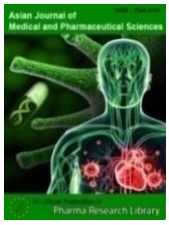

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Formulation and Evaluation of Microparticle Controlled Release Solid Dosage form of Remogliflozin

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A B S T R A C T

This study investigates the influence of different concentrations of controlled-release (CR) polymers on the release profiles of tablets. It was observed that as the concentration of CR polymers increased, the order of CR also increased, with formulations F2 exhibiting superior CR compared to F1 (HPMC), F4 to F3 (GG), and F6 to F5 (SA). When natural CR polymers, sodium alginate (SA) and guar gum (GG), were used alone at concentrations of 30% and 45%, no CR effect was sustained up to 12 hours, indicating their ineffectiveness as sole CR agents. Among all the polymers tested, 45% HPMC (F2) demonstrated the most effective CR. Consequently, further studies explored the effect of combining natural CR polymers (SA and GG) with HPMC while maintaining a constant 45% HPMC concentration (formulations F7, F8, and F9). The results indicated that the formulation comprising 45% HPMC + 10%SA + 10%GG (F9) provided the best CR due to the synergistic release mechanisms of the three polymers. The order of CR efficacy was determined to be F9 > F7 > F8. The dissolution data clearly showed that the combination of HPMC with both natural polymers resulted in superior CR compared to formulations containing HPMC with a single natural polymer or HPMC alone. Thus, combining HPMC with natural polymers is a more effective strategy for achieving optimal controlled-release profiles in tablet formulations.

Keywords: Controlled-release, polymers, HPMC, Remogliflozin

A R T I C L E I N F O

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C o n t e n t s

1. Introduction

The ideal sustained release products should not only have a prolonged drug releasing function, but should also offer once or twice a day dose treatment and better control of therapeutic drug level; this will have two benefits: the first is fewer side effects and the second is improved disease management. Hence a good patient compliance is obtained due to reduction in the frequency of daily dosing [1,2]. The problem of patient compliance and its considerable effect on drug therapy is the great advances and extensive research work considering drug absorption and its pharmacokinetics, the rapid growth of polymer technology and some other factors are behind the interest and rationale design of prolonged action dosage forms [3]. Prolonged or controlled release drugs are classified into three basic types: (1) Sustained release, (2) Prolonged action, and (3) repeat action dosage forms [4]. A sustained release product is made so that part of the drug is initially available in an amount sufficient to cause pharmacological response (initial

or loading dose), and the other part is for maintenance of activity at the initial level for a desirable number of hours in excess of the activity resulting from the usual single dose of drug (maintenance dose). To maintain a certain level of activity, the maintenance dose should release the drug for absorption at constant rate, which is equal to the rate of elimination of drug from the body [5]. Prolonged action products may be considered as those in which drug is initially made available to the body in an amount sufficient to cause the therapeutic effect; these products also provide for replacement of the drug at some rate which gives a measurable increase in the duration of activity when compared to the conventional single dose. On the other hand, a repeat action preparation is one that provides a usual single dose of drug and is so constructed to provide another single dose at some later time after administration [6].

Prescribing a long acting dosage form offers several advantages to the conventional dosage forms. By the virtue of eliminating the necessity for drug administration several times a day, patient compliance is greatly improved. Patient compliance is a chronic problem for all self-administered drugs and the minimization of this problem through prolonged acting drugs is very desirable [7]. The blood level oscillations characteristic of multiple dosing conventional dosage forms are greatly reduced after using long acting medications. With oscillating blood level, drug side effects tend to predominate at the high peak concentration in the blood, whereas, an inadequate therapeutic effect may be obtained at the valley level. On the other hand, maintenance of the blood levels constant at predetermined value reduces the incidence of adverse effects and increases the safety margin of drugs [8-10].

Prolonged action dosage forms provide a slow and constant supply of drug to the body. This leads to a better control of the disease condition and to improve disease management. Proper drug delivery should lead to more prompt cure of the condition as well as better management of acute and chronic conditions [11]. Another advantage of prolonged acting drugs is economy. This economy should be viewed in a broad sense, since the unit cost of most prolonged action medications is usually greater than conventional dosage forms because of the special nature of these products. However, the use of less total drug. The total cost saving to the patient in terms of reduced lost work days, shorter periods of hospitalization, and fewer visits to the physician, make it reasonable to assume that these long-acting products are economical [12]. So, the importance and the usefulness of sustained release dosage forms are well-known and offer many advantages over the conventional dosage forms.

The disadvantages of administering prolonged action drugs
Administration of long acting medications does not permit the prompt termination of therapy. Accidental or intentional poisoning with long acting dosage forms are more difficult to manage than conventional oral solid dosage forms. The slow release of drug into the gastrointestinal tract and its extended absorption often leads to slow clearance of drug from the body [13,14]. With long acting medications, the physician has less flexibility in adjusting dosage regimen since this is affected by the dosage form design. Patient-to-patient variation is another troublesome variable in the design of prolonged action dosage forms. Prolonged action dosage forms are designed for the normal population. Thus, significant patient's variation or any disease state that alters drug disposition presents a problem [1,2].

Design of prolonged action dosage forms
Most per-oral prolonged action products have been formulated in the form of capsules or tablets [15,16]. Also, can be formulated in nanoparticles and microparticles [17,18]. The inherent difficulty of preparing prolonged action liquids has limited the availability of such dosage forms. Encapsulated long acting dosage forms have two specific advantages over tablet designs. Firstly, undisintegrated tablets may remain in the stomach for extended periods of time, excessively delaying the absorption of maintenance dose. Disintegration of the capsule shell in the gastric fluid releases particles that pass unimpeded through the pyloric valve. Also, release of drug by a significant fraction of the granules is highly probable. If a tablet fails to release drug, the entire maintenance dose is lost. Two general principles are involved in retarding drug release from most practically prolonged action formulations involving dosage form modification. These are the barrier and the embedded matrix principle [19-22].

The barrier principle
The barrier concept of controlled release implies that a layer retardant material is imposed between the drug and the elution medium; a coating film of the retardant material forms around core composed of the active ingredient. In most instances, these coated particles form a system where drug is contained in the coating film as well as in the core of the micro particles. Drug release from such systems follows a diffusion mechanism, a dissolution mechanism or a combination of both mechanisms [23-25].

Models based on diffusion
In this case, the barrier is composed of water-insoluble polymeric material that is impermeable to the elution medium. Drug will partition into the membrane and exchange with the fluid surrounding the particle. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding medium. At steady state, release rate of drug is expressed as:

$$R = SDCsmL \quad \ldots\ldots\ldots (1)$$

Where S is the surface area, D is the diffusion coefficient of the drug in the membrane; Csm is the solubility of drug in the membrane, and L is the thickness of the membrane. Two forms of release profiles may be observed in this case: a burst effect if the membrane is saturated with the drug and a time lag if drug has not penetrated the membrane [26-28]. A second possible model based on the diffusion mechanism occurs when a partially soluble membrane encloses a drug core. Dissolution of part of the membrane allows for diffusion of the constrained drug through the pores in the polymer coat. Release rate in this case can be expressed as:

$$R = SD\,(C1 - C2)L \quad \ldots\ldots (2)$$

Where C1 is the drug concentration in the core, C2 is that in the surrounding medium. The fraction of soluble polymer in the coat will be the dominant factor in controlling drug release rates. If the drug is soluble in the membrane, the release rate will be described by equations (1) and (2). The use of methylcellulose and ethyl cellulose films to coat aspirin particles using the air suspension coating technique was reported. In this case, the methylcellulose dissolves out of the film leaving small channels in the film through which drug can diffuse. The ethyl cellulose barrier left on the particle serves as restraining barrier to maintain constant diffusion area and constant diffusion path length [29-32].

2. Materials and Methods

Materials:

Remogliflozin were supplied by Qualychrome, HPMC K 100M, Sodium Alginate, Guar Gum, Avicel PH102(MCC), Aerosil and Magnesium Stearate were procured from SD Fine Chemicals, Mumbai.

Methodology:

I. Analytical Method Development

Preparation of Standard Calibration Curve for Remogliflozin:

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

a) Preparation of 0.1 N Hcl Solution:

0.1N HCl was prepared by diluting 8.5 ml of concentrated Hydrochloric acid to 1000 ml distilled water

b) Preparation of 6.8 pH phosphate buffer solution:

27.22g of monobasic potassium phosphate was weighed and diluted up to 1000 ml to get stock solution of monobasic potassium phosphate. 8g Sodium hydroxide was weighed and diluted up to 1000ml to get 0.2M sodium hydroxide solution. 50 ml of the monobasic potassium phosphate solution was taken from the stock solution in a 200-mL volumetric flask and 22.4 ml of sodium hydroxide solution from stock solution of 0.2M sodium hydroxide solution was added and then water was used to make up the volume.

3. Principle:

a) Standard solution of Remogliflozin by using 0.1 N Hcl: 100mg of drug is dissolved in 100ml of methanol. This is first stock solution.10ml of 1st stock solution is diluted with 100ml of 0.1N Hydrochloric acid buffer. This is 2nd stock solution. Now from 2nd stock, various concentrations of 2ug/ml, 4ug/ml, 6ug/ml, 8ug/ml, and 10ug/ml were prepared by using same 0.1 N Hydrochloric acid buffer. Blank was also prepared with same buffer composition except the drug. All the samples were analyzed at 271 lambda max with respect to the blank.

b) Standard solution of Remogliflozin by using 6.8 Buffer Solution:

100mg of drug is dissolved in 100ml of methanol. This is first stock solution.10ml of 1st stock solution is diluted with 100ml of 6.8 buffer. This is 2nd stock solution. Now from 2nd stock, various concentrations of 2ug/ml, 4ug/ml, 6ug/ml, 8ug/ml and 10ug/ml were prepared by using same 6.8 buffers. Blank was also prepared with same buffer composition except the drug. All the samples were analyzed at 270 lambda max with respect to the blank.

III. Preparation of matrix tablets by non aqueous wet granulation method:

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

IV. 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:

1. Angle of Repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Angle of Repose of granules was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation17.

$q = \tan^{-1}(h/r)$

Where:

q = angle of repose

h = height in cms

r = radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

In-vitro drug release studies:

The in-vitro dissolution studies were carried out using USP 24 dissolution apparatus type II14 (paddle method) at100 rpm. Dissolution test was carried out for a total period of 12 h using 0.1N HCl (pH 1.2) solution (750 ml) as hydrochloride, dissolution medium at 37 ± 0.5° for first 2 h, and pH 6.8. phosphate buffer solution (1000 ml). Ten millilitres of the sample was withdrawn regular intervals and replaced with the same volume warmed (37 ± 0.5°) fresh dissolution medium. The samples was withdrawn were filtered through 0.45 µ membrane filter and drug content in each sample was analyzed after the suitable dilution by UV-Visible spectrophotometer at respective λ max of each dissolution medium.

In-vitro Release Kinetics Studies:

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDDS was described by using zero order kinetics or first order kinetics. The mechanism of drug release from FDDS was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

Zero Order Release Kinetics:

- It defines a linear relationship between the fractions of drug released versus time.

$$Q=k0t.$$

- Where, Q is the fraction of drug released at time t and ko is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.
- First Order Release Kinetics:
- Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$\text{Log } C = \text{Log } Co - kt/2.303$$

Where C is the amount of drug dissolved at time t,
Co is the amount of drug dissolved at t=0 and
k is the first order rate constant.

A graph of log cumulative of log % drug remaining vs time yields a straight line. Will be linear if the release obeys the first order release kinetics.

Higuchi equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$$Q=K2t1/2$$

Where K2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent20.

4. Peppa's-Korsemeyer equation (Power Law):

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppa's-Korsemeyer equation (Power Law).

$Mt/ M\infty = K.tn$

Where, Mt is the amount of drug released at time t
$M\alpha$ is the amount released at time α,
$Mt/M\alpha$ is the fraction of drug released at time t,
K is the kinetic constant and n is the diffusion exponent.

To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log drug release up to 60% against log of time will be linear if the release obeys Peppa's-Korsemeyer equation and the slope of this plot represents "n" value21.the kinetic data of the formulations were included. Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using MS EXCEL.

2. Results and Discussion

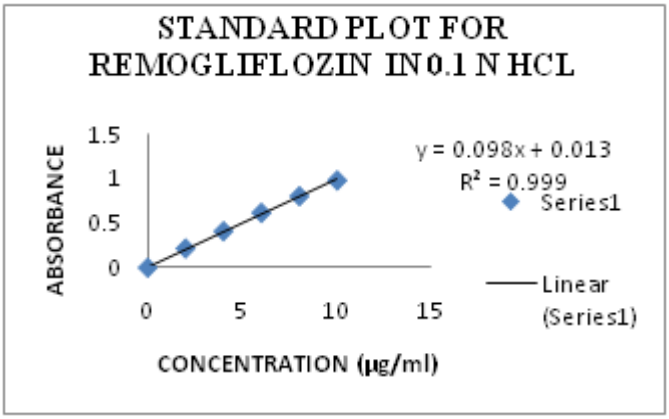

Figure 1: Standard calibration curve of Remogliflozin in 0.1N Hcl at λMax = 225 nm

Table 1: Standard Calibration graph values of Remogliflozin in 0.1N Hcl at λMax = 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

The absorbance of the solution was measured at 225 nm, using UV spectrometer with 0.1N HCl as blank. The values are shown in table no 10. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml

Construction of Standard calibration curve of Remogliflozin in 6.8 phosphate buffer:
The absorbance of the solution was measured at 225 nm, using UV spectrometer with 6.8 phosphate buffer as blank. The values are shown in table no 11. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml

Table 2: Standard Calibration graph values of Remogliflozin6.8 phosphate buffer at λMax = 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

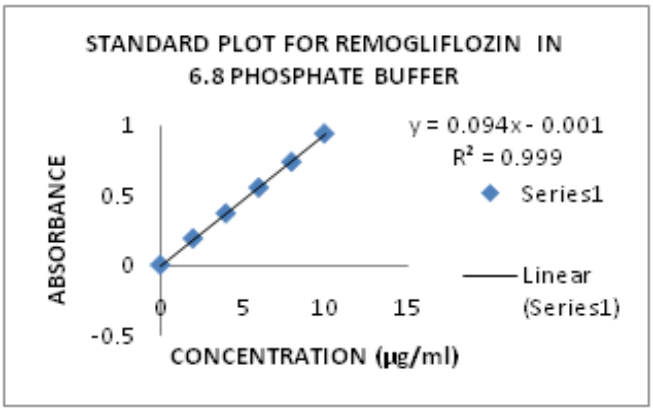

Figure 2: Standard calibration curve of Remogliflozin in 6.8 phosphate buffer at λMax = 225 nm

Table 3: Pre compression studies of Remogliflozin 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

Table 6: Post compression studies of Remogliflozin 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

*Test for Friability was performed on single batch of 20 tablets

Table 4: 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

Table 5: In-vitro Dissolution results of Formulation trails of Remogliflozin

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

Table 6: 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

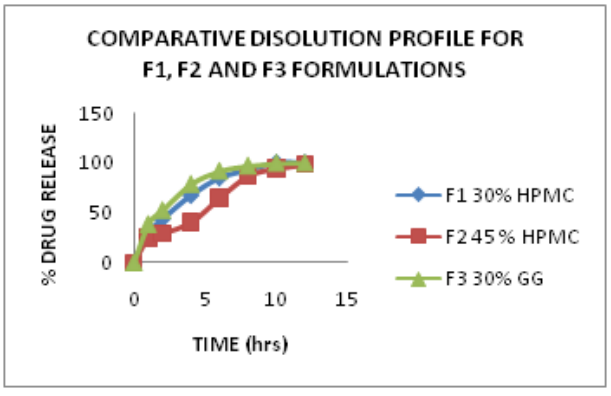

Figure 3: comparative dissolutionF1, F2 and F3 formulations of Remogliflozin

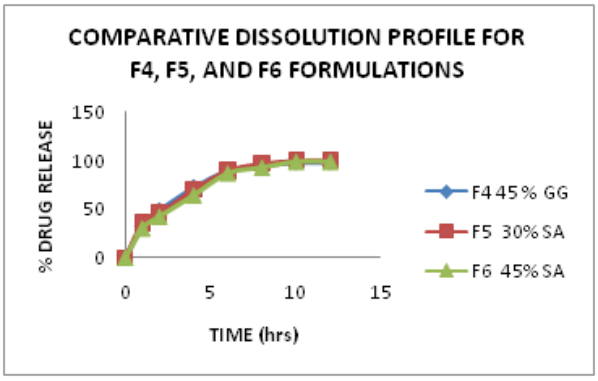

Figure 4: comparative dissolutionF4, F5 and F6 formulations of Remogliflozin

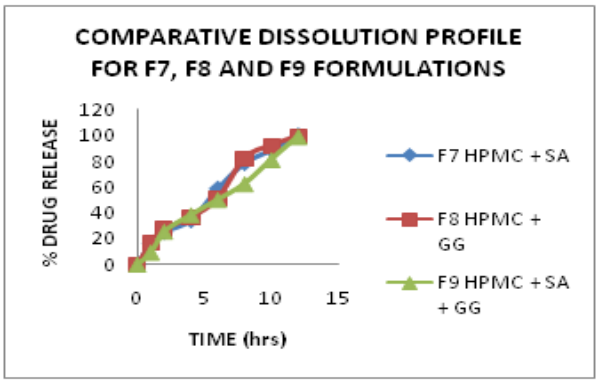

Figure 5: comparative dissolutionF7, F8 and F9 formulations of Remogliflozin

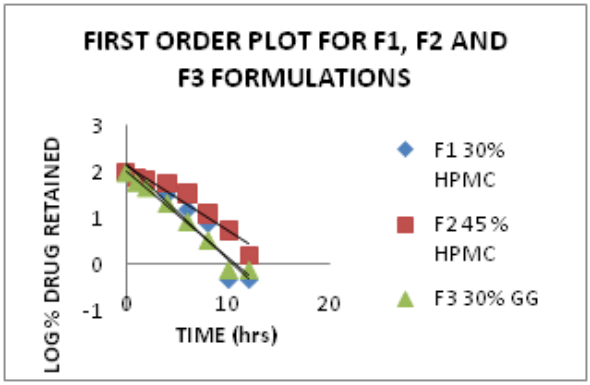

Figure 6: First order plot for F1, F2 and F3 formulations

Discussion

This study explores the impact of various concentrations and combinations of controlled-release (CR) polymers on tablet formulations. It was found that increasing the concentration of CR polymers generally improved the order of CR, with specific formulations (F2, F4, and F6) showing better performance compared to their counterparts (F1, F3, and F5). Notably, CR tablets composed solely of natural polymers, sodium alginate (SA) and guar gum (GG), failed to sustain CR up to 12 hours at both 30% and 45% concentrations, rendering them ineffective as standalone CR agents. Among the polymers tested, 45% HPMC (F2) provided the most effective CR. Further investigations were conducted to assess the effect of combining natural polymers with HPMC, keeping HPMC concentration constant at 45% (formulations F7, F8, and F9). The combination of 45% HPMC + 10% SA + 10% GG (F9) emerged as the most effective, showcasing superior CR due to the synergistic release mechanisms of all three polymers. The CR efficacy followed the order F9 > F7 > F8, indicating that combining HPMC with both natural polymers resulted in better CR compared to using HPMC with a single natural polymer or HPMC alone

4. Conclusion

The study concludes that higher concentrations of CR polymers enhance the order of CR in tablet formulations. However, natural CR polymers (SA and GG) are ineffective on their own for achieving sustained CR up to 12 hours. Among the tested formulations, 45% HPMC demonstrated superior CR properties. Further combination studies revealed that integrating natural polymers with HPMC, particularly in the formulation of 45% HPMC + 10% SA + 10% GG (F9), yields the best CR performance. The findings suggest that using a combination of HPMC with natural polymers is a more effective approach for achieving optimal controlled-release profiles in tablet formulations than using HPMC alone or with a single natural polymer.

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