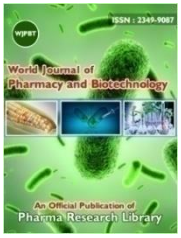

World Journal of Pharmacy and Biotechnology
Home Page: https://pharmaresearchlibrary.org/journals/index.php/wjpbt
e-ISSN: 2349-9087 | Publisher: Pharma Research Library
W. J. Pharm. Biotech., 2025, 12(1): 01-09.
DOI: https://doi.org/10.30904/j.wjpbt.2025.4755

Formulation and Assessment of Solid Dosage Form of sotagliflozin with Controlled Release

Aligi Akhila[1], K. Kishore[2], Dr. Vijay Kumar Gampa*[3]
[1]Department of Pharmaceutics, KGR Institute of Technology and Management, Rampally, Keesara(m), Medchal-Malkajgiri District, Hyderabad -501302, Telangana, India.
[2]Professor and HOD, KGR Institute of Technology and Management, Rampally, Keesara(m), Medchal-Malkajgiri District, Hyderabad -501302, Telangana, India.
[3]Principal and Professor, KGR Institute of Technology and Management, Rampally, Keesara(m), Medchal-Malkajgiri District, Hyderabad -501302, Telangana, India.

A B S T R A C T
This study focuses on the development and evaluation of controlled-release (CR) tablets of Sotagliflozin, an anti-diabetic drug. A calibration curve in 6.8 phosphate buffer showed linearity in the 2-10 µg/ml range, with a regression coefficient of 0.999. Pre-compression assessments, including Carr's index (≤ 18), Hausner's ratio (1.09-1.21), and angle of repose (22.17-31.11°), indicated good flow properties. Post-compression results showed tablet weights from 498.0 to 502.2 mg, thicknesses between 5.82 and 5.91 mm, hardness values from 5.9 to 6.3 kg/cm², and friability below 1%, indicating robust tablets. Drug content was within the 98-102% range. In vitro dissolution studies, conducted using a USPType2 apparatus in 6.8 sodium phosphate buffer, demonstrated over 99% drug release within 12 hours, with release rates depending on polymer composition. FTIR analysis confirmed the absence of significant interactions among Sotagliflozin, HPMC, and Sodium Alginate. The findings suggest that Sotagliflozin CR tablets possess suitable physicochemical properties and effective release profiles for diabetes management.
Keywords: Sotagliflozin, HPMC, Sodium Alginate, Carr's index, Hausner's ratio

A R T I C L E I N F O

***Corresponding Author:**
Dr. Gampa Vijaya Kumar
Principal and Professor,
KGR Institute of Technology and Management,
Rampally, Keesara(m), Hyderabad -501302, Telangana, India

Article History:
Received 07 Oct 2024
Revised 30 Oct 2024
Accepted 21 Nov 2024
Published 12 Jan 2025

Citation: Gampa Vijaya Kumar *et al*, Formulation and Assessment of Solid Dosage Form of sotagliflozin with Controlled Release, 2025,12(1): 01-09.

C O N T E N T S

1. Introduction. 01
2. Methodology. 02
3. Results and Discussion. 04
4. Conclusion. 08
5. References.. 08

1. Introduction

The development of solid dosage forms with controlled release characteristics has become a pivotal area of pharmaceutical research, aiming to enhance the therapeutic efficacy and patient compliance of various drugs. Sotagliflozin, a dual inhibitor of sodium-glucose co-transporter 1 (SGLT1) and sodium-glucose co-transporter 2 (SGLT2), represents a novel therapeutic approach for the treatment of diabetes mellitus. By inhibiting these transporters, sotagliflozin facilitates glucose excretion in the urine and reduces glucose absorption in the gastrointestinal tract, offering a dual mechanism of action that addresses both fasting and postprandial blood glucose levels. The formulation of a controlled release solid dosage form of sotagliflozin holds promise for optimizing its pharmacokinetic profile and improving overall clinical outcomes.

Controlled release (CR) formulations are designed to release the active pharmaceutical ingredient (API) at a predetermined rate, maintaining consistent drug levels in the bloodstream and reducing the frequency of dosing. This approach not only enhances the therapeutic efficacy but also minimizes the potential for adverse effects associated with peak plasma concentrations. The formulation of sotagliflozin into a solid dosage form with controlled release properties involves careful consideration of various factors, including the selection of appropriate polymers, excipients, and manufacturing techniques. The goal is to achieve a balanced release profile that aligns with the drug's pharmacodynamic and pharmacokinetic characteristics.

Significance and Rationale

Sotagliflozin's unique dual inhibition of SGLT1 and SGLT2 makes it an attractive candidate for controlled release formulation. By controlling the rate of drug release, it is possible to maintain optimal blood glucose levels throughout the day, providing more effective glycemic control with potentially fewer side effects. Additionally, the reduction in dosing frequency associated with controlled release formulations can significantly enhance patient adherence to therapy, which is a critical factor in the management of chronic conditions such as diabetes.

The rationale for developing a controlled release solid dosage form of sotagliflozin also stems from its pharmacokinetic properties. Sotagliflozin has a relatively short half-life, necessitating multiple daily doses to maintain effective plasma concentrations. A controlled release formulation can extend the duration of action, allowing for once-daily dosing and thereby improving convenience and compliance. Moreover, by modulating the release rate, it is possible to reduce the incidence of dose-dependent side effects and achieve a more favorable therapeutic index.

Formulation Considerations

The formulation of sotagliflozin into a controlled release solid dosage form involves several key considerations. The choice of polymers is paramount, as they play a crucial role in modulating the drug release profile. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and hydrophobic polymers like ethylcellulose are commonly used in controlled release formulations due to their ability to form matrix systems that control drug release through diffusion and erosion mechanisms. The selection of excipients, including fillers, binders, and lubricants, also influences the physical and mechanical properties of the dosage form, affecting drug release kinetics.

Manufacturing techniques such as direct compression, wet granulation, and hot melt extrusion are employed to produce controlled release tablets. Each technique offers distinct advantages and challenges, requiring careful optimization to achieve the desired release profile. The use of advanced technologies like 3D printing and multiparticulate systems can further enhance the precision and flexibility of controlled release formulations.

Evaluation and Assessment

The assessment of the controlled release solid dosage form of sotagliflozin involves rigorous in vitro and in vivo evaluations. In vitro dissolution studies are conducted to characterize the drug release profile and ensure compliance with regulatory standards. Various dissolution media and conditions are employed to simulate physiological environments and predict in vivo performance. In vivo pharmacokinetic studies in animal models and clinical trials in human subjects are essential to validate the controlled release formulation's efficacy and safety.

Additionally, stability studies are conducted to assess the formulation's robustness under different storage conditions. The evaluation of key parameters such as hardness, friability, and uniformity of content ensures the dosage form's quality and consistency. Advanced analytical techniques, including high-performance liquid chromatography (HPLC) and mass spectrometry, are utilized to quantify drug levels and monitor the presence of degradation products.

The formulation and assessment of a controlled release solid dosage form of sotagliflozin represent a significant advancement in diabetes management. By leveraging the principles of controlled release technology, it is possible to enhance the therapeutic profile of sotagliflozin, providing sustained and effective glycemic control with improved patient compliance. The meticulous selection of polymers, excipients, and manufacturing techniques, coupled with comprehensive evaluation studies, ensures the development of a robust and reliable dosage form. As the prevalence of diabetes continues to rise globally, the development of innovative drug delivery systems such as controlled release formulations will play a crucial role in addressing the unmet needs of patients and improving clinical outcomes.

2. Materials and Methods

Materials

The formulation of the controlled release solid dosage form of Sotagliflozin involves several key ingredients sourced from reputable suppliers. Sotagliflozin is supplied by Qualychrome, while Aarti Drugs provides essential polymers such as HPMC K 100m, sodium alginate, and guar gum. Excipients like Avicel Ph102 (MCC), Aerosil, and magnesium stearate are supplied by SRL, ensuring high-quality components for the development of an effective and reliable drug formulation. These carefully selected ingredients play a crucial role in achieving the desired controlled release profile and therapeutic efficacy.

The equipment utilized in this study comprises high-precision and industry-standard instruments from renowned manufacturers. A Shimadzu balance ensures accurate weighing, while Labindia'sfribilator and dissolution apparatus facilitate crucial testing processes. Temperature control during experiments is maintained using an oven from Dwaraka Scientific, and tablet compression is achieved with a Karnavathi Make machine. Additionally, Pfizer Hardness tablet hardness tester, Shimadzu's UV spectrophotometer, and Mitutoyo's verniercallipers (model 530-118) play key roles in ensuring precise measurements and reliable results.

Methodology:

Making a phosphate buffer solution with a pH of 6.8:

Take 40.8g of Kh2Po4 dissolved in 6000ml of water and adjust the pH6.8 with NaoH solution.

Determination of Sotagliflozin λmax in 6.8 Phosphate Buffer:A working standard of Sotagliflozin (100 mg) was dissolved in 10 ml methanol and diluted with 6.8 phosphate buffer to prepare a 1000 µg/ml stock solution. From this, a 100 µg/ml solution was prepared by further dilution, followed by a 10 µg/ml solution in subsequent dilutions. The absorption spectrum was scanned from 200 to 400 nm to determine λmax.

Construction of Calibration Curve of Sotagliflozin in 6.8 Phosphate Buffer: A working standard of Sotagliflozin (100 mg) was dissolved in water and diluted with 6.8 phosphate buffer to prepare a 1000 µg/ml stock solution. From this, a 100 µg/ml solution was prepared by dilution, and then concentrations ranging from 2 to 10 µg/ml were prepared by diluting appropriate volumes with 6.8 phosphate buffer. Absorbance measurements were taken at 270 nm.

Preparation of tablets by non aqueous wet granulation method:

- Sotagliflozin+ polymers+ Diluent are cosifted through sieve no. 60# and mix 10 min in polybag.
- Then blend granulated with isopropyl alcohol. granules dried at 60°C in hot air oven for 1 hr
- Granule passedthrough sieve no.30
- The above granules were lubricated with sieve no. 60#.Sifted colloidal silicon dioxide (Aerosil-200) and magnesium stearate together and mixed 5 min in poly bag.
- Lubricated granules compressed by rotary machine having round concave shaped punches with an average wt of 500 mg, & min hardness of 5-6 kg/cm^2.

Evaluation Of Tablets

B) Post compression studies:

General appearance: The general look of the prepared tablets was evaluated, and comments were provided on their shape, colour, texture, and smell.

Avg.weight /Wt. Variation: Twenty pills were chosen, and they were weighed both individually and collectively. The average weight was computed from the total weight. The weight of each pill was then compared to the average weight to ensure that it was within acceptable bounds. For 300 mg pills, no individual weight varied from the average weight by more than double that amount, and no two weights differed by more than 7.5%.

$$\%\text{weight variation} = \frac{\text{Avg.wt - wt of each tablet}}{\text{Avg.wt}} \times 100$$

Thickness: Three tablets' thicknesses were measured with Vernier callipers.

Hardness test: by using Monsanto hardness tester determined hardness of the tabletThe bottom plunger was pressed against the tablet, and a zero result was obtained. After that, a threaded bolt was turned to push the plunger up against a spring until the tablet broke. A pointer travels along a gauge in the barrel to show the force when the spring is squeezed.

Friability test:

The purpose of this test is to assess the tablets' resistance to abrasion during handling, packaging, and transportation. After weighing twenty pills, they are put in the Friabilator and rotated for four minutes at 25 rpm. The weight difference is recorded and given as a percentage. If possible, it should be in the range of 0.5 to 1.0%.

$$(W1\text{-}W2)/W1 = \text{Friability} \times 100$$

where W1 is the tablet weight prior to the test and W2 is the tablet weight following the test

Assay Procedure.

At least 20 pills should be weighed and coarsely powdered. Fill a 10 ml volumetric flask with a precisely weighed fraction of the powder, which is equal to around 10 mg of the model medicine. To finish the extraction, add around 6 ml of 6.8 phosphate buffer, mix, and sonicate for 10 minutes. Mix the methanol after diluting it to volume. One millilitre of the aliquot should be pipetted into a 10-milliliter volumetric flask, diluted with mobile phase to volume, mixed, and filtered. Take a 1 ml aliquot out of it and use buffer to label it. Determine the model drug's dosage in milligrammes. In the section extracted using the formula assay = test absorbance/standard absorbance*standard concentration/sample concentration *drug purity /100*100, hydrochloride

C) In vitro Release Kinetic Studies:

Either zero order kinetics or first order kinetics were used to characterise the sequence of drug release from FDDS. The Peppa's-Korsemeyer equation and the Higuchi equation were used to investigate the mechanism of drug release from FDDS.

Zero Order Release Kinetics:

It establishes a linear correlation between the drug release fractions and time.

$Q = k0t.$

First Order Releas Kinetics:

Wagner proposed that first-order kinetics could effectively represent the drug release from the majority of slow-release tablets,

$LogC=Log\ Co-kt/2.303.$

where

C represents the drug's dissolution at time t.

k is the firstorder rate constant, and Co is the amount of medication dissolved at t=0.

A straight line appears on a graph of the log cumulative of the log percentage of medicine left over time. If the release follows the first order release kinetics, it will be linear.

3. Higuchi equation:

It establishes a linear relationship between the square root of time and the active percentage emitted per unit of surface (Q).

$Q = K2t1/2$

4. Peppa'sKorsemeyerequation(Power Law):

Peppa'sKorsemeyer equation (Power Law) was used to further evaluate the dissolving data in order to develop a model that would better suit the formulation.

$Mt/M\infty = K.tn$

where Mt is the drug's release quantity at time t.

K is the kinetic constant, n is the diffusion exponent, Mα is the quantity released at time α, and Mt/Mα is the proportion of medication released at time t.

It may be used as an abstract to describe the mechanism for both medication release and solvent penetration. The correlation coefficients derived from the kinetic model plots were used to estimate the nature of the drug's release from the designed tablets. MS Excel was used to handle the data for regression analysis.

3. Results and Discussion

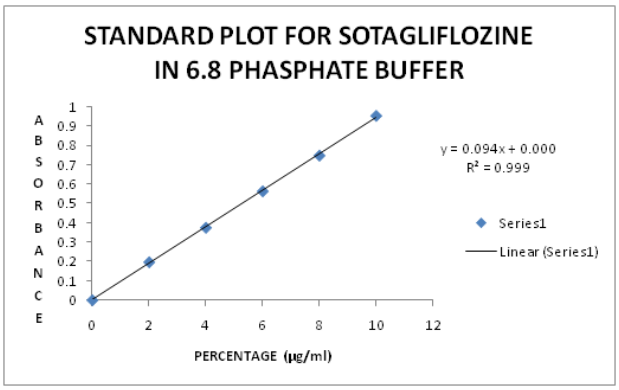

Figure 1: Sotagliflozin standard calibration curve at λMax = 230 nm in 6.8 phosphate buffer

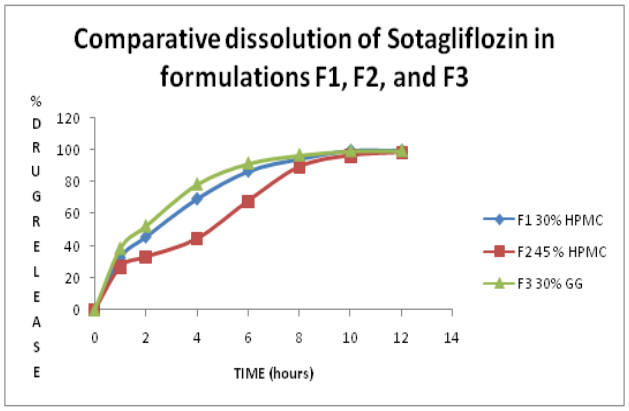

Figure 2: Comparative dissolution of Sotagliflozin in formulations F1, F2, and F3

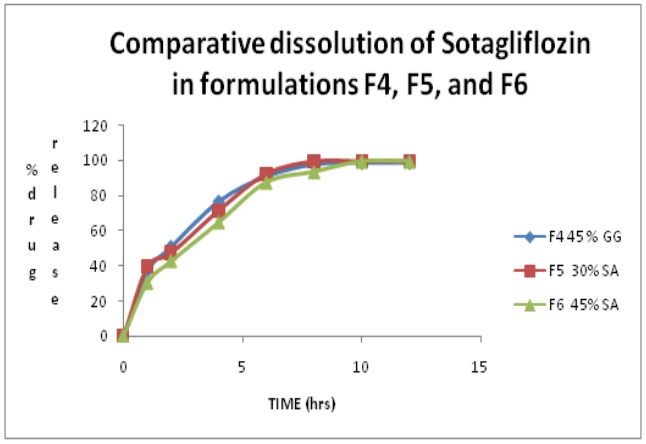

Figure3: Comparative dissolution of Sotagliflozin in formulations F.4, F.5, and .F6

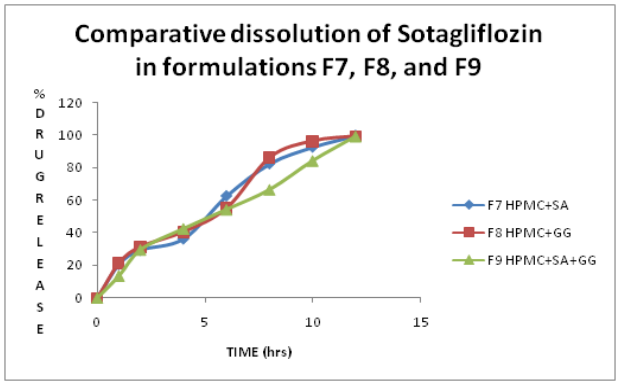

Figure 4: Comparative dissolution of Sotagliflozin in formulations F7, F8, and F9

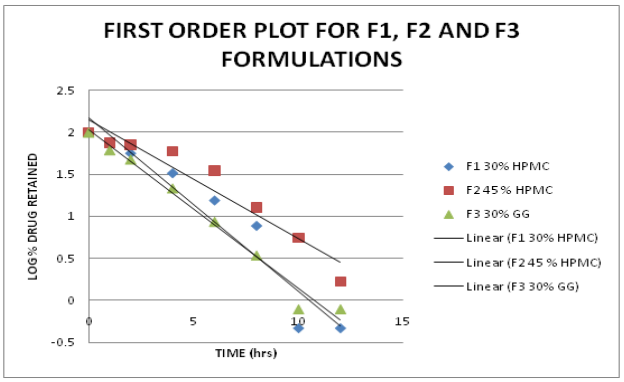

Figure 5: First order plot for F.1, F.2 and F.3formulations

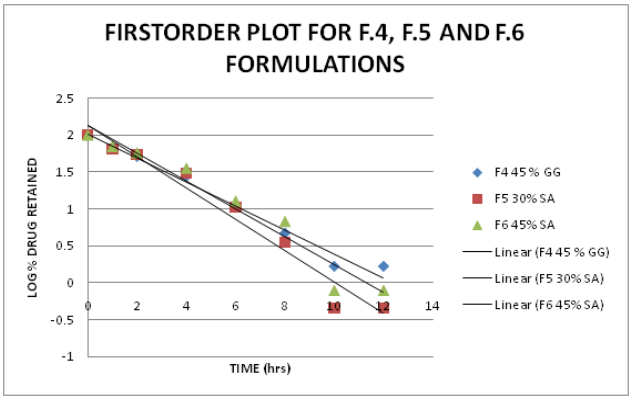

Figure 6: First order plot for F.4, F.5 & F.6formulations

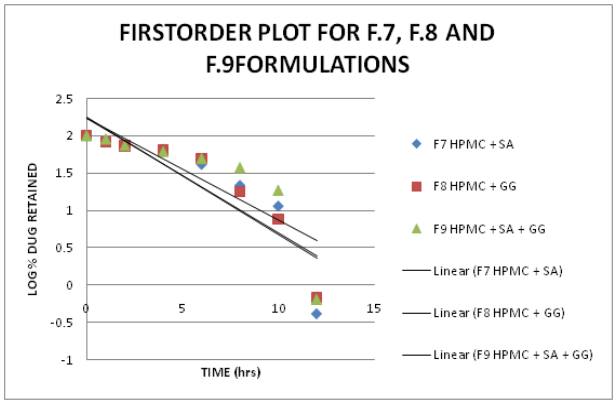

Figure7: higuchiplot for F.4, F.5 & F.6formulations

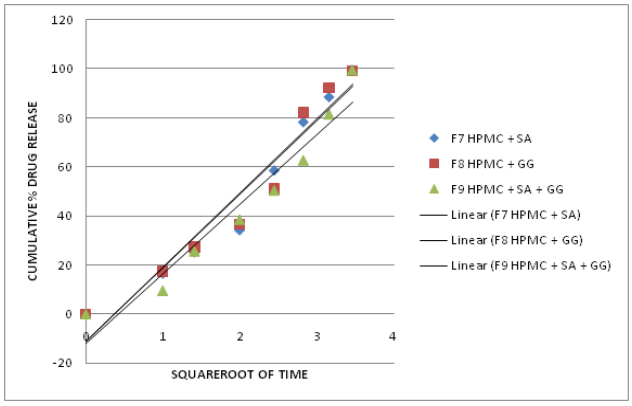

Figure 8: higuchi plot for F.7, F.8 and F.9formulations

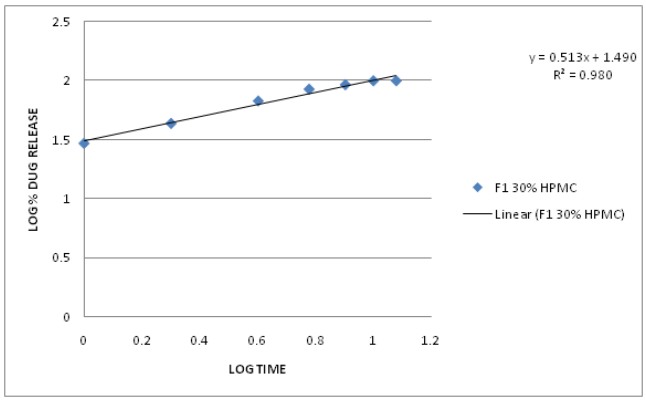

Figure 9: korsmayerspepas plot for formulation F1

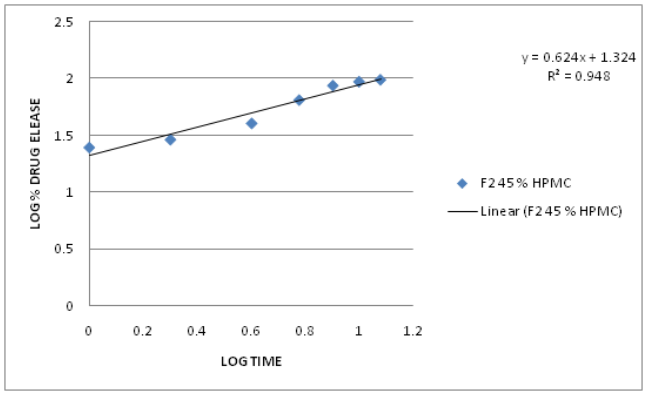

Figure10: korsmayerspepas plot for formulation F2

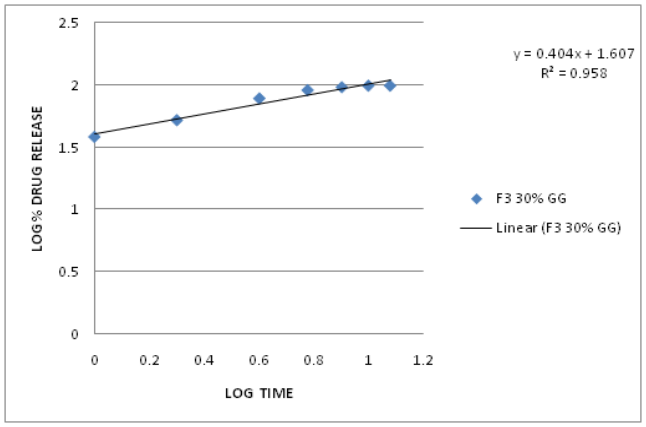

Figure11: korsmayerspepas plot for formulationF3

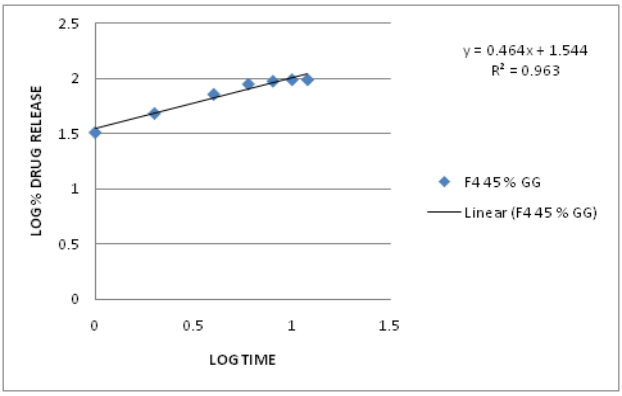

Figure12: korsmayerspepas plot for formulation F4

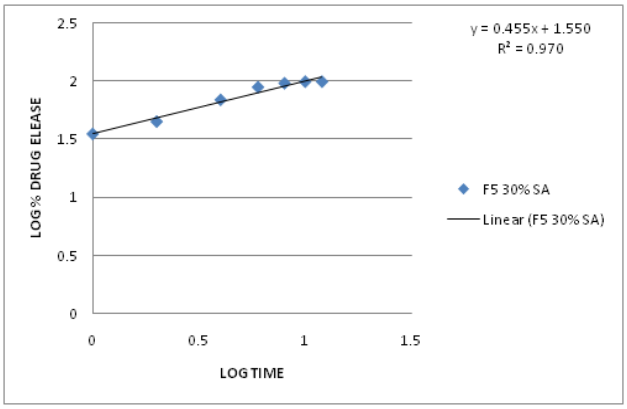

Figure13: korsmayerspepas plot for formulationF5

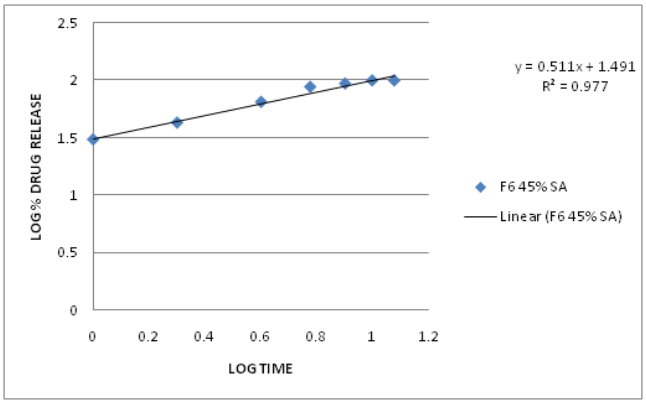

Figure14: korsmayerspepas plot for formulation F6

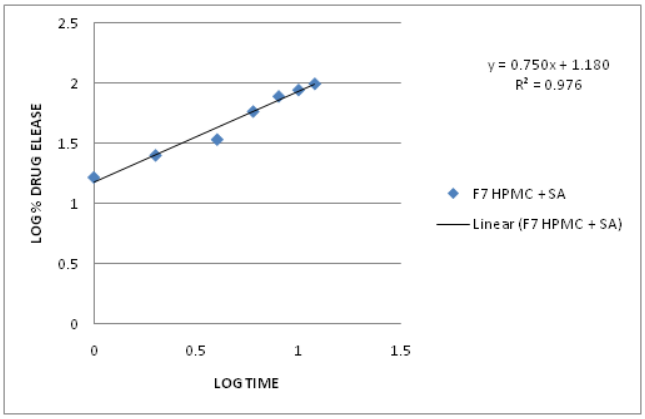

Figure15: korsmayerspepas plot for formulationF7

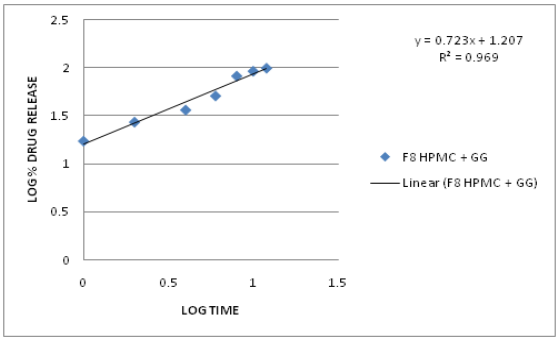

Figure 16: korsmayerspepas plot for formulation F8

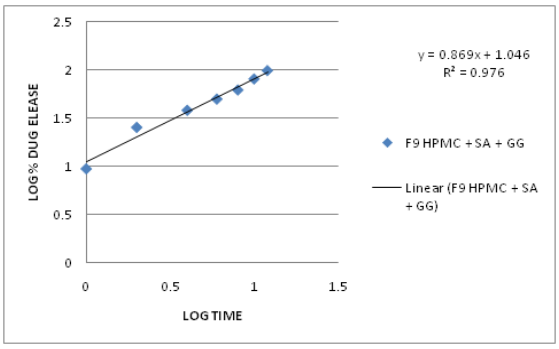

Figure 17: korsmayerspepas plot for formulationF9

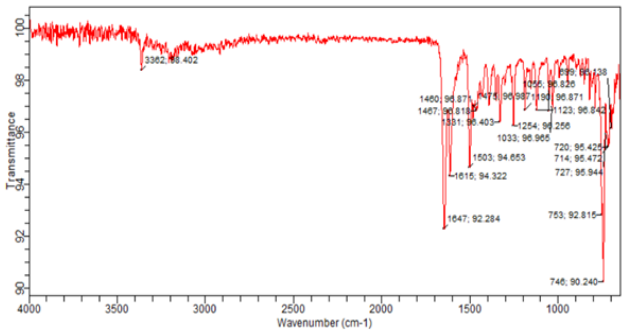

Figure 18: FT-IR Studies: HPMC

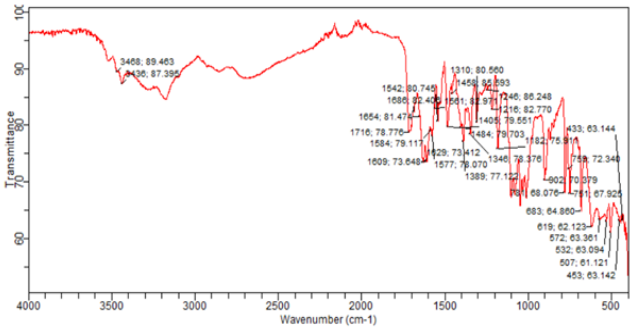

Figure 19: FT-IR Studies: Sodium alginate

Table1: Sotagliflozin formulation table for f1 –f6 formulations

Sno	Ingredients	F1 HPMC	F2 HPMC	F3 GG	F4 GG	F5 SA	F6 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
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	

Table 3: Dissolution parameters

Parameter	**Details**
Disso.Apparatus	USP2
Buffer	PH6.8 Kh2Po4
Vol.	900ml
RPM	100rpm
Temp.	37±0.5 ºC
collection	10ml
Intervals	1h,2h,4h,6h,8h,10h and 12hr
technique	UV Spectroscopy
λ_{max}	271nm

Table 4: Sotagliflozin CR tablet post-compression trials

Code of Formulation	**Studies conducted after compression**				
	Avg. Wt(mg) (n=20)	**Thickness (mm)(n=3)**	**Hardness (kp) (n=3)**	***%Friability**	**%Drug content (n=3)**
F.1	500.4±0.6	5.86±0.29	6.1±0.26	0.56	99.94±0.16
F.2	502.2±0.4	5.94±0.21	6.2±0.24	0.66	100.21±0.21
F.3	499.6±0.4	5.81±0.2	6.3±0.21	0.58	99.18±0.15
F.4	498.0±0.3	5.85±0.2	5.9±0.23	0.57	100.15±0.12
F.5	499.6±0.4	5.86±0.2	6.3±0.21	0.53	99.54±0.14
F.6	502.2±0.4	5.90±0.25	6.2±0.25	0.59	100.05±0.18
F.7	500.4±0.6	5.80±0.31	6.0±0.26	0.57	99.86±0.22
F.8	502.2±0.4	5.89±0.22	6.2±0.25	0.66	99.98±0.18
F.9	499.6±0.4	5.84±0.1	6.3±0.21	0.58	99.85±0.14

Table 5: Dissolution profile

Requirments	**conditions**
Disso.apparatus	USP -Type II (paddle)
Buffer	6.8 sodium phosphate buffer
Vol.	900 ml
R.P.M	100rpm
Temp.	37 ºC±0.5ºC
Collection ofsample	5ml
intervals	1h,2h,4h,6h,8h,10h & 12h
Analytical method	UV-Vis
λ_{max}	271 nm

Table 6: In-vitro Dissolution results of Formulation trails of Sotagliffiozin

Time (hr)	**F.1**	**F.2**	**F.3**	**F.4**	**F.5**	**F.6**	**F.7**	**F.8**	**F.9**
	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	32.52	26.7	38.32	36.52	39.5	30.32	20.54	21.38	13.52
2	45.51	32.9	52.25	50.57	47.32	42.54	29.28	31.38	29.6
4	69.32	44.32	78.35	76.32	71.55	64.54	36.24	40.57	42.52
6	86.56	68	91.32	90.54	92.32	87.24	62.58	55.22	54.32
8	94.32	89.32	96.55	97.32	99.47	93.23	82.32	86.34	66.58
10	99.54	96.45	99.21	98.34	99.54	99.21	92.54	96.35	84.35
12	99.54	98.34	99.21	98.34	99.54	99.21	99.58	99.32	99.35

Table 7: R^2value & n result table

Formulation code	**R square value**				
	Zero order	**First order**	**Higuchi plot**	**Peppas plot**	**n value**
F.1	0.939	0.962	0.991	0.982	0.515

F.2	0.987	0.975	0.979	0.952	0.626
F.3	0.980	0.984	0.976	0.960	0.408
F.4	0.904	0.992	0.982	0.954	0.468
F.5	0.921	0.990	0.986	0.976	0.457
F.6	0.948	0.966	0.986	0.980	0.513
F.7	0.993	0.882	0.975	0.978	0.761
F.8	0.989	0.914	0.969	0.971	0.725
F9	0.996	0.832	0.971	0.978	0.871

4. 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.

5. References

[1] Yie.W.Chien, "Novel Drug Delivery System, 2nd edn, revised and expanded" pg 182.

[2] Robinson JR, and LeeVHI(eds)(22Edition),New York Controlled Drug Delivary Fundamentals and Applications,"1987.Pg.09

[3] D.M.Brahmankar and Sunil B.Jaiswal, Biopharmaceutics and Pharmacokinetics A Treatise",Pg.335-350.

[4] Robert E. Nortari, "Biopharmaceutics and pharmacokinetics An Introduction" 4th edn revised and expanded,pg no.208

[5] S.PVyas,RoopK.Khar, Controlled Drug Delivary Concepts and Advances"Pg.155-158.

[6] MiloGibaldi and Donald Perzier vol.15, Pharmacokinetics" 2nd edn,"revised and expanded Pg.185

[7] Lisa Brannan-Peppas,Polymers in Controlled Drug Delivary"nov.1997.

[8] Syed NisarHussain Shah , SajidAsghar , Muhammad AkramChoudhry , Muhammad Sajid Hamid Akash , **"**Formulation and evaluation of natural gum-based sustained release matrix tablets of flurbiprofen using response surface methodology" Drug Development and Industrial Pharmacy 2009, 35, (12), Pg 1470-1478.

[9] Vinayak Dhopeshwarkar, Janet C. O'Keeffe, Joel L. Zatz, Robert Deete and And Michael Horton Development of An Oral Sustained-Release Antibiotic Matrix Tablet Using In-Vitro/In-Vivo Correlations, Drug Development and Industrial Pharmacy, 1994, 20, (11), Pg 1851-1867.

[10] John W. Skoug, Martin V. Mikelsons, Cynthia N. Vigneronand Nick L. Stemm "Qualitative evaluation of the mechanism of release of matrix sustained release dosage forms by measurement of polymer release"Control Development, April-1993.

[11] AyhanSavaşer, YalçınÖzkan and AşkınIşımer, **"**Preparation and in vitro evaluation of sustained release tablet formulations of diclofenac sodium" Department of Pharmaceutical Technology, Gülhane Military Medical Academy, Etlik, 06018 Ankara, Turkey.October-2008.

[12] P.G.Yeole, U.C.Galgatte, I.B.Babla, "Design and evaluation of xanthan gum based sustained release matrix tablets of diclofenac sodium" International Journal of pharmaceutical sciences.2006, pg 185-189.

[13] D.M. Morkhade, S.V. Fulzele, "Gum Copal and Gum Damar: Novel Matrix forming Materials for Sustained Drug delivery", International Journal of pharmaceutical sciences.2006, pg 53-58.

[14] UmitGonullu, MelikeUner, GulgunYener, "introduction of sustained release Opipramol Di hydrochloride matrix tablets as a new approach in the treatment of depressive disorders", International Journal of Biomedical science, 2006, 2, (4), pg 337-343.

[15] A.K.Srivastava, Saurabhwadhwa, B.mishra, "oral sustained delivery of Atenolol from floating matrix tablets - formulation and in vitro evaluation." Drug development and industrial pharmacy, 2005, 31, (4-5), pg 367-374.

[16] Neal M.Davies, "sustained release and enteric coated NSAIDS: Are they really GI safe?", J pharm pharmaceutsci, 1999, 2, (1), pg 5-14.

[17] Mohammad Reza Siahi, Mohammad Barzegar-Jalali, Farnaz Monajjemzadeh, "Design and Evaluation of 1- and 3-Layer Matrices of Verapamil Hydrochloride for Sustaining Its Release". AAPS Pharm Sci Tech. 2005; 6(4): E626-E632.

[18] Mohammad Siahi, Mohammad Barzegar-Jalali, Farnaz Monajjemzadeh, Fatemeh Ghaffari Shirzad Azarmi, "Design and evaluation of 1- and 3-layer matrices of verapamil hydrochloride for sustaining its release", AAPS Pharm Sci Tech. 2005; 6(4): E626-E632.

[19] Giovanna Corti, Marzia Cirri, Francesca Maestrelli, NatasciaMennini, “Sustained-release matrix tablets of metformin hydrochloride in combination with triacetyl-β-cyclodextrin” Europian Journal of pharmaceutics and biopharmaceutics 2008, 68, (2), pg 303-309.