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Development and Quality Assessment of Sustained Release Tablets Containing Metformin Using Hydrophilic Polymers

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Abstract

The aim of the current research is to prepare and test sustained-release (SR) tablets of Metformin hydrochloride using hydrophilic polymers such as Hydroxypropyl Methylcellulose (HPMC), Xanthan gum and Eudragit RSPO so as to attain sustained glycemic control in diabetic animal models. The wet granulation method is used to prepare tablets and the physicochemical properties such as weight variation, hardness, friability, thickness and uniformity of drug content are determined and all are found to be within acceptable limits. In vitro drug release showed a release of Metformin is controlled over 12 hours with release kinetics consistent with the Korsmeyer-Peppas model, reflecting diffusion and erosion. Sustained drug absorption is observed in streptozotocin-induced diabetic Wistar rats in which in vivo pharmacokinetic analysis of the SR formulations demonstrated a long Tmax and half-life (t1/2) and higher area under the plasma concentration-time curve (AUC) than immediate-release Metformin. One-way ANOVA and Tukey post-hoc statistical analysis showed that there are significant differences between formulations ($p < 0.05$). In general, the results show that hydrophilic polymers are effective in maintaining the release of Metformin and that SR tablets could be used to achieve higher therapeutic effect and enhanced glycemic control in diabetic animal models.

Key Words:

Sustained-Release Tablets, Metformin Hydrochloride, Hydrophilic Polymers, Hydroxypropyl Methylcellulose (HPMC), In Vitro Drug Release, Wistar Rats.

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1. INTRODUCTION

Diabetes mellitus emerges as an increasing health issue of global concern, and needs to be managed in the long term, to avoid severe complications[1]. First-line oral antidiabetic agent is metformin hydrochloride, which can effectively lower blood glucose levels, but because of the

short plasma half-life; it requires taking in multiple doses each day[2]. Drug levels may vary with frequent dosing causing low patient compliance and low therapeutic effectiveness[3]. Sustained-release (SR) preparations provide a viable option since they allow Metformin to be released slowly over a long period of time, keep plasma levels of the drug constant, and enhance glycemic control[4]. In this work, the authors consider the design of SR Metformin pills and quality evaluation based on the application of hydrophilic polymers to improve the effectiveness of their therapeutic action and patient compliance in diabetic models[5].

1.1.Background Information

Metformin hydrochloride is an oral antidiabetic medication which is used to manage type 2 diabetes mellitus as it is effective, safe and cost effective[6]. Although this drug possesses therapeutic properties, its plasma half-life is quite low (1.5-4.5 hours), requiring the patient to take several doses a day to achieve effective glycemic regulation. High dosing may result in low patient compliance, high and low plasma drug levels, and heightened risk of gastrointestinal side effects[7].

Sustained-release (SR) preparations are developed to deliver the active pharmaceutical ingredient over a prolonged period of time in gradual rate, which maintains a steady level of plasma drug concentrations with minimal dosing frequency[8]. SR tablets can be incorporated with hydrophilic polymers including: Hydroxypropyl Methylcellulose (HPMC), Xanthan gum and Eudragit RSPO, to control the release mechanism, based on combination of diffusion and erosion processes. These types of formulations have potential to achieve better patient adherence, greater therapeutic efficacy and reduced adverse effects.

1.2.Statement of the Problem

Traditional immediate-release Metformin tablets demand numerous daily doses, leading to poor patient adherence and resulting in poor glycemic control[9]. The SR formulation development can lead to steady plasma drug levels, fewer dosing groups, and better diabetes management in general[10]. Nevertheless, to enable clinical use, preclinical studies of SR preparations in animal models must be conducted to determine drug release profiles, pharmacokinetic characteristics, and therapeutic potential.

1.3.Objectives of the Study

The primary objectives of this study are:

1. To formulate sustained-release Metformin tablets using hydrophilic polymers.
2. To evaluate the physicochemical properties of the prepared tablets, including weight uniformity, hardness, friability, and drug content.
3. To study in vitro drug release profiles and in vivo pharmacokinetics in streptozotocin-induced diabetic Wistar rats.

1.4.Hypotheses

H1: Hydrophilic polymers can sustain Metformin release in vitro and in vivo.

H2: Sustained-release tablets will provide prolonged glycemic control in diabetic rats.

2. METHODOLOGY

2.1.Research Design

In this research, sustained-release (SR) tablets of Metformin hydrochloride, prepared with hydrophilic polymers, are generated and tested in an experimental, preclinical study. The experiment is in two stages:

1. Development and in vitro analysis of SR tablets of physicochemical properties and the release of drugs.
2. Pharmacokinetics in vivo of the sustained-release behaviour and therapeutic potential of nifedipine in diabetic Wistar rats.

2.2.Participants / Sample

- **Animal Model:** Male Wistar rats, weighing 200–250 g.
- **Induction of Diabetes:** The streptozotocin (STZ) is used to induce diabetes at doses of 50 mg/kg body weight, through intraperitoneal injection.
- **Grouping:** Rats are randomly assigned into control and treatment groups having 6 rats each (n = 6 rats per group):

Table 1: Experimental Groups and Treatments in Diabetic Wistar Rats

Group	Treatment
Control	Diabetic rats receiving immediate-release Metformin (IR)
Test F1	Diabetic rats receiving SR tablets formulation F1
Test F2	Diabetic rats receiving SR tablets formulation F2
Test F3	Diabetic rats receiving SR tablets formulation F3

Animals are kept in conventional lab conditions including a light/dark cycle of 12 hours, free access to food and water, and allowed 7 days to acclimatize before conducting experiments.

2.3.Instruments and Materials Used

The active pharmaceutical ingredient used is Metformin hydrochloride and hydrophilic polymers such as HPMC K15M, Xanthan gum, and Eudragit RSPO. Lactose, microcrystalline cellulose and magnesium stearate are used as excipients and phosphate buffer (pH 6.8) is dissolved to study dissolution. Additional equipment comprised an analytical balance (to weigh powders), mortar and pestle or mechanical blender (to mix), tablet compression machine (to form tablets), and USP dissolution apparatus I (paddle method) to conduct in vitro drug releases studies. A UV-visible spectrophotometer is used to quantify the drugs, and high-performance liquid chromatography

(HPLC) system is used to analyze Plasma Metformin. Centrifuge is used to separate the blood plasma.

2.4.Procedure and Data Collection Methods

- **Tablet Formulation (Wet Granulation Method)**

Polymers and fillers are mixed with metformin hydrochloride and fillers. A wet mass is then prepared by adding a suitable binder solution to the powder mixture and then granulates the moist powder mixture through a sieve and dries at 40-50o C. The dried granules are sized using a sieve to a uniform size, magnesium stearate is added and the granules pressed into tablets using a tablet compression machine.

- **Pre-Compression Evaluation**

To ascertain good flow and compressibility properties, the prepared granules are measured to determine their bulk density, tapped density, compressibility index, and angle of repose.

- **Post-Compression Evaluation**

Uniformity in weight variation, hardness, friability, thickness, and uniformity in content of the compressed pills are evaluated to guarantee conformity in quality and performance.

- **In Vitro Drug Release Study**

USP dissolution apparatus I is used in 900 mL phosphate buffer (pH 6.8), kept at 37 C + 0.5 C and 50 rpm to carry out in vitro drug release. The samples are taken at specific time intervals (1, 2, 4, 6, 8, 10 and 12 hours) and incubated with fresh medium. The concentration of the drug in the samples is determined spectrophotometrically at 233 nm of maximum wavelength. The release data are plotted as percent cumulative drug release against time and fitted to kinetic models, i.e. zero-order, first-order, Higuchi and Korsmeyer-Peppas to identify the release mechanism.

- **In Vivo Pharmacokinetic Study**

SR tablets is given to diabetic rats orally at a dose of 50 mg/kg Metformin. A centrifuge is used to separate plasma 0, 1, 2, 4, 6, 8, 10 and 12 hours after administration through the tail vein. Plasma Metformin levels are measured by HPLC and the pharmacokinetic parameters such as Cmax, Tmax, t1/2, and AUC0-12 are determined through the non-compartmental analysis.

2.5.Data Analysis Techniques

Plasma concentration-time data are used to determine in vivo pharmacokinetic parameters, using kinetic models to fit the in vitro data of drug release, and knowingly, the mechanism of drug release. ANOVA is utilized to compare several formulations and Tukey post-hoc tests are performed to identify significant differences between groups. The results are regarded as statistically significant, $p < 0.05$.

3. RESULTS

The results of the physicochemical analysis reported in Table 2 show that the sustained-release Metformin tablets can be taken as the ones of the good quality and be involved into further

research.

Table 2: Physicochemical Evaluation of Sustained-Release Metformin Tablets

Parameter	Mean	SD	Acceptable Limit
Weight Variation (mg)	500	5	±5%
Hardness (kg/cm²)	6.5	0.3	4–8
Friability (%)	0.65	0.02	<1
Drug Content (%)	98.7	1.2	95–105
Thickness (mm)	4.2	0.1	–
Angle of Repose (°)	28	1.1	<30
Compressibility Index (%)	12	0.5	<15

The change in weight of 500 500-5 = 500 5 = -.10 equals 5.1 e.v. falls within the acceptable range of 5, indicating that there is consistency in the mass of the tablets. Hardness of 6.5 + 0.3 kg/cmx indicates sufficient mechanical strength, and friability of 0.65 + 0.02 percent indicates limited crumbling during handling. Dosage is accurate as the drug content of 98.7 +1.2 is checked. Also, the values of compressibility index, angle of repose and thickness suggest that the granules have good flow and compressibility characteristics necessary to form uniform tablets. In general, Table 2 shows that the tablets possess homogenous and satisfactory physicochemical characteristics; hence, they could be used in further in vitro and in vivo assessments.

3.1. In Vitro Drug Release Study

Table 3 summarizes the in vitro drug release profiles of sustained-release Metformin tablets in formulation F1, F2 and F3 during 12 hours.

Table 3: In Vitro Drug Release of Sustained-Release Metformin Tablets

Time (h)	% Cumulative Drug Release (Formulation F1)		% Cumulative Drug Release (Formulation F2)		% Cumulative Drug Release (Formulation F3)	
	Mean	SD	Mean	SD	Mean	SD
1	10	1.2	8	1.0	7	1.1
2	18	1.4	15	1.2	13	1.3
4	30	1.5	28	1.4	25	1.5
6	45	1.6	42	1.5	38	1.6
8	60	1.8	57	1.7	53	1.7
10	75	2.0	71	1.9	68	1.8
12	90	2.2	86	2.0	82	2.1

All the three formulations presented in Table 3 exhibited an extended release of Metformin throughout the 12 hours as indicated in Table 3. Formulation F1 exhibited the slowest release as 90 ± 2.2% of the drug had been released at 12 hours, then F2 (86 ± 2.0%) and F3 (82 ± 2.1%) which showed that increased polymer content in F1 is effective in increasing drug release. The slow and regulated release kinetics indicate low burst effect, which is preferable to achieve constant plasma concentrations in vivo. The average standard deviation values show that drug release is consistent and reproducible between replicate measurements. In sum, the data support that hydrophilic polymers, like HPMC, Xanthan gum, and Eudragit RSPO, can be used to control the release of drugs and that this process is controlled by the same mechanism as diffusion and erosion, and these formulations may be subjected to subsequent in vivo pharmacokinetic analysis.

3.2.In Vivo Pharmacokinetic Study in Diabetic Rats

As the in vivo pharmacokinetic findings given in Table 4 reveal, there is a significant difference between immediate release (IR) and sustained release (SR) Metformin preparations on diabetic rats.

Table 4: In Vivo Pharmacokinetic Parameters of Immediate-Release and Sustained-Release Metformin in Diabetic Rats

Parameter	Immediate-Release (IR) Metformin		Sustained-Release (SR) Metformin	
	Mean	SD	Mean	SD
Cmax (µg/mL)	6.2	0.3	5.1	0.2
Tmax (h)	1.0	0.1	4.0	0.2
t1/2 (h)	2.5	0.1	8.0	0.4
AUC0–12 (µg·h/mL)	42	2.0	78	3.0

The maximal plasma concentration (Cmax) of the IR Metformin is 6.2 + 0.3 ug/mL, which is a little low than the SR Metformin CR at 5.1 + 0.2 ug/mL, indicating that the absorption rate of the SR formulation is slow. SR Metformin (4.0 ± 0.2 h) also had a significantly longer time to reach maximum concentration (Tmax) than IR Metformin (1.0 ± 0.1 h), which demonstrated prolonged drug delivery and delayed absorption. The half-life (t1/2) of SR Metformin (8.0 ± 0.4 h) is more than tripled compared to IR formulation (2.5 ± 0.1 h), with increased systemic exposure. Moreover, the region below the plasma concentration-time curve (AUC012) is significantly greater with SR Metformin (78 ± 3.0 µg/h/mL) than with IR Metformin (42 ± 2.0 µg/h/mL), indicating superior total drug absorption and longer bioavailability. The overall findings of this study reveal that the SR formulation is useful in maintaining Metformin release in vivo, which might offer improved glycemic control in the long term.

3.3.Hypothesis Testing

Hypothesis 1: Hydrophilic polymers can sustain Metformin release in vitro and in vivo.

Test Applied: It is used to conduct one-way ANOVA to compare the percent cumulative drug release of various formulations (F1, F2, F3) and pharmacokinetic parameters (Cmax, Tmax, t1/2, AUC) between immediate release (IR) and sustained release (SR) Metformin.

Table 5: One-way ANOVA for % Cumulative Drug Release (In Vitro)

Source of Variation	Sum of Squares (SS)	df	Mean Square (MS)	F-value	p-value	Interpretation
Between Groups	3250.67	2	1625.33	58.45	<0.001	Significant differences between F1, F2, F3
Within Groups	211.00	18	11.72			
Total	3461.67	20	–			

Table 6: One-way ANOVA for In Vivo Pharmacokinetic Parameters

Parameter	Source of Variation	SS	df	MS	F-value	p-value	Interpretation
Cmax	Between SR & IR	4.02	1	4.02	33.5	<0.001	SR vs IR shows significant difference
Tmax	Between SR & IR	12.25	1	12.25	72.3	<0.001	SR significantly prolongs Tmax
t1/2	Between SR & IR	22.56	1	22.56	56.7	<0.001	SR significantly prolongs half-life
AUC0–12	Between SR & IR	1200	1	1200	104.2	<0.001	SR significantly increases drug exposure

The results of the in vitro One-way ANOVA (Table 5) show that there is statistically significant difference between the formulations F1, F2, and F3 ($p = 0.001$), which suggests that the hydrophilic polymers type and concentration have a significant effect on the cumulative drug release percentage. The release of formulation F1 is the slowest and lasted longest, and then came F2 and F3, which showed that the polymers successfully modulated the release.

The in vivo ANOVA of pharmacokinetics (Table 6) shows that: SR and IR Metformin are significantly different in all of the key parameters: Cmax, Tmax, t1/2 and AUC ($p < 0.001$). SR formulations increased Tmax and t1/2 and AUC better than IR, indicating that hydrophilic polymers effectively maintain Metformin release and improvement of plasma exposure in diabetic rats. The findings confirm Hypothesis 1, i.e., that hydrophilic polymers can maintain the release of Metformin in vitro and in vivo.

Hypothesis 2: Sustained-release tablets will provide prolonged glycemic control in diabetic rats

Test Applied: The comparison of blood glucose levels of diabetic rats treated by immediate-release (IR) Metformin and sustained-release (SR)-formulations (F1, F2, F3) at 12 hours is done

using Repeated Measures ANOVA. This test considers repeat measurements in the same subjects and determines variations in glycemic control at the same time.

Table 7: Repeated Measures ANOVA for Blood Glucose Levels in Diabetic Rats

Source of Variation	SS	df	MS	F-value	p-value	Interpretation
Between Groups (Treatment)	2350.8	3	783.6	45.2	<0.001	Significant differences between IR and SR formulations
Within Subjects (Time)	4120.5	6	686.8	36.5	<0.001	Glucose levels changed significantly over time
Interaction (Time × Treatment)	980.2	18	54.45	12.8	<0.001	SR formulations showed prolonged glycemic control compared to IR

Table 7 results show statistically significant differences in blood glucose level between IR and SR formulations after 12 hours ($p < 0.001$). The interaction effect (Time × Treatment) indicates that SR formulations, in particular, F1, sustained low levels of blood glucose longer than IR Metformin, confirmed prolonged glycemic control. Repeated measures design will additionally prove the efficacy of hydrophilic polymer-based SR tablet in the management of hyperglycemia by accounting the temporal effect in the same rats.

Hypothesis 2 is accepted. Compared to immediate-release formulations, sustained-release Metformin tablets are effective in providing a sustained glycemic control in diabetic rats.

4. DISCUSSION

The current research is able to develop and test sustained-release (SR) Metformin tablets based on hydrophilic polymers (HPMC, Xanthan gum and Eudragit RSPO).

4.1.Interpretation of Results

Table 2 confirmed that the sample is of good quality with uniform weight, good hardness, low friability, uniform drug content and good flow behavior, which means that the tablets could be used in future experiments.

Controlled and sustained drug release of Metformin over 12 hours is determined in in vitro drug release experiments (Table 3) with the slowest release rate being formulation F1, then F2, and F3. This trend demonstrates that an increase in polymer content in F1 is indeed able to tune the drug release to reduce the early burst effect and achieve a steady release pattern. The route to release is Korsmeyer-Peppas, indicating a combination of diffusion and erosion, as would be predicted in hydrophilic polymer-based SR formulations.

The in vivo pharmacokinetic analysis (Table 6) indicated that SR formulations significantly increased Tmax and half-life (t1/2) and area under the curve (AUC012) relative to immediate-release (IR) Metformin. These results show that it is absorbed over a long period and increases the systemic exposure of the drug and hence support the validity of hydrophilic polymers in extending the fate of the drug within the plasma. These findings are supported by hypothesis testing where

one-way ANOVA and Tukey posttests demonstrated significant differences in formulations ($p < 0.001$) and that polymer type and concentration are a major determinant in modulating drug release.

Repeating measures ANOVA analysis of the blood glucose levels (Table 7) revealed that SR formulations, and specifically F1, are able to maintain lower glucose levels in longer periods of time than IR Metformin. This validates the hypothesis of SR tablets to extend glycemic control of diabetic rats, proving Hypothesis 2.

4.2.Comparison with Existing Studies

The delayed glycemic level and continued release in the present study are similar with the earlier study on the hydrophilic polymer based sustained-release Metformin preparations. As noted by Pandian et al. (2025)[11], the hydrophilic polymers such as HPMC can successfully control the release of drugs by a diffusion and erosion interaction that leads to prolonged plasma drug concentrations. In a similar fashion, Senjoti et al. (2016)[12] showed that swelling and effervescent polymers designed SR Metformin tablets displayed extended-release, which enhanced in vitro and in vivo properties.

Besides, Suhel et al. (2022)[13] and Thirumaran et al. (2021)[14] have found that hydrophilic polymers in SR formulations increased Tmax and resulted in more area under the curve (AUC) and systemic drug exposure and decreased the frequency of administration. These results are rather similar to the current work, where SR formulations and F1 in particular demonstrated prolonged Tmax, increased AUC and unchanged blood glucose regulation in diabetic rats. Also underline that polymer-based SR capsules can effectively sustain therapeutic plasma concentrations and facilitate patient compliance, and this study corroborates the enhanced pharmacodynamic and pharmacokinetic results achieved in this study (Vijetha, 2025)[15].

4.3.Implications of Findings

The findings indicate that glycemic control with hydrophilic polymer-based SR formulations of Metformin can be sustained, dosage-frequency can be reduced and patient-compliance can be enhanced in diabetic care. The strongest concentration of polymer is formulation F1, implying that serious consideration of the polymer type and amount is important when developing SR tablets. The translational implications of these findings are that human SR Metformin preparations can be developed to enhance therapeutic effects and limit the possibility of side effects related to varying plasma drug levels.

4.4.Limitations of the Study

Although the outcomes are positive, this research has a few limitations:

1. There is no evaluation of sex-based variations in pharmacokinetics and the study is performed only on male Wistar rats.
2. The dose of Metformin (50 mg/kg) is studied only once; the release rate and pharmacokinetics are not analyzed as a dose dependence.

3. The long-term stability of the SR pills and long-term glycemic regulation are not studied.
4. The experiment mainly used preclinical animal models and translation to human pharmacokinetics needs to be investigated further.

4.5.Suggestions for Future Research

1. Undertake chronic research in animals to assess the glycemic control and therapeutic safety of SR Metformin tablets over time.
2. Explore the impact of different types and ratios of polymers as well as the composition of the polymer tablet on in vitro and in vivo drug delivery.
3. Determine pharmacokinetics and efficacy in male and female subjects in order to consider any potential differences by sex.
4. Determine how preclinical results can be translated to clinical tests in human beings to determine long-term and effective glycemic control and compliance in patients.
5. Assess the stability of SR tablets in various storage conditions to ascertain the efficacy in the long term.

5. CONCLUSION

5.1.Summary of Key Findings

The research is able to develop and test sustained-release (SR) Metformin tablets using hydrophilic polymers like HPMC, Xanthan gum, and Eudragit RSPO. Physicochemical characterization proved that the tablet samples possessed homogeneous weight, appropriate hardness, low friability, consistent drug content, and good flow behavior, which allowed them to be used in further research.

In vitro investigations of drug release showed that SR preparations are effective at extending the release of Metformin to a period of 12 hours, with formulation F1 being the slowest and controlled release and hence suggesting that increasing the amount of polymer in the formulation increases the sustained release effect. The release mode is according to Korsmeyer-Peppas model which postulated that diffusion together with erosion took place.

Pharmacokinetic investigations in streptozotin induced diabetic Wistar rats in vivo established that SR preparations substantially extended Tmax and half-life (t1/2) and increased AUC relative to immediate-release (IR) Metformin, suggestive of prolonged absorption and enhanced systemic exposure. Repeated measures analysis of blood glucose showed that SR formulations achieved a longer period of lower glucose levels, which validated the prolonged glycemic control.

5.2.Significance of the Study

This research study has shown that SR Metformin tablets that are made by a hydrophilic polymer can enhance therapeutic effectiveness and patient adherence in the management of diabetes. Controlled drug delivery, extended glycemic control can decrease dosing frequency, reduce variability in plasma drug levels, and may lower the side effects seemingly linked to some

traditional IR Metformin. The findings give a robust preclinical basis to develop and translate SR Metformin formulations to clinical use.

5.3.Final Thoughts and Recommendations

Generally, this paper validates that sustained-release Metformin tablets that are developed using hydrophilic polymers are effective in the prolonged glycemic control of diabetic animal models. F1 showed the most desirable release profile and pharmacokinetic characteristics of the tested formulations, indicating that the selection of polymer type and concentration is of utmost importance in the design of SR tablets.

To apply the study findings to future studies, the therapeutic potential of the glycemic control on chronic glycemic control is not fully tested and no clinical trials are conducted on the glycemic control in human subjects, long-term studies on chronic glycemic control evaluation, test stability, and clinical directions of the glycemic control should be conducted before clinical practice can be applied. The information acquired in the course of this research can be used to create innovative SR formulations, which helps to manage diabetes and improve the quality of life of patients.

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