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Research Article

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Formulation and Development of Sustained Release Floating Tablets of Metformin Hydrochloride

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia, necessitating continuous blood glucose management to prevent complications. Conventional oral antidiabetic therapies often suffer from limitations such as poor bioavailability, short half-life, and frequent dosing requirements. Gastroretentive drug delivery systems (GRDDS) offer a solution by enhancing gastric retention, leading to prolonged drug release and improved therapeutic efficacy. The present study focuses on the formulation and development of a sustained-release floating tablet of Metformin Hydrochloride (MH) aimed at improving bioavailability and enhancing patient adherence.Various formulations were prepared using hydrophilic matrix-forming polymers, including HPMC K15M, kappa-carrageenan, sodium alginate, and xanthan gum, along with sodium bicarbonate as an effervescent agent. The tablets were evaluated for pre-compression and post-compression parameters, including bulk density, compressibility index, swelling ability, friability, floating lag time, and drug release kinetics.

Among the six formulations (F1-F6), F2 exhibited superior characteristics, demonstrating prolonged gastric retention and sustained drug release following zero-order kinetics (R^2 = 0.9257). The release mechanism was best described by the Higuchi model (R^2 = 0.9879) and Korsmeyer-Peppas model (R^2 = 0.9938), indicating diffusion-controlled drug release. Stability studies confirmed that F2 remained stable under accelerated conditions. The sustained-release floating tablet of Metformin Hydrochloride represents a promising approach to improve diabetes management through extended drug release and enhanced patient compliance.

Keywords: Metformin Hydrochloride, Sustained-Release, Floating Tablets, Gastroretentive Drug Delivery System, Diabetes Mellitus, Controlled Release

Introduction

Diabetes mellitus is a progressive metabolic disorder resulting from insulin resistance or deficiency, characterized by chronic hyperglycemia. Long-term complications include cardiovascular diseases, nephropathy, neuropathy, and retinopathy. Metformin Hydrochloride (MH) is the first-line oral hypoglycemic agent for Type 2 diabetes mellitus, known for its ability to reduce hepatic glucose production and enhance insulin sensitivity.

However, Metformin has a short biological half-life (4-6 hours), requiring multiple daily doses to maintain therapeutic levels, often resulting in poor patient adherence. Sustained-release (SR) formulations can address these limitations by reducing dosing frequency and maintaining consistent plasma drug concentrations. Gastroretentive drug delivery systems (GRDDS), specifically floating drug delivery systems (FDDS), enhance gastric retention, improving drug absorption and bioavailability.

The current research focuses on developing a gastroretentive floating SR tablet of MH using hydrophilic polymers like HPMC K15M and other gel-forming agents in combination with sodium bicarbonate to generate buoyancy, optimizing drug release and therapeutic efficacy.

Materials and Methods

Materials

Metformin Hydrochloride was obtained as a gift sample. HPMC K15M, sodium alginate, kappa-carrageenan, xanthan gum, and sodium bicarbonate were purchased from reputable commercial suppliers. Other excipients included microcrystalline cellulose (MCC) and magnesium stearate.

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Methods of Preparation

The direct compression method was employed to formulate tablets containing 750 mg of MH. Metformin, the active ingredient, along with kappa carrageenan, xanthan gum, sodium alginate as a gas-forming agent, NaHCO3, and the release-retarding polymer HPMC K15M, were all separately passed through a 20-mesh sieve. Several powder mixtures were then prepared by blending these ingredients in a mortar and pestle for ten minutes (Table 1). The mixed powders were further enriched with magnesium stearate and microcrystalline cellulose. After an additional minute of blending, the mixture was assessed for pre-compression characteristics. The necessary amount of the powder blend was manually weighed & transferred into the die of a rotary tablet press, using a capsule-shaped punch die to form caplet tablets (Dimensions: 8mm x 17mm with a breakline).

MH's gastroretentive floating matrix tablet was made of hydroxyl propylmethyl cellulose (HPMC K15M) and additional polymers in different concentrations, such as sodium alginate, xanthan gum, and kappa carrageenan. A variety of batches of metformin floating matrix tablets were made in order to maximise the amount of HPMC K15M. There was no change in the quantity of HPMC K15M. To maintain the tablet's overall weight at 1150 mg, the weight of the microcrystalline cellulose was changed. The prepared formulations' gastroretentive floating matrix tablet properties were assessed.

While the amounts of other polymers fluctuated, the amount of HPMC K15M remained constant. Pre-compression analyses of powder mixes were conducted, including Bulk Density, Tapped Density, Carr's Index, Hausner's Ratio & Angle of Repose. Using the direct compression technique, 750 mg of metformin tablets were made, the tablets were made with a variety of release-delaying polymers, including xanthan gum, sodium alginate, kappa-carrageenan, and HPMC K15M [1-10].

Table 1: Materials Used in the Formulation of Sustained Release Floating Tablets of Metformine Hydhrochloride

Sr No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Metformin	750	750	750	750	750	750
2	HPMC K15M	120	120	120	120	120	120
3	Sodium Alginate	90	130	-	-	-	-
4	k-Carrageenan	-	-	90	130	-	-
5	Xanthan gum	-	-	-	-	90	130
6	Sodium bicarbonate	130	130	130	130	130	130
7	MCC	50	10	50	10	50	10
8	Magnesium stearate	10	10	10	10	10	10
9	TOTAL	1150	1150	1150	1150	1150	1150

Pre-Compression Evaluation

Bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose were evaluated for all formulations.

Post-Compression Evaluation

Tablets were evaluated for weight variation, hardness, friability, drug content, floating lag time, total floating duration, adhesion retention period, and swelling index.

Drug-Excipient Compatibility

FTIR and DSC analyses were performed to assess drug-excipient compatibility.

In Vitro Drug Release

Dissolution studies were performed using USP Type II (paddle) apparatus in 0.1 N HCl for 24 hours.

Results and Discussion

Pre-Compression Evaluation

All powder blends demonstrated good flowability, with Carr's index < 15% and Hausner's ratio < 1.2 (Table 2).

Table 2: Precompression parameters of F1-F6 (Values expressed as mean ± SD)

Parameters					
Formulations	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**Angle of repose (θ)**	**Carr's Index (%)**	**Hausner's ratio**
F1	0.45±0.03	0.51±0.02	34.96±0.05	14.80±0.02	1.19±0.02
F2	0.46±0.01	0.53±0.01	31.31±0.03	14.79±0.07	1.18±0.01
F3	0.46±0.02	0.55±0.06	31.17±0.20	14.29±0.20	1.17±0.02
F4	0.47±0.03	0.55±0.01	31.24±0.10	14.30±0.02	1.15±0.01
F5	0.52±0.02	0.60±0.09	30.25±0.20	11.50±0.04	1.20±0.01
F6	0.53±0.01	0.62±0.02	30.92±0.03	12.40±0.03	1.12±0.01

Post-Compression Evaluation

Tablets were evaluated for weight variation, hardness, friability, drug content, floating lag time, total floating duration, adhesion retention period, and swelling index (Table 3).

Post Compression Evaluation of Metformin Hydrochloride

Table 3: Results of the Physical Properties of the MH Floating Matrix Tablets

Batch code	Weight variation	Hardness (kg/cm²)	Drug content (%)	Friability (%)	Floating Time (hrs.)	Tablet adhesion retention period (min.)	Swelling index (ratio)
F1	Conforms	4.1±0.28	98.92±0.94	0.23±0.16	> 8	74.25±2.54	1.734
F2	Conforms	5.7±0.95	100.91±0.43	0.22±0.17	> 8	73.37±4.43	3.864
F3	Conforms	5.7±0.43	99.04±0.74	0.29±0.08	> 8	120.30±3.67	2.755
F4	Conforms	5.2±0.55	99.62±0.31	0.29±0.21	> 8	69.52±2.44	2.851
F5	Conforms	5.2±0.95	99.43±0.65	0.13±0.14	> 8	81.41±2.31	2.501
F6	Conforms	4.7±0.54	99.56±0.42	0.19±0.11	> 8	88.43±1.53	2.827

Drug Excipient Compatibility Using FTIR

FTIR analysis is used to assess the drug's compatibility with the excipients. This investigation was done to look for any changes in the drug's chemical makeup after it was combined with the excipients.

Infrared spectra of the best formulation, drug containing polymers, and pure Metformin Hydrochloride were analysed to verify that the drug was intact in the formulation. Figure 1.

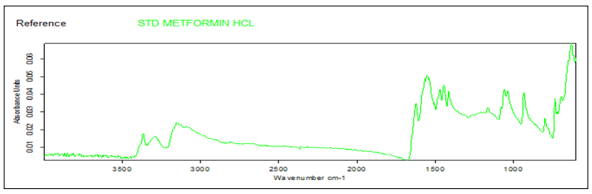

Figure 1: FTIR of Pure Drug Metformin Hydrochloride

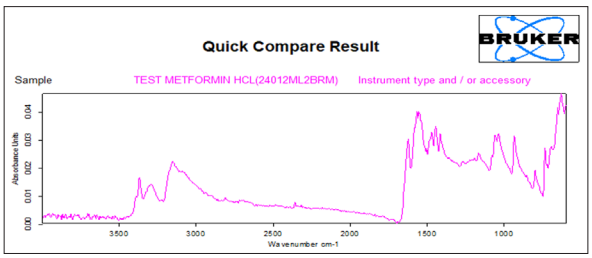

Figure 2: FTIR Spectrum of Metformin Hydrochloride along with all the Polymers and Excipients

FTIR Spectra of physical mixture of Metformin Hcl along with HPMC K15M, Sodium Alginate, k-Carrageenan, Xanthan Gum along with other excipients: The FTIR Spectra of physical mixture of Metformin Hcl along with HPMC K15M, Sodium Alginate, k-Carrageenan, Xanthan Gum along with other excipients shows that there is no interaction b/w the drug and polymers, as there is no characteristics change in the peaks of Metformin Hcl final FTIR. Hence the drug is compatible with these polymers and can be preceded for final formulation and evaluation parameters.

Differential Scanning Colorimetery (DSC) Studies

DSC curves obtained for pure Metformin Hydrochloride alone and Metformin Hydrochloride+ Excipients formulation were determined and results were shown in Figure No. 3&4. DSC thermogram of Pure powdered Metformin Hydrochloride showed a sharp endothermic peak at 165.7˚C. DSC thermo grams of Metformin Hydrochloride and Excipients showed endothermic peaks at 164.8˚C.

Since DSC profile of both Metformin Hcl pure drug as well as Metformin Hydrochloride and Excipient depicted the almost similar endothermic peaks that indicated that no physical interaction between drug and Excipients.

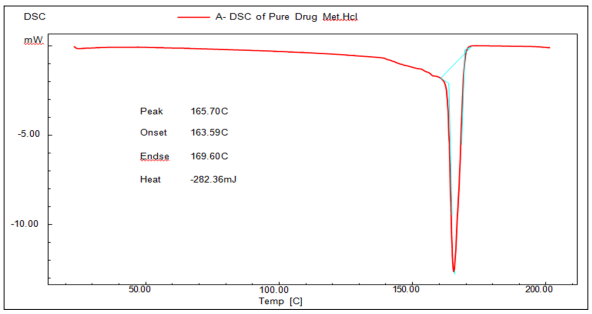

Figure 3: DSC of Pure Metformin Hydrochloride Drug

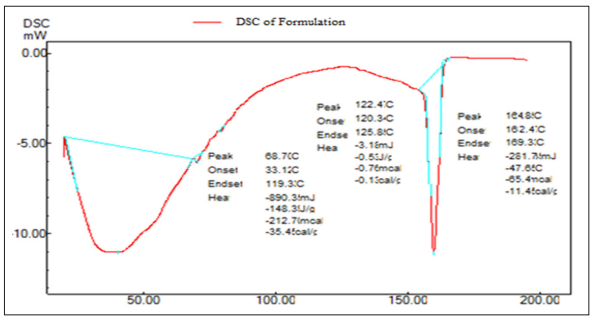

Figure 4: DSC of Metformin Hydrochloride with Excipients

In vitro Drug Release

The in vitro dissolution of the FDT was examined in a dissolution apparatus USP XXIII type-II with a paddle stirrer operating at 50 Rotation Per Minute, using 900 millilitre of phosphate buffer with a pH of 6.8 at 37±0.5oC as the dissolution medium.

Table 4: In Vitro Drug Release Data (F1-F6)

Time (hrs)	Formulation Code					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
3	25.28	6.06	6.53	11.72	30.63	5.53
6	41.02	14.13	13.42	20.67	50.55	11.31
9	50.99	24.68	25.21	30.11	64.12	19.7
12	58.05	33.11	35.39	40.33	71.48	25.67
15	76.96	45.88	57.33	66.23	82.50	40.45
18	90.07	71.32	75.58	87.12	91.20	55.66
21	92.12	88.10	86.68	95.22	93.39	73.33
24	94.01	99.60	87.80	98.76	94.01	74.95

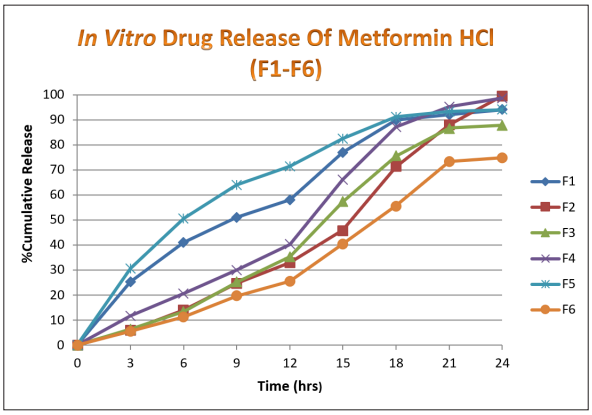

Figure 5: In Vitro Drug Release Data (F1-F6)

Drug Release Kinetics

Model-dependent release kinetics elucidates the mechanisms controlling the overall release of the drug from dosage forms. The findings from the evaluation of model dependent drug release kinetics are presented in Table 5.

F2 followed zero-order kinetics (R^2 = 0.9257), Higuchi model (R^2 = 0.9879), and Korsmeyer-Peppas model (R^2 = 0.9938), indicating non-Fickian, diffusion-controlled release.

Table 5: Results Table for in vitro Drug Model-Dependent Kinetics of MH Tablets

Batch code	Higuchi model (R) H	Korsmeyer Peppas model (RP)	Hixson Crowell model (RHC)	First order (R1)	Zero order (R0)
F1	0.9913	0.9965	0.9923	0.9765	0.9365
F2	0.9879	0.9938	0.9772	0.9663	0.9257
F3	0.9917	0.9898	0.9939	0.9201	0.9282
F4	0.9883	0.9838	0.9747	0.9284	0.9094
F5	0.9873	0.9788	0.9651	0.8529	0.9203
F6	0.9869	0.997	0.9904	0.9774	0.9305

Accelerated Stability studies of Formulation F2

Different temperature conditions were taken, at room temperature (25±20C), 300C/65% RH, 400C/75% RH, for a period of 2 months. Following parameters were analysed such as drug release, entrapment efficiency and swelling index of optimized formulations. The Metformin Hydrochloride SR Floating tablet after subjected to various condition as shown in Table 6. It was found that formulation was stable at room temperature.

Table 6: Accelerated Stability Studies of Formulation F2

Conditions of Stability	Time in Months	Appearance	Drug Content %
25°C/60% RH	0	Initial	99.90
	1	Unchanged	99.10
	2	Unchanged	98.90
30°C/65% RH	0	Initial	99.90
	1	Unchanged	99.00
	2	Unchanged	98.50
40°C/75% RH	0	Initial	99.90
	1	Unchanged	98.90
	2	Unchanged	97.90

Future Prospects

The development of sustained-release (SR) floating tablets of Metformin Hydrochloride using natural polymers such as kappa carrageenan presents a promising strategy for prolonged drug release and improved glycemic control in Type 2 diabetes. Future research can be significantly enhanced through the integration of Artificial Intelligence (AI) & Machine Learning (ML) technologies.

AI can optimize formulation development by predicting the ideal combination and concentration of polymers and excipients, minimizing the need for extensive experimental trials. This can reduce development time, lower costs, and enhance the efficiency of the formulation process. In silico simulations powered by AI can model gastrointestinal conditions more accurately, helping to predict the in vivo behavior of floating tablets, including gastric retention and drug release kinetics.

Furthermore, AI can facilitate personalized medicine by analyzing patient-specific factors to design individualized SR formulations. It can also aid in real-time monitoring of critical quality attributes (CQAs) during manufacturing, ensuring consistent product quality through Quality by Design (QbD) approaches. Additionally, AI-driven stability prediction models

can forecast long-term product stability, expediting regulatory approvals.

Overall, AI has the potential to transform SR floating drug delivery systems, enhancing therapeutic efficacy, patient adherence, and advancing the field toward precision healthcare.

Summary

The present study focused on the formulation and development of sustained-release (SR) floating tablets of Metformin Hydrochloride to enhance the therapeutic management of Type 2 diabetes mellitus. The primary objective was to design an oral dosage form capable of maintaining buoyancy in the gastric environment while releasing the drug in a controlled manner over an extended period. This was achieved by employing hydrophilic polymers, particularly hydroxypropyl methylcellulose (HPMC K15M), in combination with gas-generating agents such as sodium bicarbonate. These components facilitated tablet floatation, prolonged gastric retention, and controlled drug release.

A comprehensive preformulation and formulation development strategy was employed, including the evaluation of multiple formulations to optimize the concentration and combination of polymers and excipients. Critical parameters such as tablet density, swelling index, and in-vitro buoyancy were systematically assessed to ensure prolonged floatation (more than 8–12 hours) and consistent drug release. In-vitro dissolution studies simulated gastric conditions and demonstrated sustained drug release over a 12- to 24-hour period.

Among the various formulations, the optimized formulation (F2), comprising HPMC K15M and kappa carrageenan, exhibited a near zero-order release profile. This profile ensures steady plasma concentrations, thereby minimizing the fluctuations associated with conventional immediate-release tablets. The sustained release behavior supports once-daily dosing, improving patient adherence and enhancing the convenience of therapy.

The SR floating Metformin Hydrochloride tablets developed in this study offer multiple therapeutic advantages. These include prolonged gastric retention, controlled drug release, improved glycemic control, reduced dosing frequency, enhanced patient compliance, minimized gastrointestinal side effects, improved bioavailability, and the potential for dose reduction. Collectively, these benefits position the formulation as a valuable advancement in the pharmacological management of Type 2 diabetes mellitus [11-20].

Conclusion

In this study, sustained-release floating matrix tablets of Metformin Hydrochloride were successfully developed using the direct compression method. Preliminary formulations incorporated HPMC K15M as the release-retarding polymer, along with ionic and anionic polymers such as sodium alginate, kappa carrageenan, and xanthan gum. These formulations were evaluated for critical parameters including swelling behavior, floating duration, and in-vitro drug release. Among them, formulation F2, comprising HPMC K15M and kappa carrageenan, demonstrated superior performance with excellent floating behavior, prolonged gastric retention, and sustained drug release, achieving a cumulative drug release of 99.60% over 24 hours.

The gastroretentive mechanism of flotation was supported by additional mucoadhesion and swelling effects, particularly under conditions of low gastric fluid volume. Kappa carrageenan contributed significantly to these properties, creating a stable polymeric matrix ideal for prolonged gastric residence. A statistical mixture design further validated the optimal combination of HPMC K15M, kappa carrageenan, and sodium bicarbonate in achieving the desired release characteristics.

Kinetic modeling of the optimized F2 formulation indicated a zero-order release mechanism, supported by high regression values for Higuchi (R^2 = 0.9879), Korsmeyer-Peppas (R^2 = 0.9938), and Hixson-Crowell (R^2 = 0.9772) models, confirming consistent and controlled drug release. FTIR and DSC studies confirmed the compatibility of the drug with the selected excipients, with no evidence of physical or chemical interaction. Stability studies conducted under accelerated conditions (40°C ± 2ºC and 75% RH ± 5% RH) over a two-month period demonstrated the formulation's stability, with no significant changes in drug content or performance.

In conclusion, the optimized SR floating tablet formulation (F2) of Metformin Hydrochloride exhibits excellent gastroretentive properties, sustained drug release up to 24 hours, and stability, making it a promising candidate for further development and potential clinical application in the management of Type 2 diabetes mellitus.

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