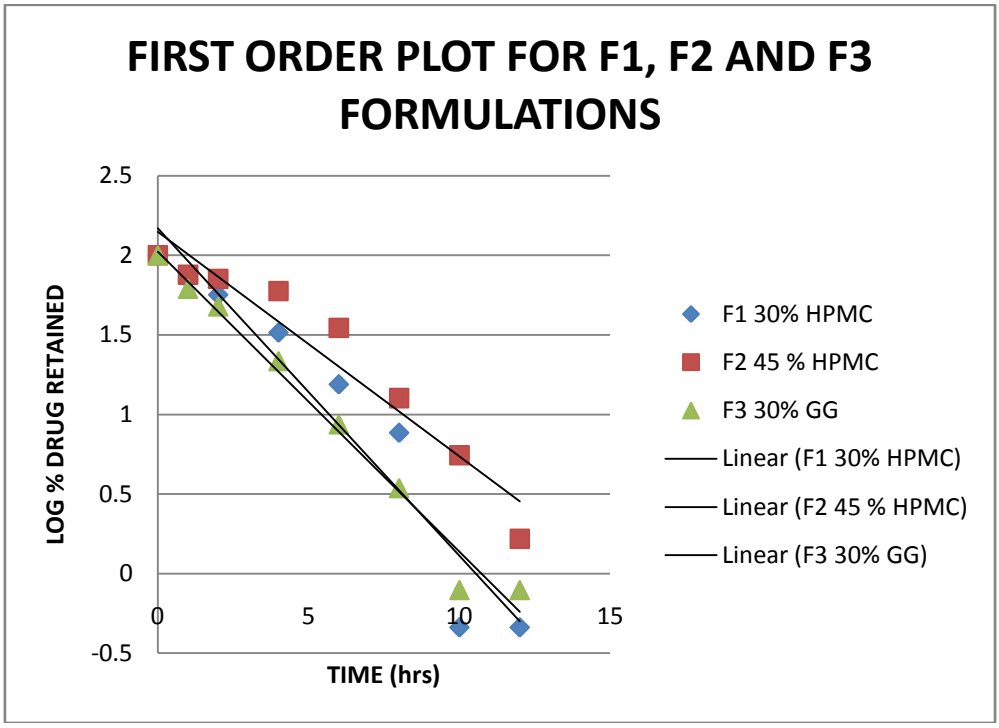

Figure 7: First order plot for F1, F2 and F3 formulations

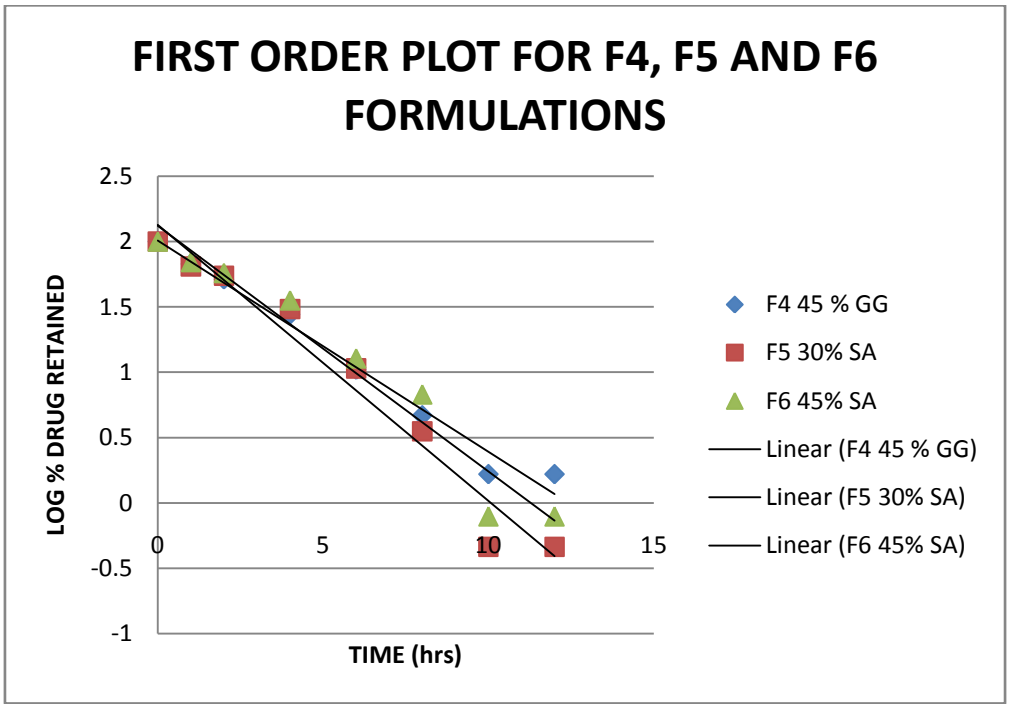

Figure 8: First order plot for F4, F5 and F6 formulations

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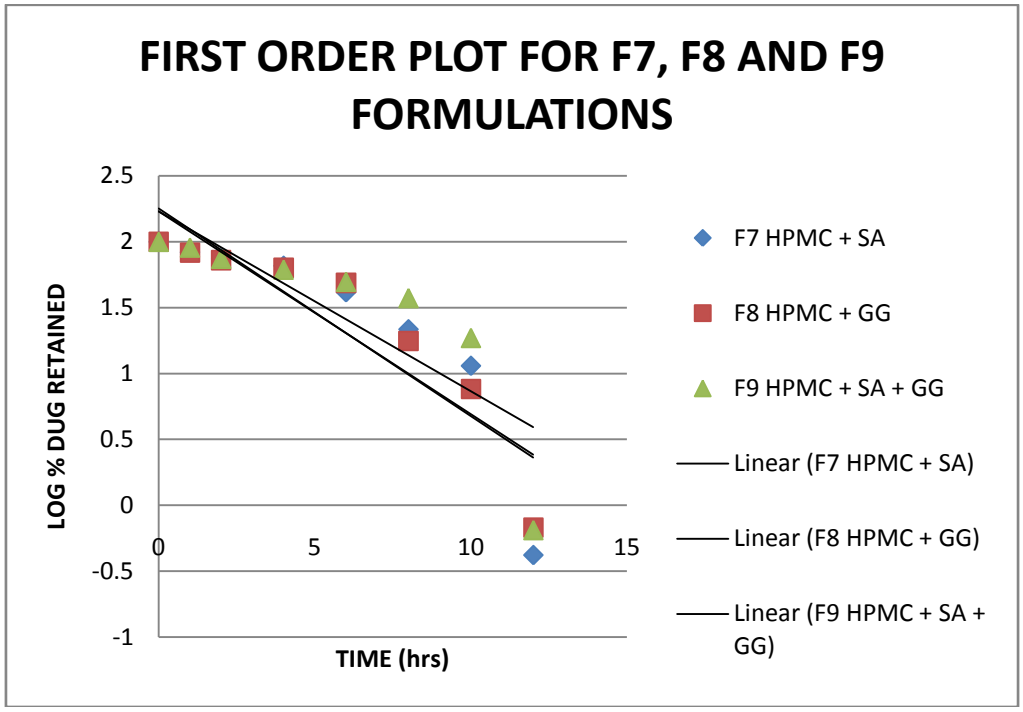

Figure 9: First order plot for F7, F8 and F9 formulations

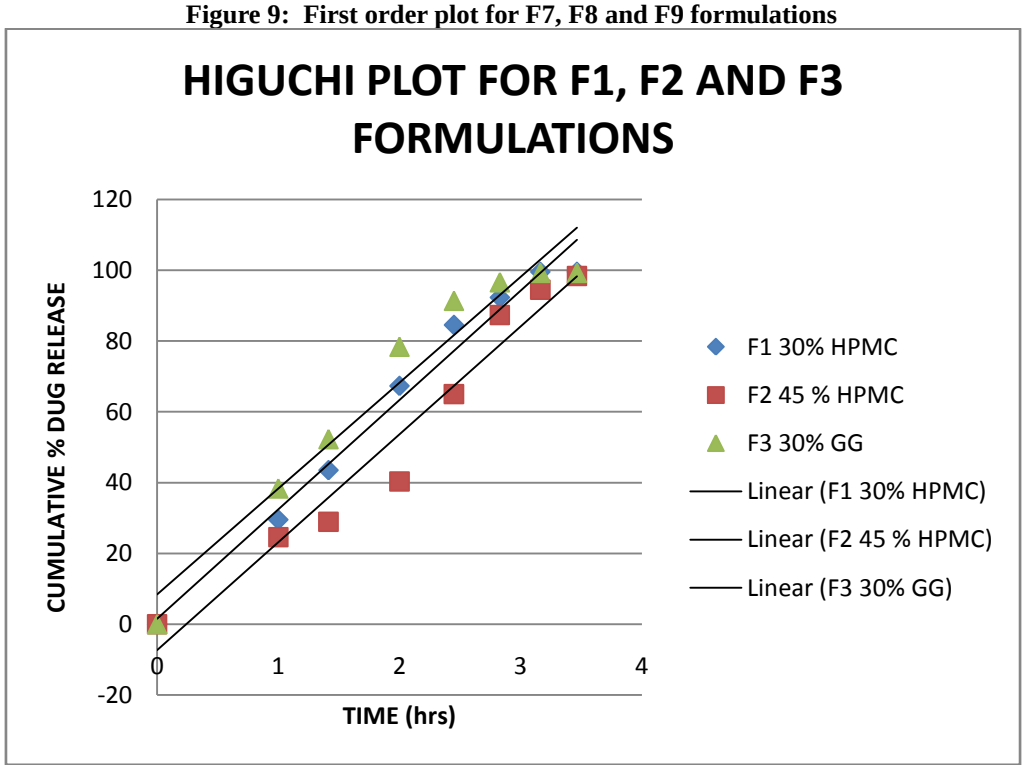

Figure 10: higuchi plot for F1, F2 and F3

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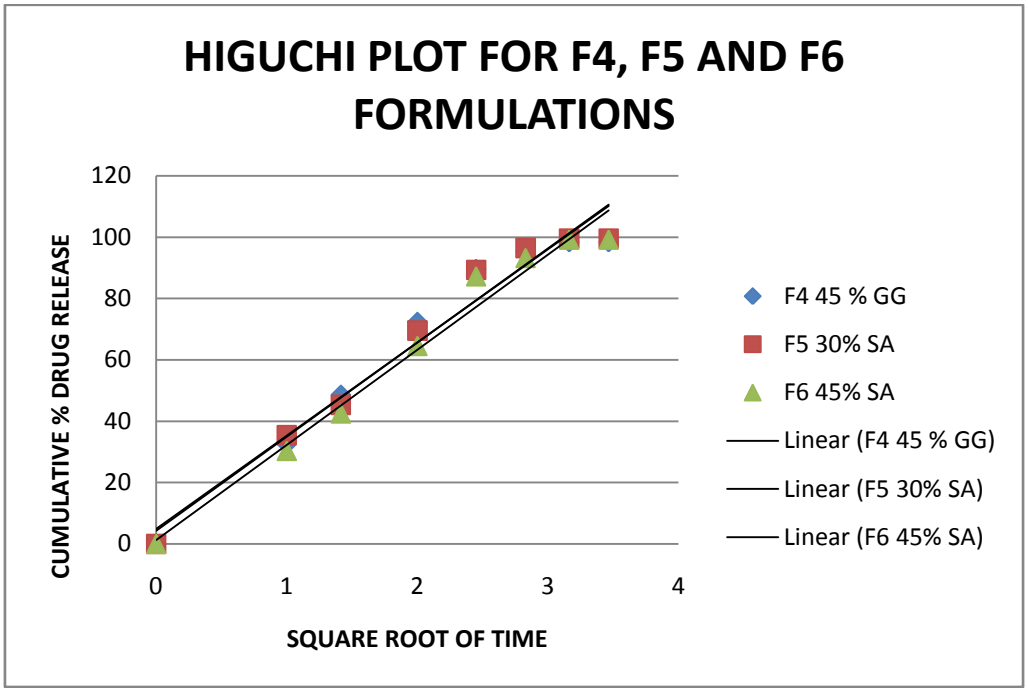

Figure 11: Higuchi plot for F4, F5 and F6 formulations

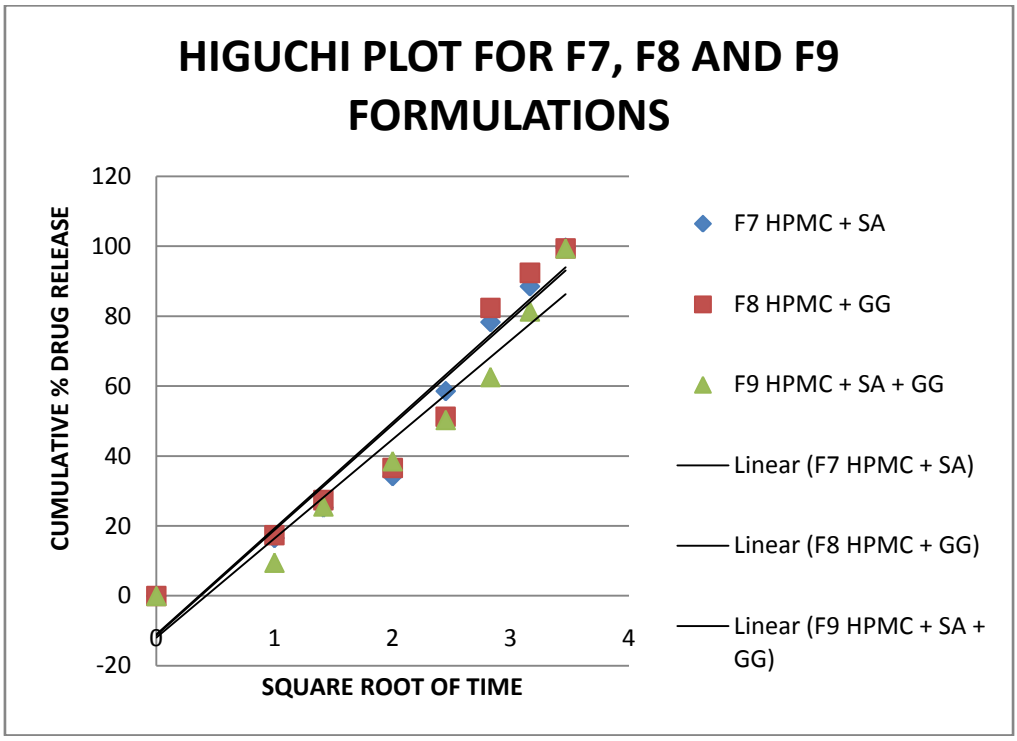

Figure 12: Higuchi plot for F7, F8 and F9 formulations

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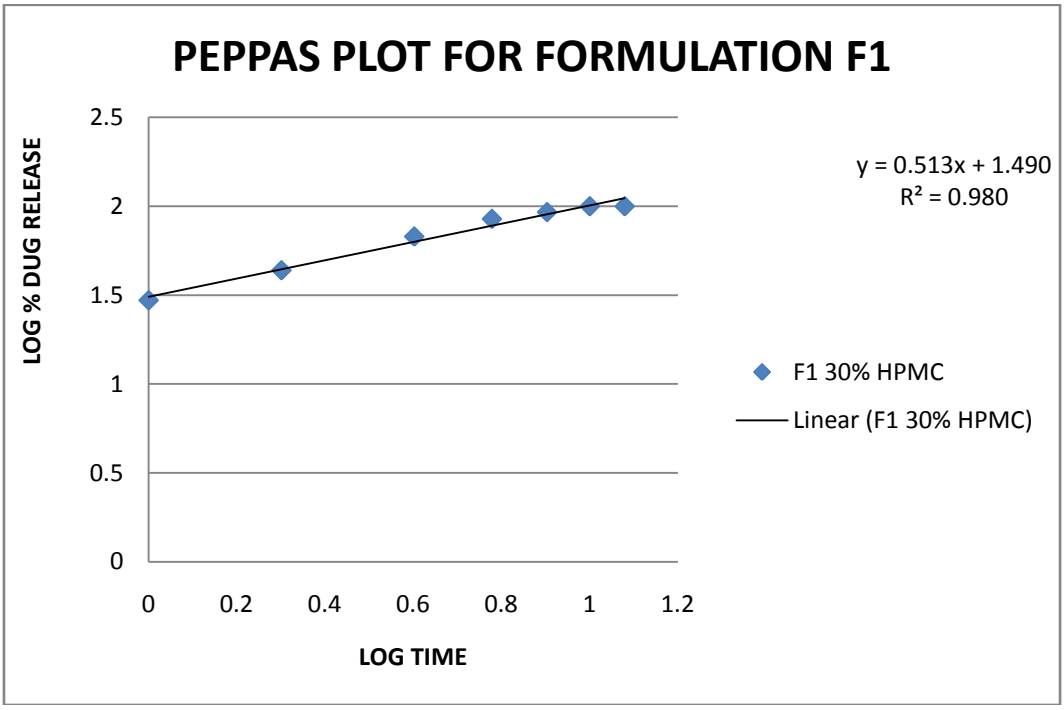

Figure13: korsmayerspepas plot for formulationF1

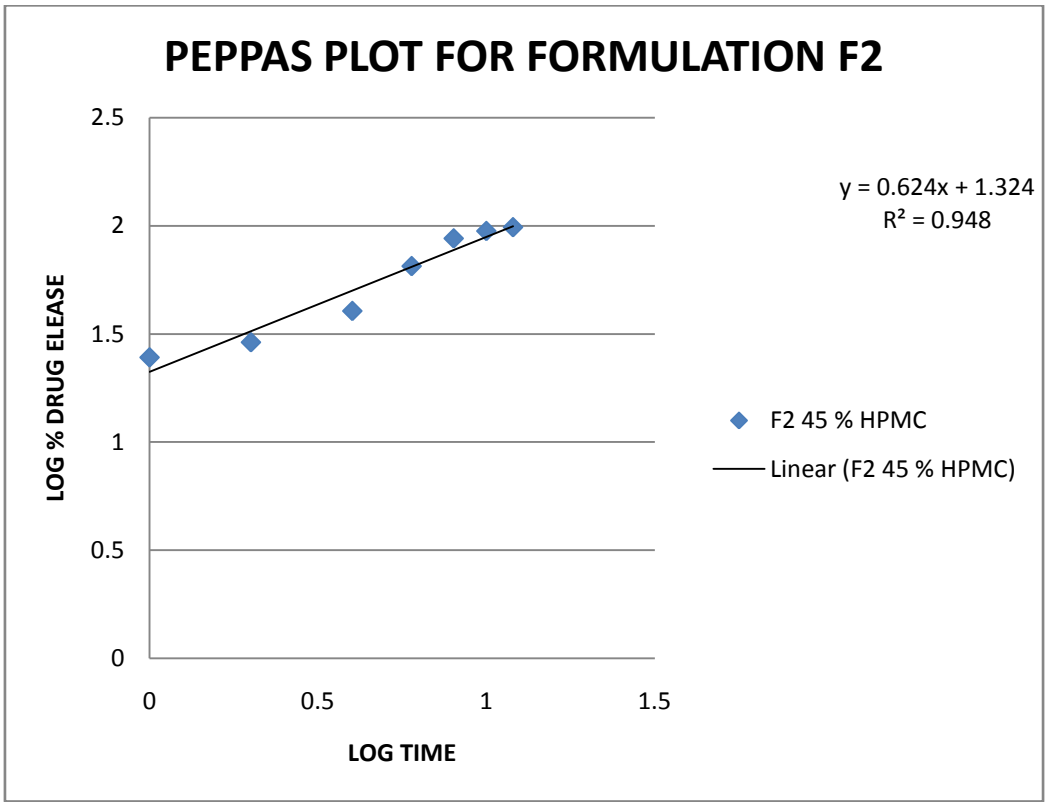

Figure14: korsmayerspepas plot for formulationF2

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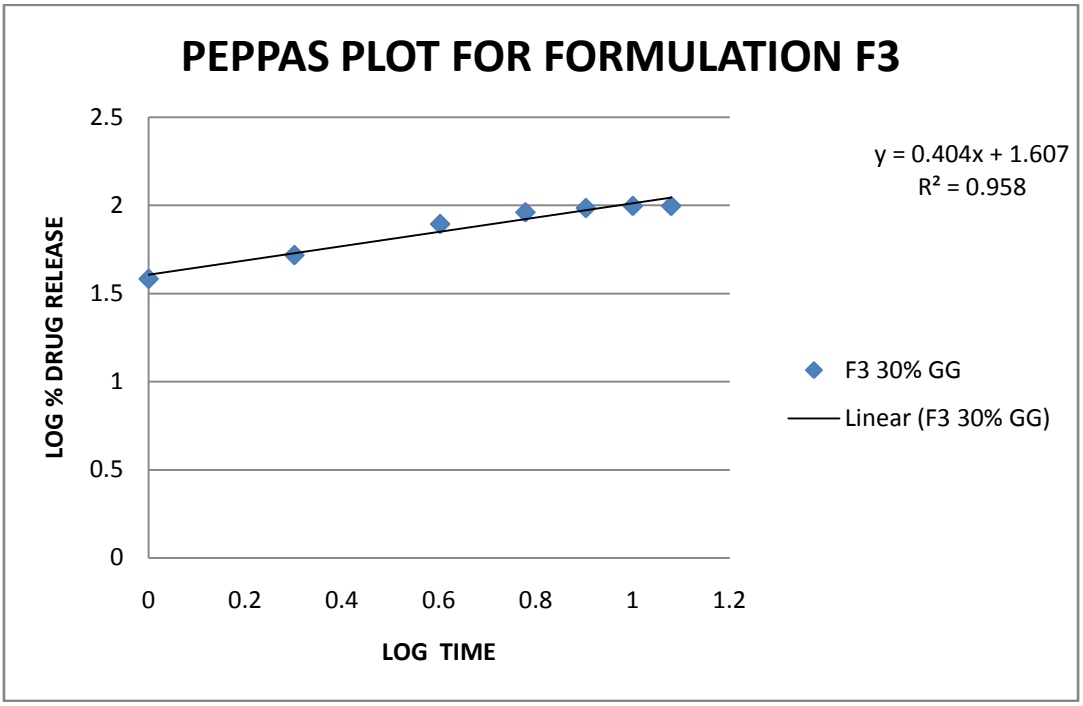

Figure15: korsmayerspepas plot for formulationF3

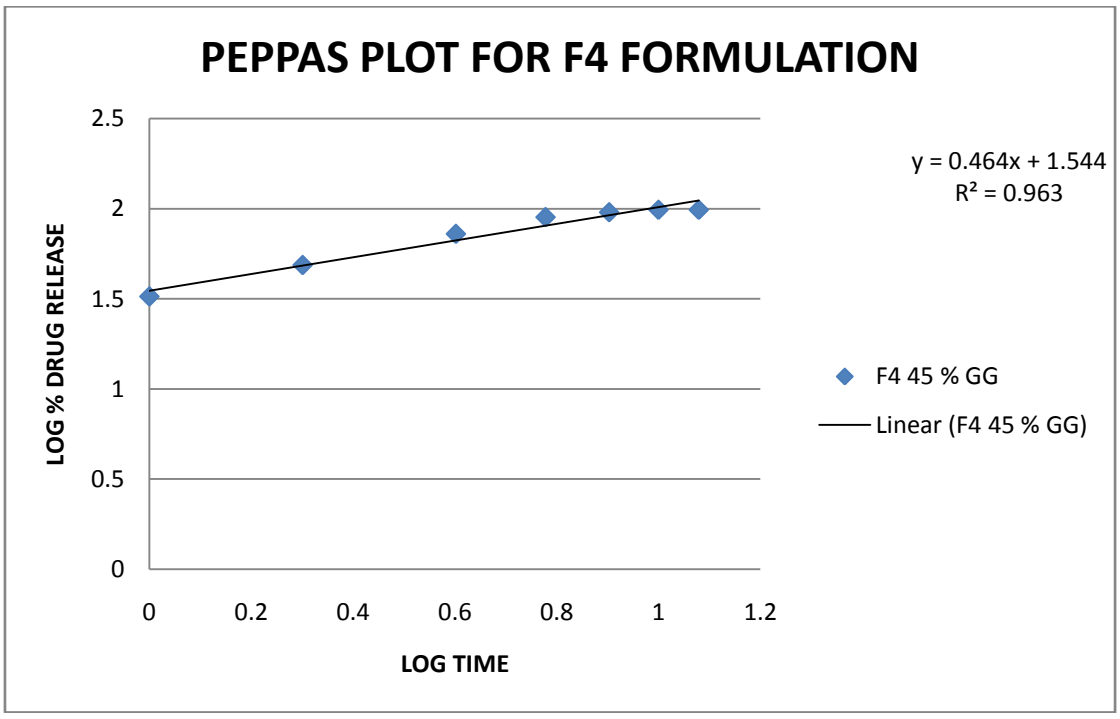

Figure16: korsmayerspepas plot for formulationF4

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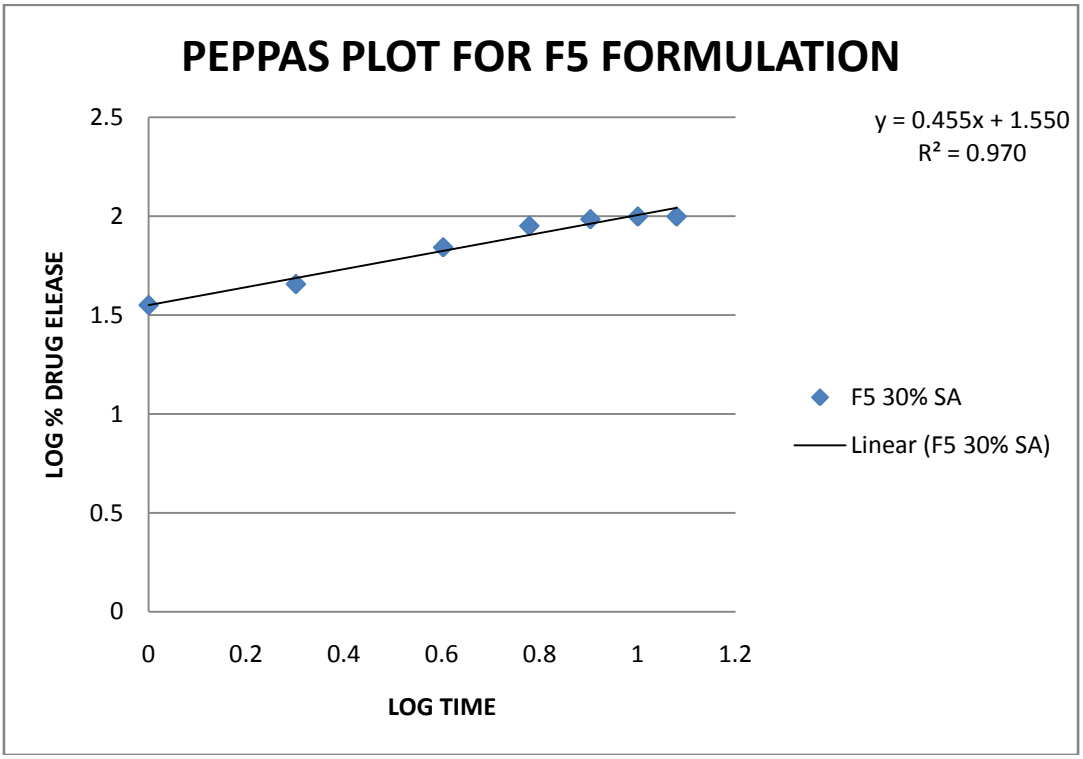

Figure17: korsmayerspepas plot for formulationF5

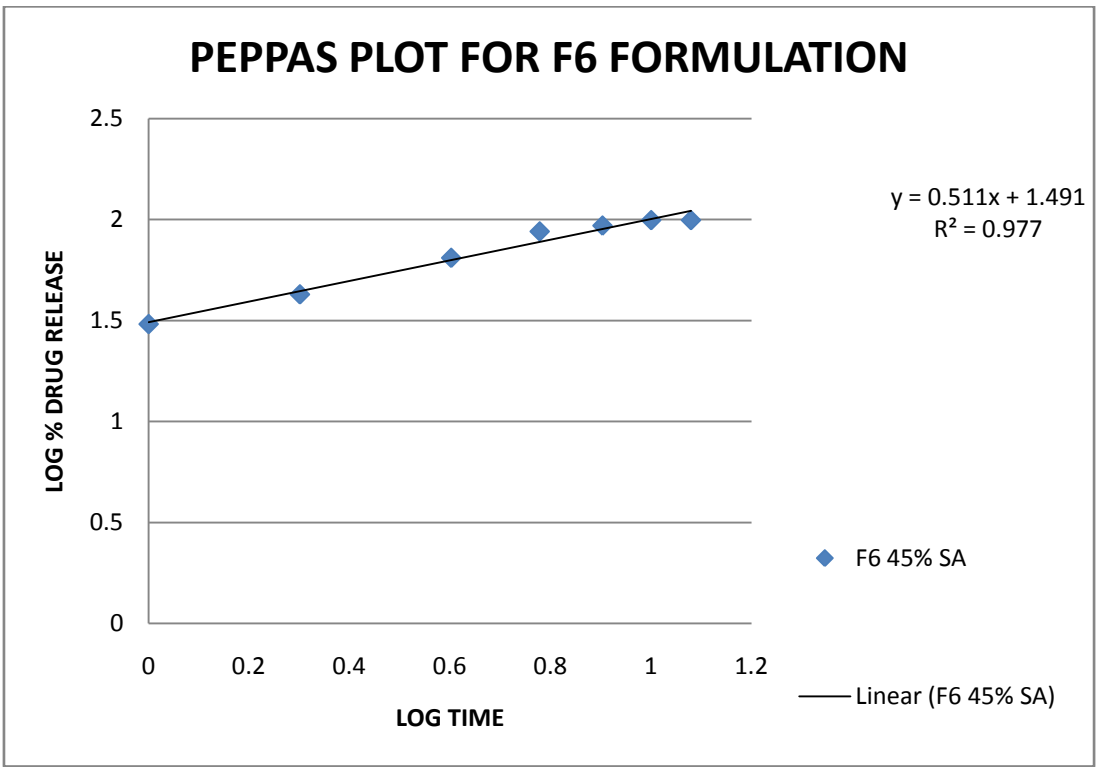

Figure-18: korsmayerspepas plot for formulationF6

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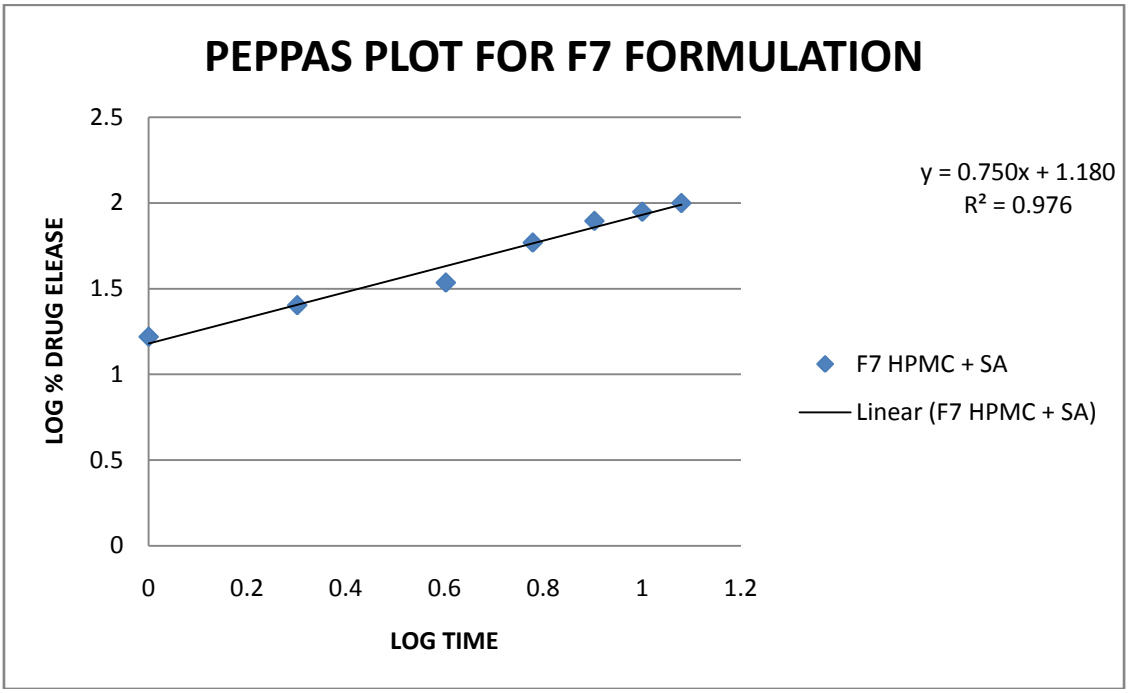

Figure-19: korsmayerspepas plot for formulationF7

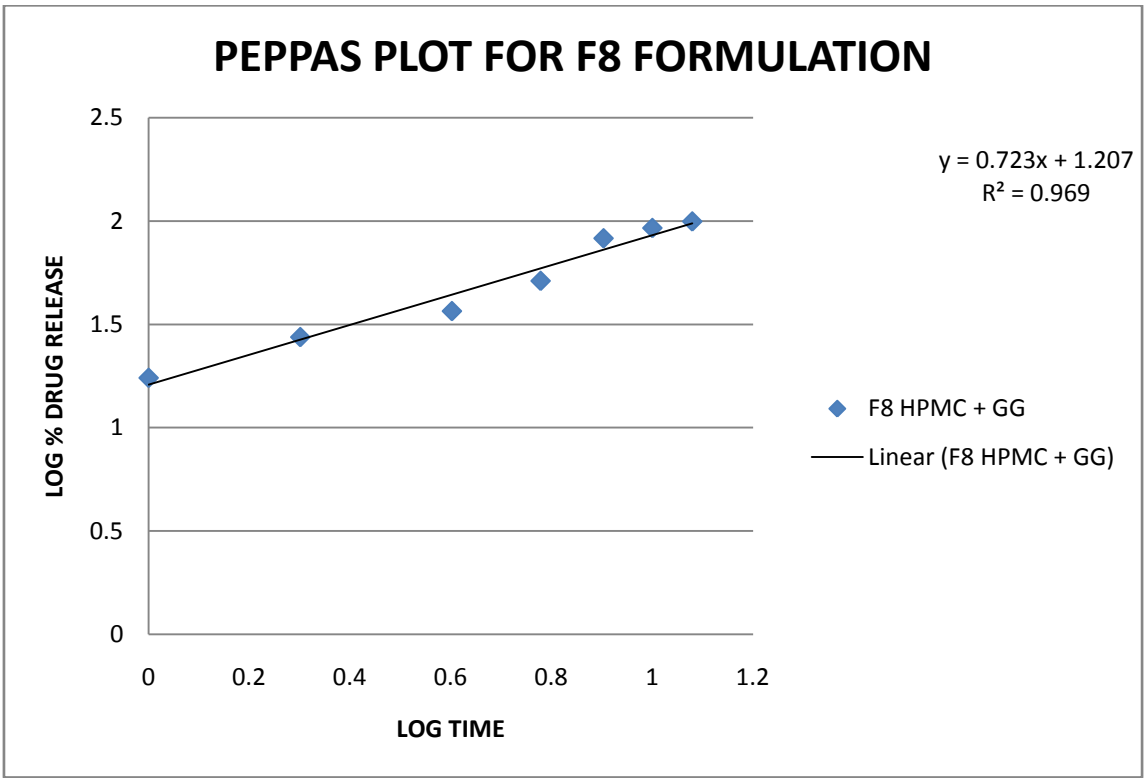

Figure-20: korsmayerspepas plot for formulationF8

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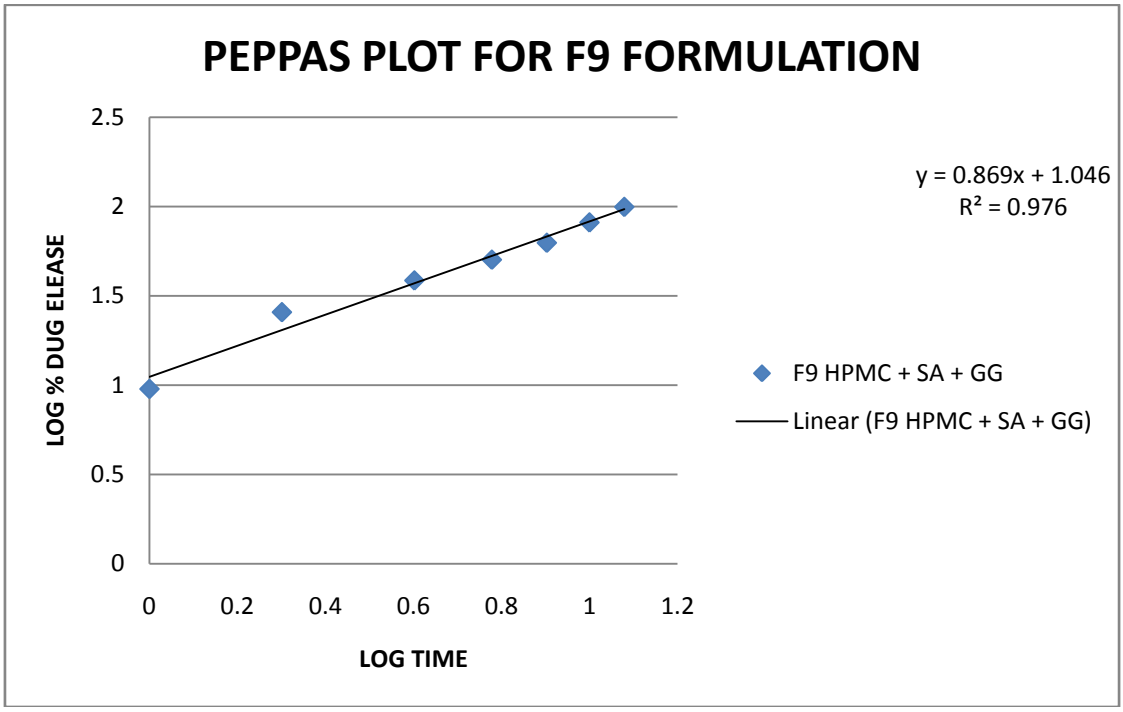

Figure-21: korsmayerspepas plot for formulationF9

IV. SUMMARY AND CONCLUSION

As the conc. of CR polymer increases the order of CR is also increasing

F2 >F1(HPMC)

F4 > F3 (GG)

F6 > F5 (SA)

When the CR tablets with only natural CR polymers (SA & GG) were tried in both concs. (30% & 45%) no CR was obtained upto 12 hrs, hence there are not intended to use alone for CR.

In all the CR polymers 45 % of HPMC (F2) is showing better CR, hence for further studies to know the effect of natural CR polymers (SA & GG) with HPMC, the 45% OF HPMC is kept constant.(F7,F8 & F9).

Out of all formulations the 45% HPMC + 10%SA + 10% GG, (F9) is having better CR, due to combination of various release mechanism characters of all three polymers.

The order of CR F9>f7>F8 From the dissolution data evident that the order of CR was It is evident that CR was better attained with combination of HPMC & the two natural polymers, than HPMC + single Natural polymer or HPMC alone.

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