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Research Article

Formulation and Evaluation of Extended-Release Bilayer Tablets Containing Empagliflozin and Metformin Hydrochloride for Diabetes Mellitus Management

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ABSTRACT

This study systematically evaluates the formulation development of bilayer tablets combining empagliflozin and metformin hydrochloride for diabetes mellitus management. The formulation design encompassed drug-excipient compatibility, flow characteristics, and the development of immediate and extended-release layers. Differential scanning calorimetry (DSC) confirmed compatibility between empagliflozin, metformin hydrochloride, and selected excipients (HPMC and Avicel), showing no significant variations in onset and peak melting points after 4 weeks of incubation. Flow properties were assessed and demonstrated excellent flow characteristics suitable for tablet formulation. Both pre and post-compression analyses were found to be within pharmacopoeial limits, in an attempt to define the best formulation parameters, a concept known as central composite design (CCD) as well as full factorial design (FD) were used. CCD experiments pointed to the strong impact of hydroxypropyl cellulose and croscarmellose content on the tableting properties. It was useful while employing the FD method in conducting a comprehensive evaluation of several factors affecting empagliflozin formulation to accomplish optimization. This detailed investigation underscores the importance of systematic assessments in formulating bilayer tablets with empagliflozin and metformin hydrochloride, ensuring stability, efficacy, and compliance, ultimately contributing to advancements in drug delivery systems and improved patient outcomes.

Introduction

Diabetes mellitus (DM) is a global health concern and the necessity of the improvement of the treatment approaches means that it is a constant concern. This, therefore, calls for the need to identify and expand the effectiveness and patient-oriented pharmaceutical technology of anti-diabetic drugs. Controlled-release systems are of great use while designing solid dosage forms that provide for extended release of therapeutic agents that should be employed in the effective management of diabetes.

Empagliflozin is an SGLT2 inhibitor for diabetes and metformin hydrochloride is a first-line drug in the oral diabetic agents. Empagliflozin reduces the reabsorption of glucose in the kidneys, and metformin – slows down the production of glucose in the liver. These mechanisms relate to several aspects of the disease pathophysiology. However, the conventional immediate-release formulations have drawbacks, evidently requiring more frequent doses and highly variable plasma drug concentration.[1]

Bilayer tablets represent an advanced formulation technique, integrating two distinct drug layers into a single dosage form. This method allows for precise control over drug release, utilizing extended-release technology to maintain consistent therapeutic levels, thus minimizing fluctuations and enhancing pharmacodynamic effects. This design improves patient compliance and mitigates adverse effects associated with peak drug levels.

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Thus, the objective of this research is to synthesize and characterize ER bilayer tablets of empagliflozin and metformin hydrochloride. With the help of pharmaceutical knowledge and experience concerning formulation concepts, an improved drug release profile is targeted in order to increase the effectiveness of anti-diabetic treatment regimes. Characterization of physicochemical properties and *in-vitro* dissolution studies will be employed to evaluate the performance of the developed formulation with the prospect for clinical applications.[2] This study seeks to contribute to the field of pharmaceutical sciences by advancing diabetic drug delivery systems, addressing the growing prevalence of diabetes, and meeting the demand for effective treatments. By exploring the intricate relationship between formulation design and therapeutic outcomes, this research aims to expedite the development of patient-centric pharmaceutical solutions for diabetes management.

Material and Method

Material

Empagliflozin (EMP), an API, was received from USV Pvt. Ltd., a reliable provider known for quality. This trusted provider provided high-quality empagliflozin for our research tasks. Metformin hydrochloride (MET), a vital API, was purchased from Alkem Laboratories Pvt. Ltd., a pharmaceutical business known for its high quality. APIs and excipients like microcrystalline cellulose (PH112), lactose spray dried (Supertab 11SD), hydroxypropyl cellulose, Ac-Di-Sol, and talc were carefully selected to perform specific functions.

Drug-Excipient Compatibility Study

Differential scanning calorimetry (DSC) was used to study the compatibility between the drug and excipient. Empagliflozin and metformin hydrochloride, together with additional substances, underwent controlled heating. Heat flow analysis revealed possible physical or chemical changes. Compatibility was evaluated by comparing thermograms of drug-excipient combinations with individual drug and excipient samples. DSC assisted in choosing suitable excipients and refining formulation parameters. [3]

Flow Properties

Bulk density

For determination of the bulk density, 10 g of the medication, which has been sieved through 30# sieve, was taken and poured into a 100 mL graduated cylinder. The powder used in the cylinder was packed in the same condition that it is used in and the apparent volume of the powder, referred to as Vo, was found before any compaction of the powder had occurred.

Tapped density

As for the mechanical taping the procedure involved the addition of 10 g of the medication into a 100 mL graduated cylinder. First, the cylinder was tapped with the aim of finding its volume. Then, the cylinder was filled with water, mounted and tapped 500 times (V1). Further, 750 taps were performed and the quantity of the content collected was described as volume V2.

Compressibility index

The flow characteristic of the powdered sample was measured through Carr's index to determine the compressibility index of the powder. An accurate amount of the powder was initially weighed and then filled into a graduate cylinder and the initial apparent density volume was taken. The cylinder was then tapped in the manner of a tapped density tester until the required quantity of powder inside the cylinder did not change anymore. The final tapped volume was documented.

Hausner's ratio

In which powder flow ability is measured, arching was determined by dividing the tapped density of the powder by its bulk density. For these values, a particular volume of the powder was accurately measured by using a graduated cylinder to get the bulk volume in order to get the bulk density. The oil powder was tapped in a tapped density tester until it gave a constant value of tapped density was obtained.

Angle of repose

The funnel flow test was extended to determine the flowability characteristics of the API powder, which includes the angle of repose. A right measure of the powder was put through a funnel onto a surface having no hindrance to the flow of the powder. From the compacted powder cone, the height (H) and the diameter (d) were measured.

Preliminary Trial Determination

Super-disintegrating agent for empagliflozin immediate-release layer screening

The direct compression method was employed to create the immediate-release layer containing 25 mg of empagliflozin. Ten batches (E1–E10) were prepared with varying amounts (2–5%) of super-disintegrants. These batches were evaluated for different parameters. [4]

Preliminary screening of polymer for extended-release of metformin

The extended-release layer containing 1,000 mg of metformin was formulated using the direct compression technique with carefully selected components and polymers. Ingredients such as HPMC K100M, colloidal silicon dioxide (Aerosil 200 Pharma), and sodium CMC (7HF PH) were incorporated in varying amounts, as

detailed in Table 1. Multiple batches were evaluated for different parameters (weight variation, thickness, hardness, friability, disintegration time, and drug content) to ensure consistent quality of the prepared layer. [5]

Experimental design for bilayer tablet formulation: central composite design (CCD)

During the initial phase, formulation factors at each manufacturing process stage were methodically analyzed for their importance using analysis of variance (ANOVA). The concentrations of binder and disintegrant had a substantial impact on the medication release of both the immediate release (IR) component containing empagliflozin and metformin. [6]

CCD for both parts

A CCD was used to fully analyze how independent factors affect both the immediate-release (IR) portion containing empagliflozin and the extended-release portion with metformin HCl. Both portions had independent variables of binder concentration (X1) and disintegrant concentration (X2). Y1 replies focused on tablet hardness in the immediate-release section, whereas Y2 responses were about drug release properties in the extended-release section.[7]

Experimental Design Using Design Expert

Utilizing Design Expert software (Stat-Ease, Version-12), the CCD was instrumental in exploring quadratic response surfaces. This advanced design approach aimed to provide a comprehensive understanding of the formulation variables and their effects on tablet hardness (Y1) and drug release percentage (Y2) for both parts.[8]

ANOVA Analysis

ANOVA was crucial in the experimental design to evaluate the relevance of the model and selected responses for both the immediate-release (IR) and extended-release parts. This statistical method was used to assess how changes in binder and disintegrant concentrations affect tablet hardness (Y1) and drug release percentage (Y2) for both components. Polynomial equations were created using ANOVA to measure the connections between variables and specified responses.

Evaluation Parameters of Bilayer Tablet

Evaluation of pre-compression and post-compression parameters.

Weight variation test

Weight variation test was performed according to IP standard; therefore, it can be concluded that the tablets in this batch have no variation in their weight. Altogether, 20 tablets were taken at random with the aim of calculating the weight of each of them. The percentage weight variation found was compared with the standards as mentioned in the Indian Pharmacopoeia and the percentage weight variation along with standard and percentages allowed are given in Table 2.[9]

Thickness

From each of the formulation tables, tablets were selected at random and their thickness was determined with the help of a vernier caliper scale, which is precise. This measurement was done with the purpose of ensuring timely compliance with certain guidelines. The thickness of the tablets was maintained at a standard level in order

Table 1: Preliminary screening of polymer for extended-release layer

Ingredients (mg)	*M1*	*M2*	*M3*	*M4*	*M5*	*M6*
Metformin HCL	1000	1000	1000	1000	1000	1000
Sodium CMC (7HF PH)	88.8	88.8	88.8	88.8	88.8	88.8
HPMC (K15M)	60	-	00	60 .00	-	-
HPMC (K100M)	60.00	-	-	-	60 .00	60.00
Colloidal silicon dioxide	60 .00	-	60.00	-	60 .00	-

Table 2: Primary screening of the disintegrating agent for EMP immediate release layer

Ingredients	*Quantity. (mg/tab)*									
	E1	*E2*	*E3*	*E4*	*E5*	*E6*	*E7*	*E8*	*E9*	*E10*
Empagliflozin	25	25	25	25	25	25	25	25	25	25
Microcrystalline cellulose (PH112)	51	50	48	51	50	49	51	50	49	48
Lactose spray dried (Supertab 11SD)	20	20	20	20	20	20	20	20	20	20
Hydroxy propyl cellulose (Klucel LF)	2	3	5	0	0	0	0	0	0	0
Croscamellose sodium	0	0	0	2	3	4	0	0	0	0
Croscarmellose sodium (Ac-Di-Sol)	0	2	0	2	0	3	2	0	0	5
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Total	100 mg/tab									

to achieve a variation that was not more than ± 0. About 5% of the standard value is added as an injunction so as to maintain standards of formulations. [10]

Hardness

It was measured using a Monsanto tablet hardness tester. The results were expressed in kg/cm^2, where the tablet was positioned lengthwise between two plungers. To maintain the tablet's physical integrity, the hardness limits were carefully controlled within a range of 4 to 6 kg/cm^2, ensuring consistency in its physical properties.

Friability test

In which the tablets were assessed using a Roche friabilator, where they were tumbled at 25 rpm and dropped from a 6-inch height with each turn. Initially, the tablets were weighed and then subjected to 100 revolutions, followed by dust removal and re-weighing.

Wetting time

A 25 x 10 cm tissue paper sample was folded and placed in a small petri dish with an internal diameter of 5 cm. Then, 6 mL of distilled water was added. The wetting time and water absorption ratio were measured, and the time taken for the tablet to completely contact the paper was recorded in seconds.[12]

Drug Content for Empagliflozin

It was assessed by weighing 10 samples from each of the batches and measuring the average weight of each batch against the manufacturer's recommended weights. The obtained tablets were also pulverized into fine powder and 0. 5 g equivalent to empagliflozin 100 mg was dissolved in 100 mL of 1N HCl contained in a volumetric flask. The solution was sonicated for 1-hour and the solution was again diluted with water. The concentration of the drug in 1N HCl was determined through a high-pressure liquid chromatography at a wavelength of 215 nm. [13-15]

Drug Content for Metformin

The content of the drugs in the tablets was determined by weighing ten pills from every container and comparing it with the normal weight values. Metformin was quantitatively estimated by dissolving 100 mg of the crushed tablets into 100 mL of concentrated HCl-titre late 1N in a volumetric flask. The solution was sonicated for 30 minutes to make sure it was completely dissolved with the surrounding solution. Post dilution of the samples, the load of metformin was estimated using HPLC working at 215 nm wavelength. This method enables the determination of metformin content with high confidence and at the same time observing quality requirements and procedures. [16]

Disintegration Test

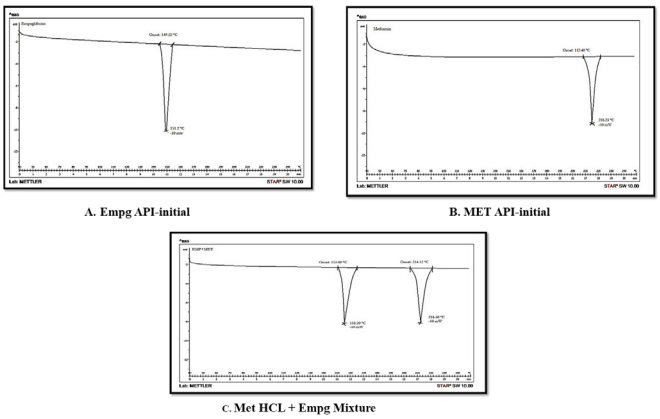
The disintegration test was done by USP XXII, which involves a USP disintegration apparatus with six tubes, all with a length of three inches and the other end closed. These tubes were deposited on a 10-mesh screen at the base of the basket rack assembly. One of the tablets, 0. 5 x 0. 5 cm in size, was then placed on the basket and 100 mL water was added to the beaker to make a total of 1 L of water at 37 ± 2°C. The assembly was vertically shifted in motion with motorized equipment. These tablets were regarded as having passed the test if all the particles had disintegrated and those that passed through the 10-mesh screen within the set time and the results were proven to dissolve appropriately in the presence of fluids as governed by the appropriate physiological conditions for efficient absorption to take place. [17-20]

Result and Discussion

Compatibility Study

The DSC drug-excipient compatibility research: Initial samples and those incubated at 40°C/75% RH for 4 weeks were compared for empagliflozin, metformin hydrochloride, and their composite blends with chosen excipients' onset and peak melting points After 4 weeks, empagliflozin API's onset melting point was 149.22 and 149.35°C, and its peak melting point was 151.2 to 153.14°C. After 4 weeks, metformin hydrochloride API's start melting point increased from 212.40 to 213.36°C, but its peak melting point climbed from 216.2 to 218.21°C (Fig. 1). The start and peak melting values of empagliflozin and metformin hydrochloride composite blends with HPMC and Avicel excipients were similar after 4 weeks. After 4 weeks, empagliflozin composite blend with Avicel increased its onset melting point from 80.10 to 85.40°C and peak melting point from 150.13 to 156.10°C.

Fig. 2 demonstrates that after 4 weeks, the metformin composite mix with HPMC raised the start melting point from 70.05 to 72.10°C and the peak melting point from 210.21 to 215.20°C Both initial and 4-week samples revealed similar onset and peak melting values for all drug components and excipients. Over the 4-week incubation period, empagliflozin, metformin hydrochloride, HPMC, and avicel did not interact. Both HPMC and Avicel

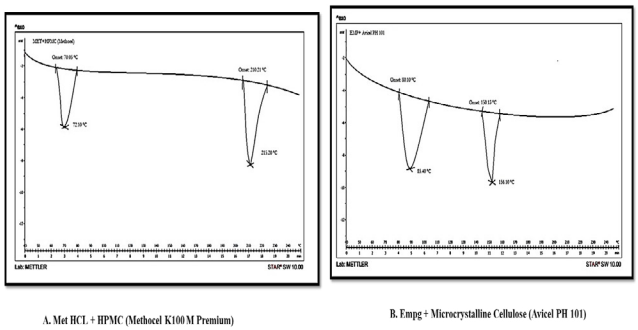


A. Empg API-initial

B. MET API-initial

C. Met HCL + Empg Mixture

Fig. 1: DSC of API and physical mixture



A. Met HCL + HPMC (Methocel K100 M Premium) B. Empg + Microcrystalline Cellulose (Avicel PH 101)

Fig. 2: DSC (API + Polymer Mixture)

were compatible with empagliflozin and metformin hydrochloride, making them acceptable for formulation development in pharmaceutical products containing these medicines, ensuring stability and efficacy. Both pure pharmaceutical substances had stable and low breakdown constants throughout incubation, according to DSC thermograms. These discoveries affect pharmaceutical development, quality assurance, and formulation.

Flow Properties of Drug and Excipients

According to Table 3, metformin HCl, empagliflozin, Avicel PH 101, Pharmatose 200M, Klucel HF, Ac-di-sol, magnesium stearate and ethyl cellulose have very good flow properties with angle of repose values which range from 19. 52 ± 2. 41 to 28. 22 ± 2. 73. Carr's index ranging between 9 relieved that the samples had excellent to good compressibility. 6 ± 0. 2 to 15. 0 ± 0. 2% while Hauser gives the ratio of 1. 10 ± 0. 3 to 1. 23 ± 0. 3.

Formulation and Development

Immediate release layer of empagliflozin

- *Evaluations of batches E1 to E10 (Pre-compression)*

The blend of granules and powder for all ten formulations demonstrated the following characteristics: bulk density varied from 0. 252 to 0. 385 g/mL, the maximum tapped density varied from 0. 285 to 0. 442 g/mL, while Carr's index ranged from 11 to 13.5%. These results observed in the study are evident in Table 4; it shows that the powder blend flows well and compresses well too.

- *Evaluations of batches E1 to E10 (Post-compression)*

Physical property tests were performed on all pill preparations after preliminary evaluation. Table 5 shows the parameters for batches E1–E10. All pill weights (H1–H10) varied within ± 7% in weight variation tests. Pharmacopoeia level 5%. From 2.57 to 2.84 mm tensile strength in 430 countries ranged from 35 to 015 mm, whereas hardness ranged from 3.14 to 3.52 kg/cm^2. Friability scores below 1% indicate good mechanical

Table 3: Flow properties of drug and excipients

Ingredients	*BD (gm/mL)*	*TD (gm/mL)*	*CI (%)*	*HR*	*AR (θ)*
Metformin	0.58 ± 0.002	0.64 ± 0.001	11.30 ± 0.12	1.24 ± 0.32	22.3 ± 0.34
Empagliflozin	0.512 ± 0.02	0.598 ± 0.4	14.38 ± 0.3	1.16 ± 0.1	25.35 ± 2.73
Microcrystalline cellulose	0.54 ± 0.01	0.63 ± 0.3	14.28 ± 0.3	1.16 ± 0.2	25.2 ± 2.94
Hydroxypropyl cellulose (Klucel LF) (Binnder)	0.51 ± 0.03	0.60 ± 0.3	15.0 ± 0.2	1.17 ± 0.3	23.34 ± 2.75
Croscarmellose sodium (Ac-di-sol) (Disintegrant)	0.56 ± 0.02	0.64 ± 0.2	12.5 ± 0.3	1.14 ± 0.3	27.21 ± 2.65
Lactose monohydrate (Pharmatose 200M)	0.56 ± 0.03	0.62 ± 0.3	9.6 ± 0 .2	1.10 ± 0.3	26.31 ± 2.83
Ethyl cellulose	0.62 ± 0.05	0.70 ± 0.03	11.1 ± 0.2	1.23 ± 0.3	25.20 ± 2.25
Magnesium stearate	0.58 ± 0.01	0.65 ± 0.05	10.5 ± 0.1	1.11 ± 0.5	25.16 ± 1.01

Table 4: Evaluations of batches of E1 to E10 (Pre-compression)

Batch	*BD (gm/mL)*	*TD (gm/mL)*	*CI (%)*	*HR*	*AR (θ)*
E1	0.260 ± 0.21	0.309 ± 0.20	12.91 ± 0.21	1.128 ± 0.047	24.04 ± 2.12
E2	0.275 ± 0.31	0.322 ± 0.38	12.31 ± 0.1	1.130 ± 0.025	25.14 ± 2.35
E3	0.311 ± 0.32	0.352 ± 0.34	11.33 ± 0.75	1.118 ± 0.022	24.03 ± 1.48
E4	0.265 ± 0.22	0.307 ± 0.41	13.68 ± 1.20	1.158 ± 0.010	23.56 ± 1.36
E5	0.252 ± 0.25	0.292 ± 0.29	13.69 ± 1.10	1.159 ± 0.012	28.60 ± 2.12
E6	0.274 ± 0.30	0.320 ± 0.21	14.37 ± 1.19	1.168 ± 0.007	22.52 ± 1.32
E7	0.385 ± 0.21	0.442 ± 0.39	12.89 ± 1.25	1.148 ± 0.025	26.56 ± 2.01
E8	0.275 ± 0.22	0.320 ± 0.25	14.06 ± 1.29	1.164 ± 0.05	24.20 ± 1.31
E9	0.252 ± 0.30	0.285 ± 0.20	11.57 ± 1.25	1.131 ± 0.02	24.25 ± 1.35
E10	0.268 ± 0.24	0.302 ± 0.22	12.40 ± 1.05	1.134 ± 0.12	23.55 ± 1.30

Table 5: Evaluation parameters of batches E1 to E10 (Post-compression)

Batch	*Weight variation*	*Thickness (mm)*	*Hardness (kg/cm^2)*	*%Friability*	*Disinteg ration time (sec)*	*Wetting time (sec)*	*%Drug Content*
E1	100.70 ± 0.14	2.55 ± 0.04	3.50 ± 0.05	0.43 ± 0.02	37 ± 1	28.10 ± 0.06	99.17 ± 0.07
E2	100.70 ± 0.05	2.54 ± 0.02	3.10 ± 0.04	0.46 ± 0.15	36 ± 2	27.05 ± 0.17	98.58 ± 0.04
E3	100.70 ± 1.07	2.54 ± 0.04	2.98 ± 0.14	0.46 ± 0.03	38 ± 1	28.06 ± 0.04	98.41 ± 0.08
E4	100.10 ± 0.45	2.54 ± 0.02	3.60 ± 0.11	0.46 ± 0.01	44 ± 1	35.04 ± 0.05	99.17 ± 0.06
E5	100.90 ± 0.78	2.57 ± 0.05	3.20 ± 0.09	0.47 ± 0.06	42 ± 2	34.05 ± 0.09	100.5 ± 0.05
E6	100.40 ± 0.34	2.54 ± 0.05	2.98 ± 0.07	0.47 ± 0.02	41 ± 2	34.13 ± 0.12	102.4 ± 0.09
E7	100.70 ± 1.89	2.54 ± 0.03	3.50 ± 0.03	0.46 ± 0.02	33 ± 1	27.14 ± 0.14	98.17 ± 0.04
E8	100.50 ± 0.22	2.55 ± 0.03	3.12 ± 0.05	0.49 ± 0.03	32 ± 1	26.12 ± 0.16	99.48 ± 0.17
E9	100.90 ± 0.67	2.56 ± 0.04	2.98 ± 0.08	0.49 ± 0.02	31 ± 2	23.10 ± 0.14	101.4 ± 0.11
E10	100.80 ± 1.35	2.55 ± 0.04	2.97 ± 0.08	0.40 ± 0.32	33 ± 1	24.95 ± 0.13	102.5 ± 0.13

Table 6: Pre-compression evaluations (Preliminary Batches)

Batch code	*BD (gm/mL)*	*TD (gm/mL)*	*CI (%)*	*HR*	*AR (θ)*
M1	0.27 ± 001	0.31 ± 0.001	12.73 ± 0.001	1.15 ± 0.001	23.52 ± 0.001
M2	0.28 ± 001	0.32 ± 0.001	12.76 ± 0.001	1.15 ± 0.001	23.54 ± 0.001
M3	0.28 ± 001	0.33 ± 0.001	12.21 ± 0.001	1.15 ± 0.001	22.55 ± 0.001
M4	0.29 ± 001	0.32 ± 0.001	11.62 ± 0.001	1.11 ± 0.001	22.06 ± 0.001
M5	0.27 ± 001	0.31 ± 0.001	12.73 ± 0.001	1.15 ± 0.001	22.96 ± 0.001
M6	0.29 ± 001	0.33 ± 00.001	11.94 ± 0.001	1.14 ± 0.001	22.36 ± 0.001

Table 7: Pre-compression evaluations of preliminary batches

Batch code	*Weight variation*	*Thickness (mm)*	*Hardness (kg/cm^2)*	*%Friability*	*%Drug Content*
M1	Passed	3.47 ± 0.001	2.20 ± 0.001	0.30 ± 0.05	98.2 ± 0.04
M2	Passed	3.67 ± 0.001	2.22 ± 0.001	0.32 ± 0.05	98.5 ± 0.04
M3	Passed	3.54 ± 0.001	2.18 ± 0.001	0.38 ± 0.05	99.1 ± 0.04
M4	Passed	3.51 ± 0.001	2.26 ± 0.001	0.36 ± 0.05	98.7 ± 0.04
M5	Passed	3.56 ± 0.001	2.35 ± 0.001	0.32 ± 0.05	97.6 ± 0.04
M6	Passed	3.58 ± 0.001	2.28 ± 0.001	0.34 ± 0.05	96.4 ± 0.04

strength in tablets. The samples were wetted for 12 to 35 seconds and absorbed 50 to 81% water. For 41% of the 30 samples examined, drug content variability ranged from 98. 22 ± 0. 43% to 99. 85 and 29 ± 0.5, 38 seconds. All manufactured pills had improved physical characteristics.

Extended-release layer of metformin HCL

- *Evaluations of granules of preliminary batches (Pre-compression)*

The average particle density of the six formulations ranged from 0.27 to 0.29. Water was added to the powder to obtain these densities, with bulk density varying from 0.42 to 0.002 g/cm^3 and tapped density between 0.30 to 0.35 g/cm^3. Carr's index was calculated, ranging from 11.39 to 12.76%. The angle of repose was between 22 and 28º, indicating good flowability. As shown in Table 6, the compressibility and flowability of the powder mix were rated from excellent to very excellent.

- *Evaluation of Preliminary Batches (Post compression)*

The tablets were tested for parameters for samples M1-M6. All met the ±5% weight variation limit, with thickness between 4.51 to 4.67 mm, hardness of 3.18 to 3.35 kg/cm^2, and friability at 0.26 to 0.48%. The drug content ranged from 99 to 101%, indicating good mechanical strength and optimal physical properties (Table 7).

Experimental design for bilayer tablet formulation

Central composite design (CCD) was used to examine the effects of X1–Hydroxypropyl cellulose and X2–Croscarmellose on the critical quality attributes of bilayer tablet formulation. The CCD trials' results, displayed in Table 8, provide useful insights into the correlations between formulation factors and critical responses: The dependent variables were hardness (Y1), drug release percentage (Y2) and friability percentage (Y3).

Table 8: Central composite design (CCD) for the formulation and their results

S. No.	*Hydroxypropyl cellulose (mg) (X1)*	*Croscarmellose (mg) (X2)*	*Hardness (Kg/cm^2) (Y1)*	*Drug release (%) (Y2)*	*Friability (%) (Y3)*
B1	11	30	9.5	55.7	0.67
B2	30	11	13.7	92.2	0.98
B3	20.50	33.94	12.3	76.7	0.83
B4	20.50	20.50	12.3	86.6	0.86
B5	11	11	11.3	79.6	0.74
B6	20.50	20.50	12.6	79.4	0.86
B7	7.06	20.50	9.4	65.6	0.54
B8	20.50	20.50	13.4	78.5	0.84
B9	20.5	20.50	12.9	79.8	0.82
B10	33.94	20.50	13.6	98.2	0.77
B11	30	30	13.6	95.1	0.67
B12	20.50	7.06	11.8	72.6	0.87
B13	20.50	20.50	12.4	84.3	0.66

The analysis of the results revealed differences in the responses, proving how formulation variables influenced tablet qualities. That is why formulations B2 and B10 have the highest drug release percentages equal to 92.2% and 98.2%, respectively. On the other hand, the friability percentages that were obtained for formulations B7 and B;1 were the lowest and noted to be 0. 54 and 0. 67%, respectively.

- *Evaluation of CCD design for empagliflozin*

The formulation optimization study was assessed using a CCD. Each component of this design was explored in all possible ways making it quite exhaustive in its approach. This method is very useful in analyzing the effects of particular variables, which are known as the main effects, as well as interactions, all of which impact the overall number of tests significantly. The factorial design enabled the assessment of a number of factors affecting the formation of empagliflozin, which proved to be valuable in the optimization context.

Table 9: Evaluations of batches ED1 to ED9 (Pre-Compression)

Batch code	*Bulk density (gm/mL)*	*Tapped density (gm/mL)*	*Carr's index (%)*	*Hausner's ratio*	*Angle of repose (θ)*
ED1	0.250 ± 0.30	0.290 ± 0.24	13.79 ± 1.23	1.15 ± 0.035	22.54 ± 0.02
ED2	0.290 ± 0.35	0.330 ± 0.30	12.12 ± 1.21	1.14 ± 0.015	22.36 ± 0.09
ED3	0.320 ± 0.33	0.350 ± 0.35	8.57 ± 1.80	1.14 ± 0.057	22.38 ± 0.09
ED4	0.250 ± 0.28	0.280 ± 0.37	10.71 ± 1.28	1.16 ± 0.05	23.82 ± 0.07
ED5	0.280 ± 0.22	0.320 ± 0.27	12.50 ± 1.15	1.18 ± 0.07	23.38 ± 0.06
ED6	0.220 ± 0.27	0.270 ± 0.24	18.51 ± 1.10	1.12 ± 0.071	24.80 ± 0.05
ED7	0.270 ± 0.25	0.300 ± 0.29	10.00 ± 1.24	1.16 ± 0.025	23.81 ± 0.03
ED8	0.290 ± 0.28	0.320 ± 0.35	9.37 ± 1.30	1.16 ± 0.025	23.86 ± 0.31
ED9	0.270 ± 0.32	0.310 ± 0.25	12.90 ± 1.45	1.11 ± 0.011	23.85 ± 0.07

Table 10: Evaluation parameters of full factorial design batches (Post-Compression)

Batch code	*Weight variation (n = 20)*	*Thickness (mm) (n = 3)*	*Hardness (kg/cm^2) (n = 3)*	*%Friability (n = 5)*	*Disintegr ation time (sec)*	*Wetting time (sec)*	*%Drug Content (n=10)*
ED1	99.40 ± 0.14	2.56 ± 0.04	3.30 ± 0.088	0.45 ± 0.06	31.10 ± 0.17	25.0 ± 0.45	99.17 ± 0.05
ED2	100.60 ± 0.07	2.53 ± 0.05	3.22 ± 0.068	0.44 ± 0.05	29.20 ± 0.29	24.33 ± 0.57	98.58 ± 0.07
ED3	100.80 ± 1.08	2.54 ± 0.07	3.18 ± 0.032	0.45 ± 0.04	28.23 ± 0.14	22.62 ± 0.87	99.41 ± 0.06
ED4	099.50 ± 0.56	2.57 ± 0.05	3.26 ± 0.028	0.47 ± 0.07	30 .34 ± 0.27	22.66 ± 0.87	99.17 ± 0.05
ED5	100.70 ± 0.57	2.58 ± 0.04	3.35 ± 0.045	0.44 ± 0.05	28.54 ± 0.24	19.34 ± 0.59	100.5 ± 0.07
ED6	100.90 ± 0.78	2.55 ± 0.07	3.28 ± 0.016	0.47 ± 0.03	26.34 ± 0.17	18.66 ± 0.32	100.4 ± 0.06
ED7	100.40 ± 1.55	2.55 ± 0.06	3.20 ± 0.035	0.49 ± 0.04	26.54 ± 0.14	15.33 ± 0.25	99.17 ± 0.05
ED8	099.40 ± 0.67	2.55 ± 0.04	3.30 ± 0.093	0.46 ± 0.06	24.43 ± 0..27	14.63 ± 0.78	99.48 ± 0.06
ED9	100.70 ± 0.56	2.53 ± 0.06	3.42 ± 0.082	0.44 ± 0.05	23.46 ± 0.89	13.16 ± 0.85	99.54 ± 0.07

Table 11: %CDR of full factorial design batches (ED1–ED9)

Time (Min)	*ED1*	*ED2*	*ED3*	*ED4*	*ED5*	*ED6*	*ED7*	*ED8*	*ED9*
0	0	0	0	0	0	0	0	0	0
5	60.7 ± 1.57	63.4 ± 2.31	63.2 ± 1.43	64.7 ± 1.77	72.1 ± 1.73	74.4 ± 1.82	70.4 ± 2.21	76.7 ± 1.12	76.9 ± 1.68
10	61.2 ± 1.25	72.7 ± 1.91	71.8 ± 1.75	75.9 ± 2.36	75.6 ± 1.92	83.3± 2.09	79.5 ± 1.85	85.4 ± 1.29	85.7 ± 1.53
15	82.4 ± 1.43	85.9 ± 2.33	85.3 ± 1.55	83.5 ± 1.89	84.3 ± 1.67	85.3 ± 2.57	89.4 ± 2.89	95.3 ± 2.40	94.9 ± 1.97
20	84.3 ± 1.23	90.1 ± 1.36	93.5 ± 1.14	91.1 ± 1.41	93.2 ± 1.39	94.7 ± 1.81	95.9 ± 1.18	97.3 ± 2.22	96.9 ± 1.38
30	97.1 ± 1.80	98.2 ± 1.32	97.9 ± 1.26	98.1 ± 1.71	98.4 ± 1.47	98.6 ± 1.77	96.7 ± 1.86	98.2 ± 2.36	99.0 ± 1.39

Table 12: Evaluations of batches MD1 to MD9 (Pre-compression)

Batch Code	*Bulk density (gm/cm^3)*	*Tapped density (gm/cm^3)*	*%Carr's index*	*Hausner's ratio*	*Angle of repose (θ)*
MD1	0.479	0.568	11.72	1.10	21.54
MD2	0.522	0.568	10.42	1.11	22.36
MD3	0.522	0.626	11.84	1.14	21.31
MD4	0.449	0.544	11.92	1.26	22.82
MD5	0.554	0.623	12.39	1.15	23.38
MD6	0.413	0.502	11.18	1.10	20.80
MD7	0.004	0.536	11.94	1.18	23.81
MD8	0.007	0.418	10.94	1.11	22.86
MD9	0.505	0.808 7	11.	1.10	20.75

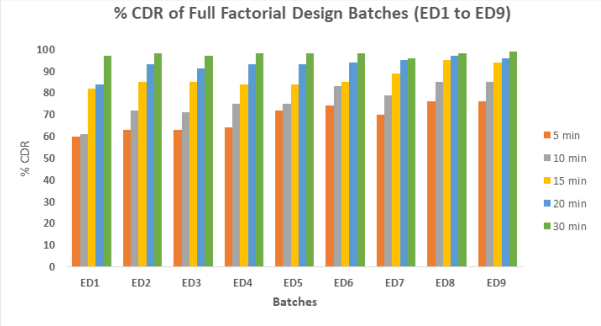


Fig. 3: % CDR Of Batches ED1–ED9

Evaluation of batches ED1 to ED9 (Pre-compression)

All the pre-compression characteristics were determined: the bulk density improved gradually (0.220–0.290 g/cm^3), the tapped density (0.270–0.350 g/cm^3), Carr's index (11.92–13%). Table 9 presents these findings as follows: Both the granules confirm a flow characteristic of the scale of excellent to satisfactory and confirm a compressibility characteristic of the scale of excellent to appreciable.

Evaluation of batches ED1 to ED9 (Post-compression)

After that, the general characteristics of tablets from each sample were evaluated. Table 10 summarises Mean ± SD values of the parameter for trial formulations containing four different types of excipients. Tablet weights varied between 249. 085 to 251. 24 Their mean values were 018 mg and all of them oscillated within the range of the pharmacopeia limits that were not more than ±5%. Thickness varied from 3. 20 to 3. 60 mm. The thickness of the vortex chamber was 041 mm and hardness varied from 5. 11. 023 to 5. 94 kg/cm^2. Friability was between 0. 44 and 0. 81%. Thus, the obtained values are on the level of 03% which proves good mechanical strength. Drug content was as follows: 98.13 to 99.86%. Periodically, the granules kept all the physical characteristics standards after the compression was attained.

In-vitro drug release

A comprehensive *in-vitro* experiment examined how super disintegrant concentration affected batch ED1 to ED9 medication release. Table 11 and Fig. 3 show

Table 13: Evaluation parameters of full factorial design batches (Post-Compression)

Batch code	*Weight variation*	*Diameter (mm)*	*Thickness (mm)*	*Hardness (kg/cm^2)*	*%Friability*	*%Drug Content*
MD1	249.40 ± 0.18	5.90 ± 0.002	4.22 ± 0.037	5.48 ± 0.018	0.73 ± 0.03	90.40 ± 0.36
MD2	250.60 ± 0.07	5.98 ± 0.003	4.57 ± 0.047	5.61 ± 0.0 58	0.68 ± 0.15	95.45 ± 1.18
MD3	251.83 ± 1.07	5.93 ± 0.004	4.36 ± 0.041	5.48 ± 0.03	0.73 ± 0.04	94.86 ± 1.52
MD4	250.50 ± 0.56	5.95 ± 0.03	4.30 ± 0.05	5.83 ± 0.098	0.53 ± 0.015	96.13 ± 2.23
MD5	250.70 ± 0.57	5.97 ± 0.002	4.28 ± 0.075	5.83 ± 0.055	0.53 ± 0.03	95.33 ± 1.52
MD6	250.90 ± 0.78	5.96 ± 0.002	4.41 ± 0.095	5.94 ± 0.036	0.44 ± 0.017	96.26 ± 1.32
MD7	251.43 ± 1.55	5.92 ± 0.004	4.48 ± 0.02	5.69 ± 0.015	0.62 ± 0.02	96.60 ± 1.87
MD8	250.45 ± 0.67	5.96 ± 0.04	4.42 ± 0.015	5.11 ± 0.023	0.81 ± 0.45	97.70 ± 0.71
MD9	250.70 ± 0.56	5.97 ± 0.01	4.25 ± 0.32	5.73 ± 0.208	0.59 ± 0.45	98.52 ± 1.47

Table 14: %CDR of full factorial design batches (MD1–M9)

Time hrs	*MD1*	*MD2*	*MD3*	*MD4*	*MD5*	*MD6*	*MD7*	*MD8*	*MD9*
0	0	0	0	0	0	0	0	0	0
0.5	12.7 ± 1.15	12.5 ± 1.24	12.2 ± 1.17	22.2 ± 2.36	11.9 ± 1.72	13.7 ± 2.67	21.1 ± 1.63	18.3 ± 2.55	30.2 ± 2.40
1	26.70 ± 2.67	29.33 ± 0.57	27.62 ± 0.87	26.66 ± 0.87	23.34 ± 0.59	17.66 ± 0.32	18.33 ± 0.25	19.63 ± 0.78	16.16 ± 0.85
2	50.08 ± 1.41	45.20 ± 0.29	68.23 ± 014	60.34 ± 0.27	54.54 ± 0.24	50.34 ± 0.17	40.54 ± 0.14	42.43 ± 0..27	45.46 ± 0.89
4	70.07 ± 1.81	59.9 ± 2.33	86.3 ±1.55	80.5 ± 1.89	74.3 ± 1.67	73.3 ± 2.57	76.4 ± 2.89	68.3 ± 2.40	69.9 ± 1.97
6	84.83 ± 1.34	86.11 ± 1.34	96.12 ± 1.34	92.18 ± 1.34	90.68 ± 1.34	92.43 ± 1.34	93.78 ± 1.34	91.38 ± 1.34	93.58 ± 1.34
8	81.92 ± 2.37	90.40 ± 1.86	97.30 ± 1.78	93.22 ± 1.23	91.5 ± 1.85	93.2 ± 2.56	95.5 ± 1.64	92.1 ± 2.17	95.6 ± 1.35
10	80.0 ± 1.55	85.87 ± 1.36	95.48 ± 2.34	93.1 ± 2.54	95.5 ± 1.52	96.6 ± 1.20	97.2 ± 1.57	97.7 ± 1.15	98.9 ± 1.25

Table 15: Fitting of drug release profile optimized (MD 9) batch to kinetic models

Batch	*Model*	*Parameters Used*				
		R^2	*R*	*K*	*SSR*	*AIC*
MD 9	Zero-order	0.7329	0.9394	13.175	2280.0511	63.6024
	First-order	0.9673	0.9912	0.352	220.073	41.4784
	Higuchi	0.9912	0.9953	33.398	75.0357	33.3172
	Korsemeyer – Peppas	0.9925	0.9978	34.104 n=0.472	62.3190	38.5197
	Hixson Crowell	0.9516	0.9872	0.090	325.4078	49.8863

that super disintegrant concentration correlated with medication release. After assaying all batches, batch ED9 with the optimal super disintegrant concentration had the best drug release profile. Batch ED9 had an outstanding 93% drug release. About 9% at 15 minutes compared to other formulations. Batch ED9 released 100% of its medicines at 30 minutes, demonstrating its performance. The detailed analyses show the importance of super disintegrant, especially in regulating the active ingredient release rate and presenting batch ED 9 as the best preparation of all the evaluated ones. The findings help accelerate the formulation process and provide innovative pharmaceutical formulations that improve patient outcomes.

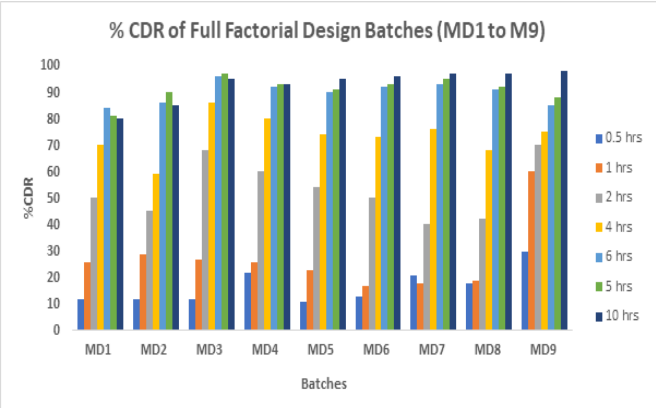


Fig. 4: %CDR of MD1–M9

- *Evaluation 3^2 full factorial design for metformin*

Full factorial design means investing all aspects of the experiment that can bring better insight into the primary effects of defined factors as well as their interactions with the least expense and effort. Hence, for the current formulation optimisation study, a CCD was chosen.

- *Evaluation of batches MD1 to MD9 (Pre-compression)*

The pre-compression attributes of the powder were determined. Variation on bulk density was between 0. 513 to 0. 654. 142 to 0. 045, having a tapped density ranging from 0. 007 to 0. 565 g/cm^3. 602 ± 0. 007 to 0. 773 ± 0. Mean cell density was recorded to be 0. 003 g/cm^3 for all the formulations. Carr's index was between 11. 92 and 13. 39%, while Hausner's ratio ranged between 1. 14 to 1. 18. The angle of repose ranged from 22 degrees. 36 ± 0. 09° to 25. 38. Table 12 showed that all the granules had variable flowability and compressibility which were from outstanding to acceptable level.

- *Evaluation of batches MD1 to MD9 (Post-compression)*

Table 13 presents the mean and standard deviations of various tablet parameters for nine formulations. Tablet weights ranged from 249.62 to 251.24 mg, within the ±5% pharmacopeia limit. Thickness varied from 3.20 ± 0.037 to 3.60 mm, and density ranged from 0.792 to 0.846 g/cm^3. Hardness was between 5.11 and 5.94 kg/cm^2, and friability ranged from 0.44 to 0.81%, indicating good mechanical strength with high-quality composite materials.

In-vitro Drug Release of Batches MD1 to MD9

A series of control experiments about the %CDR values of Batch MD1 to MD9 were conducted. The detailed results are shown in (Table 14, Fig. 4). Thus, the graphic illustrates that with increased polymer concentration, more medication is released. The findings revealed that the sample prepared from batch MD9, which depicted the ideal polymer concentration, exhibited the highest drug released 98.52 ± 1.47% after the 10 hours. It was considered the most optimized of all the formulated batches of the product.

Drug Release Kinetic

The best model was identified by the highest R^2 value, smallest SSR, and AIF index. The Korsmeyer-Peppas model showed an R^2 value of 0.9925, confirming the release kinetics. The release exponent 'n' ranged from 0.45 to 0.89, indicating a diffusion-controlled drug release mechanism (Table 15).

Conclusion

In conclusion, this research demonstrates the successful synthesis and evaluation of bilayered extended-release tablets for diabetic mellitus therapy. Upon further assessment, there was a realization that HPMC and avicel do not react with the active ingredients and thus, the formulation will remain stable for long periods. Flow properties results revealed quite high values, indicating good and reproducible methods of manufacturing tablets. The findings also show that the created formulation can accommodate other stringent pharma requirements, such as drug compatibility and optimal production. The enhancement demonstrated below suggests the likelihood of bringing positive outcomes to compliance with patients and treatment in diabetes. This is an area of concentration that could be explored in future studies for the purpose of determining the efficacy and safety profile of these extended-release bilayer tablets in the management of DM among patients.

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