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In vitro assessment of immediate release Dapagliflozin tablets for type 2 diabetes mellitus treatment

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Abstract

The study explores therapeutic strategies for diabetes mellitus, focusing on improving therapeutic outcomes and patient compliance through the development and characterization of an immediate release formulation of dapagliflozin. Eight formulations were developed using a wet granulation process with several super-disintegrating agents and characterized by pre-compression parameters such as angle of repose (40.2 to 61.02), Hausner ratio (1.30 to 1.5), Carr's index (23.5 to 33.3), physical attributes (weight (145–155 mg), thickness (4.42±0.04 to 4.46±0.05 mm), hardness (3.7–5.6 kg/cm^2), friability (<1%)), and disintegration time. Furthermore, FT-IR, SEM, and TGA were conducted, which revealed no plausible drug-excipient interaction. In-vitro dissolution studies were conducted and the release profile was determined as F1 (80.50±5.2) > F3 (75.97±1.4) > F2 (75.30±3.3) > F5 (74.14±2.3) > F8 (70.13±3.7) > F7 (68.12±4.1) > F6 (66.45±3.1) > F4 (54.74±1.3) > pure drug (38.14±2.1) within 30 minutes, while the F1 formulation complied with the USP requirements for immediate release formulation. Additionally, the F1 formulation's drug release profile significantly outperformed commercially available options, indicating its potential to enhance glycemic control and patient adherence in T2DM management, as per the findings.

Keywords: Diabetes Mellitus; Dapagliflozin; Immediate release; Super-disintegrating agents

Introduction

Diabetes is a complicated, long-term syndrome linked to a number of metabolic dysfunctions, most of which are brought on by hyperglycemia problems associated with insulin secretion, action, or both (Banday *et al.* 2020). Long-term hyperglycemia in diabetic patients results in various cardiovascular impairments and dysfunctions in several organs, including the heart, blood vessels, eyes, kidneys, and nerves (American Diabetes Association, 2012). It is one of the most common chronic diseases in the world, causes more than 50% of all fatalities that occur before the age of 70 (Sapra and Bhandari, 2023). Type II (non-insulin dependent) diabetes was the most common form of the disease in 2017, affecting 462 million people worldwide (6.28% of the population) (Khan *et al.* 2020).

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However, the WHO estimated that it affects 8.4 million people in Bangladesh, the actual figure is probably greater due to a lack of testing options (WHO, 2020).

There are several drugs for managing diabetes, such as insulin and its analogues, metformin, sulfonylurea, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors etc. (Scheen, 2016). SGLT2 inhibitors are a novel category of drugs that reduce blood glucose levels by preventing the kidneys from reabsorbing glucose. These treatments also have protective benefits for both the kidneys and the heart (Nespoux and Vallon, 2018; Thomas *et al.* 2014). A study showed that a significant reduction in the level HbA1c was observed compared to placebo when administered as monotherapy or combined with other types of antidiabetics (Kaku *et al.* 2014) as a tablet at a dose of 5 or 10 mg once daily as an adjunct to diet and exercise for the treatment of T2DM patients (Lamos *et al.* 2013; Nicholson *et al.* 2021). Dapagliflozin lowers the risk of heart attacks and heart failures by raising water excretion and lowering blood pressure (Petrie *et al.* 2020).

There are very limited studies conducted to understand the pharmacokinetic parameters of Dapagliflozin (Oroian *et al.* 2023; Ameeduzzafar *et al.* 2019; Kartikey *et al.* 2023). Dapagliflozin is used in both as a monotherapy or combinational therapy. For immediate release formulations, studies were used several super disintegrants, like Sodium starch glycolate, Croscarmellose sodium, pre-gelatinized starch, Ludiflash etc. (Kartikey *et al.* 2023). These super disintegrants were basically used to enhance the release profile and reducing disintegrating time of the product in those studies. There was no study conducting analysis on pharmacokinetic parameters on only immediate release formulation of Dapagliflozin. But Chitra *et al*. (2017) conducted a study on immediate releases kinetics of Canagliflozin, similar class drug of Dapagliflozin by developing 12 formulations of varying quantity of super disintegrants, such as Sodium starch glycolate, croscaremellose sodium, pregelatinized starch and Kyron T-314. Results displayed that formulation containing 6% Kyron T-314 (CIR12) as a super disintegrants was found to be the best having 99.10% of drug release in 30 minutes and also disintegration time of 20 seconds along with satisfactory stability studies (Chitra *et al.* 2017). Another study was conducted by on bilayer tablet which contains immediate release layer of Dapagliflozin and sustained released Saxagliptin, found that the optimized formulation of Dapagliflozin contains 4% w/w Ludiflash as a super disintegrant and observed almost 100% Drug release within 15 minutes. Moreover, a randomized crossover study was conducted by Oroian *et al*. to understand the bioavailability of Dapagliflozin 10 mg in Caucasian volunteers under fasting conditions. This study found that 90% confidence intervals for the evaluated pharmacokinetic parameters were found to be in the accepted interval for bioequivalence (80.00-125.00%) (Oroian *et al.* 2023).

The study was conducted with different four category of super disintegrants and varying their ratio in each formulation make it a more viable study. The rationale for excipient selection, their functions in altering drug release, and the scientific ideas underlying Dapagliflozin immediate release formulations were investigated in this study. The goal of this study was to improve efficacy of this SGLT-2 inhibitor drug Dapagliflozin by various formulation aspects such as excipient selection, granulation procedures, and compression parameters as well as investigate drug-excipient compatibility using TGA and FTIR. This study signifies a noteworthy advancement in the pursuit of treatment alternatives that prioritize the needs of patients with T2DM. Another objective of the current study was to facilitate more convenient and effective treatments, ultimately leading to better management of blood sugar levels and increased adherence to treatment regimens.

Methods and materials

Material Source

Dapagliflozin, Crospovidone, Sodium Starch Glycolate, Croscarmellose Sodium, Magnesium Stearate, Colloidal Anhydrous Silica, Mannitol, Avicel 101 (MCC), and different solvents used in the current study were purchased from local vendors.

Fourier transform infrared spectrometry (FTIR)

After weighing and grinding around 300 mg of KBr into a fine powder, about 1 mg of pure drug or a combination of drug-excipients was added, and this mixture was well ground to combine the sample with the KBr. This KBr mixer was then pressed, and a palate was created using an 8-ton IR press. IRSpirit Infrared Spectrophotometer developed by Shimadzu Corporation, Japan was used to perform the FTIR analysis.

Raw material compatibility and stability testing

The API and their respective mixtures were kept in a stability chamber for 30 days to assess the potential degradation and interactions between the components due to storage. The chamber was kept at a temperature of 25±2°C and the relative humidity at 30-65%. These samples were analyzed through FTIR at the initial date and after 30 days of storage. This

provides a reference point for us to assess the changes that occurred to the individual samples and the feasibility of a formulation commercially. The FTIR scanning were ranged from 4000-600 cm^{-1}

Thermal analysis

Thermogravimetric analysis (TGA) was conducted on various blends and raw material of Dapagliflozin, mixed with substances such as povidone, starch glycolate, croscarmellose sodium, and maize starch. The analysis was performed at temperatures up to 800°C. Each sample was measured to contain a specific quantity, ranging from 6 mg to 11 mg, and placed in an aluminum pan. The sample was then heated at a rate of 20°C/min in a nitrogen atmosphere.

Scanning electron microscopy

The surface structure of every sample was visualized using the SEM technique. In order to understand the morphology of the formed samples, the formulation treated with various excipients was seen using a Field Emission Scanning Electron Microscope (FESEM) (JSM 7610F, JEOL, Japan) at a 15-kV accelerating potential. Using epoxy glue or electrically conductive double-sided sticky tape, dried samples were adhered to a specimen stub. It was done to examine the micromorphological features of dapagliflozin's rapid release. The specimens were vacuum-coated in an argon atmosphere with gold before examination.

Formulation and preparation of immediate release Dapagliflozin

After a thorough assessment of the existing articles, four super-disintegrates such as sodium starch glycolate, crospovidone, and croscarmellose-Na were selected to generate the immediate-release dapagliflozin layer (Oroian *et al.* 2023*;* Ameeduzzafar *et al.* 2019*;* Kartikey *et al.* 2023). Different strengths of those super disintegrate were used to develop eight different formulations (Table I) (Levy and Gumtow, 1963; Mizumoto *et al.* 2005). Altering the amount of Avicel 101 excipients based on the changes in those super-disintegrants, the total weight of the tablets remained unchanged. The final weight of each tablet was 150 mg, while the amount of dapagliflozin was 10 mg (Table I). A wet granulation process was applied to form the tablets. Initially, the materials were weighed, and then Avicel 101 was placed inside a mortar. Using a pestle and a few drops of water, the Avicel 101 was triturated to form a mucilage. After that, the remaining ingredients—lubricant and glidant excluded—were combined. A 40-mesh screen was used to filter the resultant slurry. The entire mixture went through drying at 30-45°C as long as the loss of drying (LOD) remained below 5%. After being combined, the lubricant and glidant were filtered through a 20-mesh screen. A low particle size was maintained to improve compressibility (Suma and Shenoy, 2019).

Physical parameters

Weight and weight variability

After determining the mean mass of ten tablets, each tablet was weighed independently to get the standard deviation.

Thickness

Ten randomly chosen tablets were measured for thickness using a Mitutoyo Digital Vernier caliper.

Hardness

The Monsanto hardness tester was used to measure hardness.

Friability

Ten tablets in all were chosen at random to be utilized in the tablet friability testing apparatus, which stood up and rotated 100 times over the course of four minutes. Until they were appropriately balanced, the tablets remained still. The percentage of weight loss was calculated.

$$\% F = \{1-(Wt. /W)\}*100$$

Where, % F = Friability in %, W= Initial weight of tablets, Wt. = weight of tablets after revolution.

In vitro disintegration test

Disintegration was tested in distilled water media at 37±2°C in the Electrolab ED-2L disintegration tester. The tablets are put in the container and run at a rate of 30 strokes per minute. The tablets were monitored until the whole tablet crumbled or there were non-disintegrable fragments. In general, the time limitation for immediate-release tablets is 3-5 minutes, whereas the time limit for sustained-release tablets is 30 minutes (Mizumoto *et al.* 2005).

Preparation of the standard curve of dapagliflozin immediate release drugs

Dapagliflozin's standard calibration curve was prepared (Fig. 1). In order to do this, a quantity of 100 mg of Dapagliflozin was introduced into a volumetric flask with a capacity of 100 mL then 0.1N hydrochloric acid (HCl) was added to the flask until reach to final volume of 100 ml. Subsequently, a 10 mL portion of this solution was transferred to a fresh 100 mL volumetric flask and diluted to a final volume of 100 mL

using 0.1N HCl. Six test tubes were filled with different volumes of the solution of 0.1N HCl to obtain concentrations of 0, 2, 4, 6, 8, and 10 µg/ml (Figure 1). The absorbance measurements were conducted at a wavelength of 224 nm (Table II), as described (Unnisa *et al.* 2022).

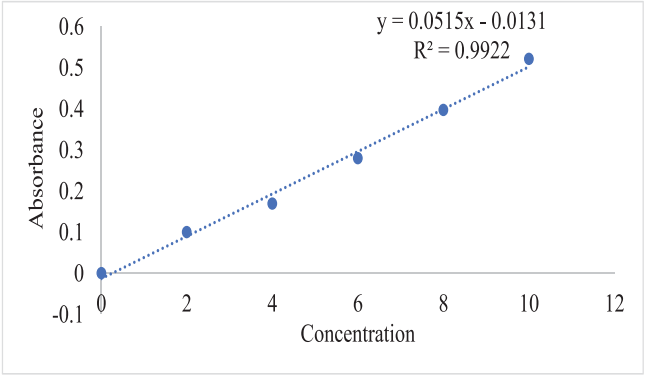

Fig. 1. Calibration curve of Dapagliflozin in 0.1N HCl

Table II. Calibration curve data of Dapagliflozin in 0.1N HCl

Concentration (µg/ml)	Absorbance
0	0
2	0.1
4	0.169
6	0.28
8	0.397
10	0.521

spinning paddle. The dissolution medium is made up of 0.1N HCl that is agitated at 50 rpm and kept at 37±0.5°C. Samples (10 ml) were taken out at predefined 15, 30, 45, and 60 minutes. An equal volume of brand-new dissolving medium was quickly added, kept at the same temperature, and the removed sample was examined to determine its absorbance. According to Unnisa *et al.* (2022), the absorbance measurements were carried out at a λ_{max} wavelength of 224 nm.

Table I. For the immediate release Dapagliflozin tablets' formulation

Ingredients	Justification	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
Dapagliflozin	API	10	10	10	10	10	10	10	10
Crospovidone	disintegrating agent	7.5	10						
Na-starch glycolate	disintegrating agent			7.5	10				
Croscarmellose -Na	disintegrating agent					7.5	10		
Maize Starch	disintegrating agent							7.5	10
Mg-stearate	Lubricant	5	5	5	5	5	5	5	5
Colloidal anhydrous silica	glidant	2	2	2	2	2	2	2	2
Mannitol	filler	75	72.5	75	72.5	75	72.5	75	72.5
Avicel 101 (MCC)	Binder	50.5	50.5	50.5	50.5	50.5	50.5	50.5	50.5
Total		150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg

In vitro dissolution study of the Dapagliflozin immediate release drugs

The *in vitro* dissolution research for immediate-release Dapagliflozin was conducted utilizing a 0.1N hydrochloric acid (HCl) solution and USP class II equipment with a

Statistical Analysis

Statistical analysis was conducted using Microsoft® Excel® 2016 MSO (Version 2405 Build 16.0.17628.20006) 32-bit. All *in vitro* analysis were performed three times and expressed as mean±standard deviation (SD).

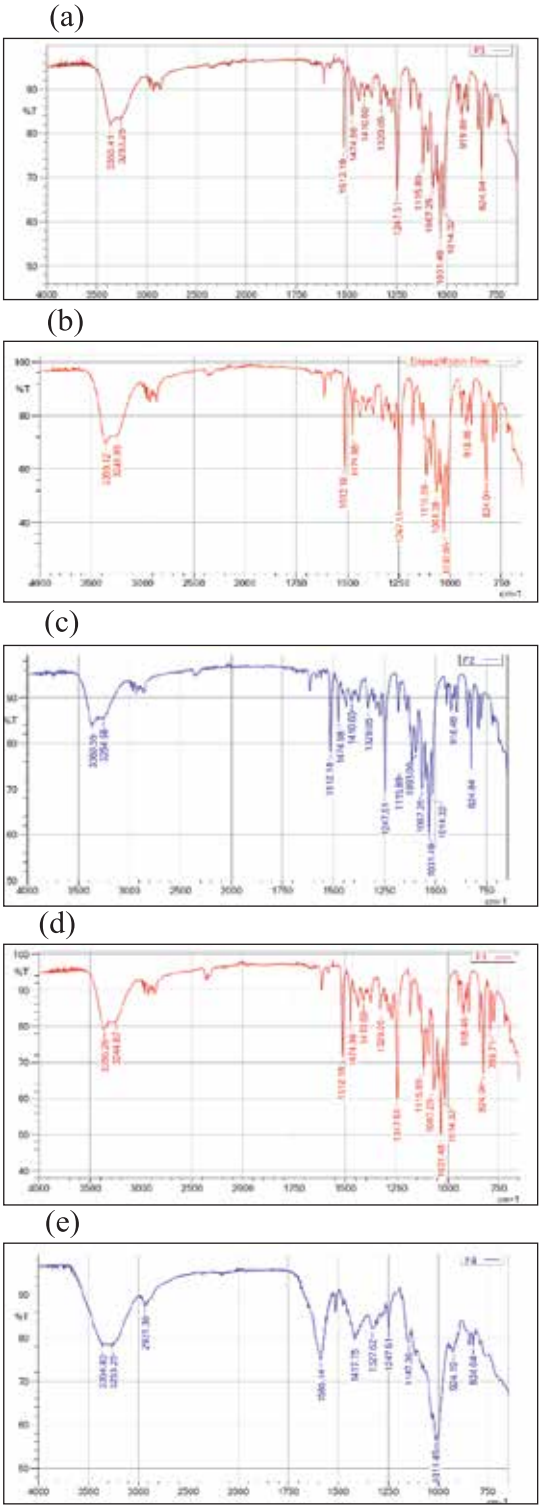

Fig. 2. FTIR Spectrum of (a) Dapagliflozin; (b) Dapagliflozin-Cross povidone Blend; (c) Dapagliflozin-Na Starch Glycolate Blend; (d) Dapagliflozin-Croscarmellose Na Blend; (e) Dapagliflozin- Maize Starch Blend

Results and discussions

Compatibility studies of drug and polymers

Fourier transform infrared spectrometry (FTIR)

Analysis revealed that there was no discernible interaction between the medicine and other excipients, both in their individual forms and when combined (Fig. 2). In pure dapagliflozin, the typical bands of O–H, C=C, aromatic C–O, O–H, C=O, and C=C groups were observed. In the FTIR spectra, absorption peaks for pure dapagliflozin were seen at 3359.12 cm^{-1} (OH stretching), 1512.18 cm^{-1} (C=C, aromatic), and 1247.51 cm^{-1} (C–O ester stretching) (Berthomieu and Hienerwadel 2009; Unnisa *et al.* 2022). The corresponding peak formed by dapagliflozin in the compounds was 1030.05 cm−1 for the C–Cl bond, 3248.96 cm^{-1} for the O–H elastic response, 824.04 cm^{-1} for the C–H bond, and 1115.89 cm^{-1} for the C–C bond. The physical mixing of the drug, super disintegrants, and other excipients did not alter its absorption bands in the FTIR spectrum, indicating that there were no chemical interactions between the medication and the excipients in solid form (Berthomieu and Hienerwadel 2009; Unnisa *et al.* 2022).

Thermogravimetric analysis (tga)

The thermodynamic behavior of Dapagliflozin along with the excipients were performed using TGA (Fig. 3). The analysis

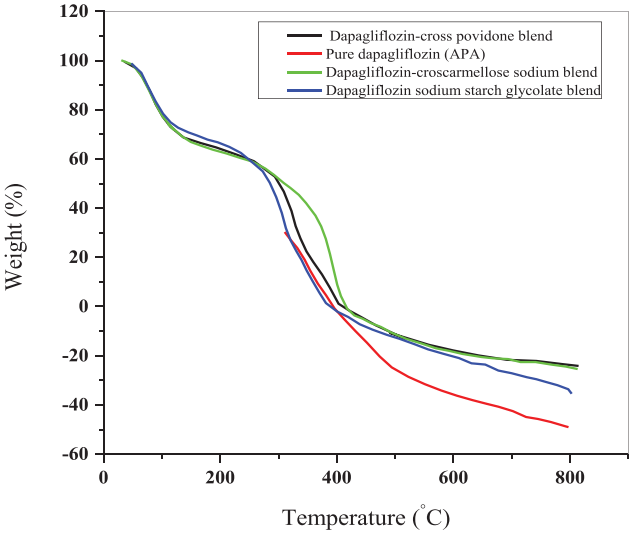

Fig. 3. Thermogravimetric analysis of (a) Dapagliflozin; (b) Dapagliflozin-cross povidone blend; (c) Dapagliflozin sodium starch glycolate Blend; (d) Dapagliflozin-croscarmellose sodium blend

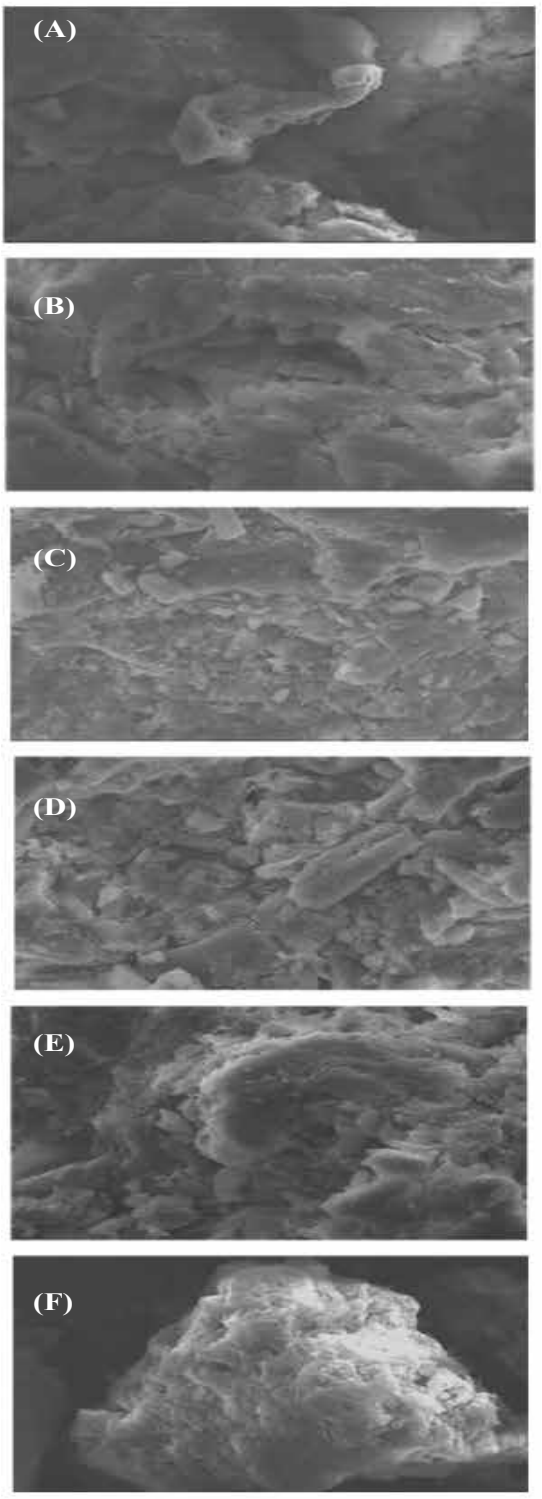

Fig. 4. SEM Images of: (a), (b) of Dapagliflozin and Crospovidone; (c), (d) of Dapagliflozin and Croscarmellose; (e), (f) of Dapagliflozin and Na-Starch glycolate

indicated that the weight loss of pure Dapagliflozin was less when it was blended with excipients. Dapagliflozin blended with cross povidone, croscarmellose sodium and sodium starch glycolate also revealed that formulations were stable. The weight loss pattern also represented that dapagliflozin with excipients were crystalline and amorphous in nature which facilitates the enhancement of dissolution.

Scanning electron microscopy

The images exhibit SEM images of Dapagliflozin with different excipients. Particles seem uneven and rough. The Crospovidone matrix seems to disperse Dapagliflozin well (Figure 4a). Roughness and porosity suggest good mixing and increased surface area for dissolution (Figure 4b). More aggregated particles are fibrous. Croscarmellose interacts differently with Dapagliflozin than Crospovidone (Figure 4c). Particles look more coherent and denser. This suggests that Croscarmellose may disintegrate differently than Crospovidone, altering drug release (Figure 4d). The more spherical and less aggregated particles may imply a different interaction that improves disintegration and dissolution (Figure 4e). Particle interactions decrease cohesiveness and increase porousness relative to other mixes. Na-Starch Glycolate may improve Dapagliflozin absorption owing to improved breakdown (Figure 4f). The SEM visuals reveal Dapagliflozin's physical interaction with super disintegrants Crospovidone, Croscarmellose, and Na-Starch Glycolate. Each excipient's morphology impacts the drug's dissolution and disintegration, which are crucial for the tablet's active pharmaceutical component delivery.

Characterization parameters of immediate release Dapagliflozin formulations

The pre-compression characteristics, including Car's Index, Angle of Repose and Hausner's Ratio were determined (Table III). The average weight of the formed tablet ranges from 145 to 155 mg. All formulation tablets (F1-F8) are designed for quick release. The data displays the crucial measurements for the angle of repose (ranging from 40.2 to 61.02), Hausner ratio (ranging from 1.30 to 1.5), and Carr's index (ranging from 23.5 to 33.3). The thickness of the produced tablet ranges from 4.42 ± 0.04 to 4.46 ± 0.05 mm. The hardness of the prepared tablets is consistently found to be within the range of 3.7 - 5.6 kg/cm^2. The tablets' friability was found to be less than 1%, specifically ranging from 0.27% to 0.62% (Table III). Formulation F7 has the shortest disintegration time, 1min 10sec compared to the other formulations (F1, 1min 58sec; F2, 1min 55sec; F3, 1min 45sec; F4,

Table III. Characterization parameters of immediate release Dapagliflozin formulations

Formulation	Car's Index	Hausner Ratio	Angle of repose	Average weight (mg)	Thickness (mm)	Friability (%)	Hardness (kg/cm^2)	Disintegration Time
F1	23.5	1.30	42.4	145	4.44 ±0.04	0.39±0.01	4.14±0.5	1min 58sec
F2	26.5	1.35	46.01	146	4.43±0.02	0.57±0.03	5.5±0.4	1min 55sec
F3	28.8	1.40	50.11	151	4.43±0.03	0.59±0.01	3.77±0.1	1min 45sec
F4	24	1.31	40.2	148	4.42±0.04	0.49±0.05	4.61±0.3	2min 15sec
F5	24	1.31	40.5	151	4.44±0.02	0.27±0.02	5.6±0.2	3min 30sec
F6	23.5	1.30	41.2	153	4.43±0.03	0.33±0.01	4.7±0.1	4min
F7	30.4	1.43	56.21	154	4.45±0.02	0.59±0.04	4.11±0.2	1min 10sec
F8	33.3	1.5	61.02	155	4.46±0.05	0.62±0.02	3.7±0.6	1 min 38sec

2min 15sec; F5, 3min 30sec; F6, 4min; F8, 1 min 38sec).

Dissolution study of the Dapagliflozin immediate release formulations

The release profile of dapagliflozin with various concentration of super disintegrants was compared along with pure drug, Dapagliflozin in the same media. The analysis clearly demonstrated that the pure drug, dapagliflozin had a 38.14% drug release within 30 minutes (Table IV). Ameeduzzafar *et al.* (2019) reported in a study that the drug release profile of pure Dapagliflozin is 38.33±1.78% in 60 minutes. The F1 and F2 formulation, containing Crospovidone as a super disintegrating agent showed that the drug release profile was increasing over the time, but inversely with the concentration of the super disintegrating agent (Table IV). The same pattern was also seen in case of F3, F4, F5, and F6 formulation, containing sodium starch-glycolate for F3 and F4, and croscarmellose for F5 and F6 formulation. But in case of F7 and F8 formulation, containing maize starch as a super disintegrant showed a positive correlation between the percent drug release and the concentration of the super disintegrating agent. For 7.5 mg of each super disintegrating agent at 30 minutes, the percent drug releases were F1 (80.50±5.2%), F3

Table IV. Dissolution study of Dapagliflozin Immediate Release Formulations

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	Pure Drug
0	0	0	0	0	0	0	0	0	0
15	76.6±3.2	72.23±1.4	74.25±1.3	34.40±2.2	70.96±4.1	64.83±2.3	55.71±3.2	53.62±1.25	32.37±3.2
30	80.50±5.2	75.30±3.3	75.97±1.4	54.74±1.3	74.14±2.3	66.45±3.1	68.12±4.1	70.13±3.7	38.14±2.1
45	82.26±3.8	81.40±4.2	81.29±1.17	65.63±3.2	76.74±3.8	71.82±3.5	72.78±2.8	76.22±1.7	44.31±3.2
60	83.90±2.3	82.43±3.5	82.31±1.6	67.10±2.4	80.40±3.8	74.39±4.8	79.10±5.2	77.35±5.1	54.3±1.7

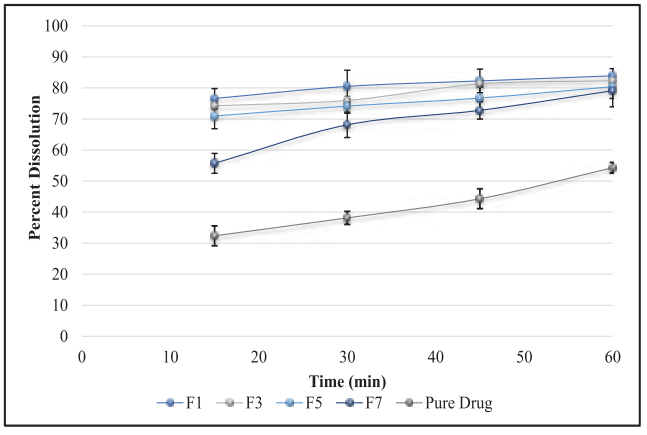

Fig. 5. Percent drug release against time for immediate release Dapagliflozin tablets with 7.5 mg of super disintegrating agents

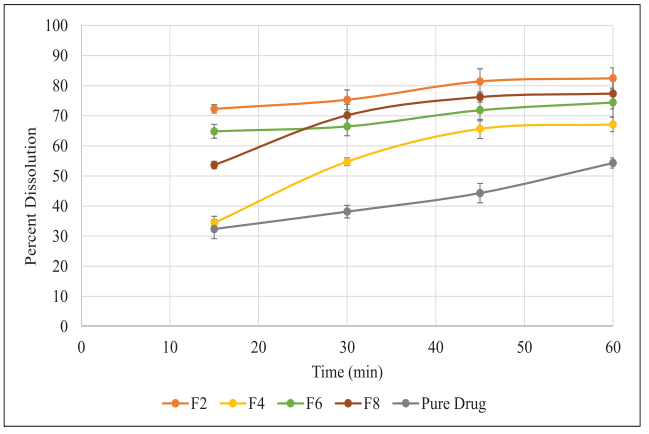

Fig. 6. Percent drug release against time for immediate release Dapagliflozin tablets with 10 mg of super disintegrating agent

(75.97±1.4%), F5 (74.14±2.3%), and F7 (68.12±4.1%), as shown in fig. 5. For 10 mg of each super disintegrating agent at 30 minutes, the percent drug releases were F2 (75.30±3.3%), F4 (54.74±1.3%), F6 (66.45±3.1%), and F8(70.13±3.7%), as displayed in fig. 6. Among them, the optimized F1 formulation had a higher and faster drug release profile of 80.50±5.2%, even twofold release profile compares to pure drug within 30 minutes. The F2 and F3 formulations exhibit solubility rates over 80% after a 45-minute timeframe, whereas the pure medication only achieves a dissolution rate of 44.31% within the same time period (Fig. 7). A comparison analysis was also performed between the preferred formulation, F1, and a commercially available preparation of dapagliflozin in terms of their dissolving profiles, as shown in fig. 7 and table V. The research indicates that dissolving profile of F1 formulation is higher and faster

Table V. Comparison of market preparation with the preferred immediate release Dapagliflozin formulation

Time (min)	F1	Market Preparation
15	76.6±3.2	53.69±6.2
30	80.50±5.2	63.44±3.8
45	82.26±3.8	72.62±5.7
60	83.90±2.3	75.91±4.6

than that of the currently available market preparation. The F1 formulation satisfies all the requirements for being used as the immediate release layer of Dapagliflozin.

The research aimed to explore the immediate release characteristics of dapagliflozin. Globally, individuals with Type-2 Diabetes Mellitus are commonly treated with SGLT-2 inhibitors (such as dapagliflozin) in various formulations. Furthermore, preclinical studies suggest that monotherapy or combining therapy of these medications may offer cardioprotective benefits through mitochondrial fission (Tanajak *et al.* 2018). The study was conducted to evaluate several aspects, including pre-formulation parameters, physical characterization parameters, and drug release profiles, with the aim of enhancing the antidiabetic efficacy and drug release profile of these medications.

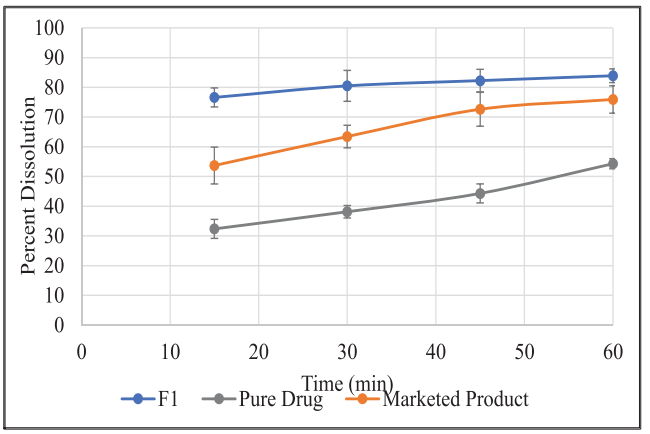

Fig. 7. Percent drug release against time Optimized immediate release Dapagliflozin, Pure Drug Dapagliflozin and Marketed Drug

The lack of any interfaces between the drug, its polymers, and excipients was verified by FTIR and thermograms. An FTIR spectrum analysis was performed on physical mixtures

of the drugs and polymer to investigate any discernible variations in the drug, both in terms of its physical and chemical properties. The findings demonstrated that there was no disruption in the functional groups, as the primary peaks of Dapagliflozin remained unchanged, showing that there was no chemical incompatibility. The thermograms revealed that there were no notable alterations in the drug endotherm peaks seen in the mixed samples.

The morphology of immediate release samples of Dapagliflozin was analyzed (Fig. 4). Dapagliflozin and cross povidone displayed strong agglomeration and varied size of the particle is formed (Fig. 4a and 4b) whereas Dapagliflozin and croscarmellose particles exhibited a uniform particle distribution as well as elongated shape (Fig. 4b and 4c). Therefore, Dapagliflozin combined with croscarmellose indicated increase rate of dissolution with immediate release. The particle shapes of Dapagliflozin and sodium-starch glycolate blend were a nearly spherical morphology. It is caused by the collision of the primary particles generated, aggregated into secondary particles, gradually growing up, and finally stabilized (Fig. 4e and 4f).

Several investigations, encompassing kinetics, stability, and pre-formulation studies, were conducted using the wet granulation procedure. The disintegration sequence of Dapagliflozin was found to be F6 > F5 > F4 > F1 > F2 > F3 > F8 > F7. The results indicated that the Dapagliflozin formulations met the established standards for disintegration, hardness, friability, and average weight. According to the dissolution test sequence, preferred immediate-release formulations for Dapagliflozin were determined as F1 > F3 > F2 > F5 > F8 > F7 > F6 > F4 > pure drug for 30 minutes. Ameeduzzafar *et al*. reported that the drug release profile of pure Dapagliflozin is 38.33±1.78% in 60 minutes (Ameeduzzafar *et al*. 2019). Notably, almost all of these formulations, F1 (80.50±0.05), F2 (75.30±0.03), F3 (75.97±0.01), F5 (74.14±0.02), F6 (66.45±0.03), F6 (68.12±0.07), F7 (68.12±0.07), F8 (70.13±0.05) exhibited a superior drug release profile compared to commercially available formulations (63.44±0.04) except F4 (54.74±0.01) in 30 minutes, among them F1 formulation meeting the USP's requirements for immediate release oral dosage forms' drug release profile and effectively enabling rapid control of blood glucose levels.

These experimental formulations, designed to address specific clinical requirements, exhibit distinct medication release profiles compared to existing options, suggesting potential for enhancing glycemic control and patient adherence. The *in vitro* release profiles align with the desired drug release characteristics: immediate release Dapagliflozin demonstrates rapid release. This formulation hold promises in diabetes management and could improve therapeutic outcomes and patient adherence. However, further investigation is necessary to assess the *in vivo* clinical safety and effectiveness of these formulations.

Conclusion

As observed, the composition features of the immediate release Dapagliflozin tablet align with the study's objectives. This tablet offer potential for simplifying the dosing schedule for Type 2 Diabetes Mellitus (T2DM) patients. Further enhancements to this formulation could involve adjusting the quantities or types of excipients utilized. Additionally, conducting *in vivo* experiments will elucidate the impact of this formulation on animal physiology. In essence, this formulation meets the required standards and hold promise for reducing the medication burden on patients. Furthermore, by pairing this with novel drugs, innovative formulations can be developed.

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References

American Diabetes Association (2012), Diagnosis and classification of diabetes mellitus. *Diabetes Care*. **35** Suppl 1(Suppl 1): S64-71. DOI: 10.2337/dc12-s064

Ameeduzzafar IE, Nabil K, Alruwaili MH, Elkomy JA, Afzal M, Ahmad N, Elmowafy M, Alharbi, KS, Alam MS (2019), Development of novel dapagliflozin loaded solid self- nanoemulsifying oral delivery system: Physiochemical characterization and *in vivo* antidiabetic activity, *J. Drug. Deliv. Sci. Technol.* **54:** 101279. DOI: 10.1016/j.jddst.2019.101279

Banday MZ, Sameer AS and Nissar S (2020), Pathophysiology of diabetes: An overview. *Avicenna. J. Med.* **10**: 174-188. DOI: 10.4103/ajm.ajm_53_20

Berthomieu C and Hienerwadel R (2009). Fourier transform infrared (FTIR) spectroscopy. *Photosynth. Res.* **101**: 157-170. DOI: 10.1007/s11120-009-9439-x

Chitra KP, Eswaraiah MC and Basaveswararao MV (2017), Effect of Various Superdisintegrants on Immediate Release Formulations of SGLT2 Inhibitor Dapagliflozin, *IJRANSS* **5**(1): 61-72.

Kaku K, Maegawa H, Tanizawa Y, Kiyosue A, Ide Y, Tokudome T, Hoshino Y, Yang J and Langkilde AM (2014), Dapagliflozin as monotherapy or combination therapy in Japanese patients with type 2 diabetes: an open-label study, *Diabetes. Ther.* **5**(2): 415-433. DOI: 10.1007/s13300-014-0086-7

Kartikey A, Gupta A and Gupta Dr V (2023), Formulation and Evaluation of Tablet of Dapagliflozin and Vildagliptin, *J. Popul. Ther. Clin. Pharmacol.* **30**(1): 714-723. DOI: 10.53555/jptcp.v30i1.3563

Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H and Al Kaabi J (2020), Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends, *J. Epidemiol. Glob. Health.* **10**(1): 107-111. DOI: 10.2991/jegh.k.191028.001

Lamos EM, Younk LM and Davis SN (2013), Canagliflozin, an inhibitor of sodium-glucose cotransporter 2, for the treatment of type 2 diabetes mellitus. *Expert. Opin. Drug. Metab. Toxicol.* **9**(6): 763-775. DOI: 10.1517/ 17425255.2013.791282

Levy G and Gumtow RH (1963), Effect of Certain Tablet Formulation Factors on Dissolution Rate of the Active Ingredient I11. *J. Pharm. Sci.* **52**: 1139-1144. DOI: 10.1002/jps.2600521209

Mizumoto T, Masuda Y, Yamamoto T, Yonemochi E and Terada K (2005), Formulation Design of A Novel Fast-Disintegrating Tablet. *Int. J. Pharm.* **306**(1-2): 83-90. DOI: 10.1016/j.ijpharm.2005.09.009

Nespoux J and Vallon V (2018), SGLT2 inhibition and kidney protection. *Clinical Science*, **132**(12): 1329-1339. DOI: 10.1042/CS20171298

Nicholson MK, Ghazal AR and Wilding JPH (2021), Dapagliflozin for the treatment of type 2 diabetes mellitus-an update. *Expert Opinion on Pharmacotherapy* **22**(17): 2303-2310. DOI: 10.1080/ 14656566. 2021.1953471

Oroian M, Vlase AM, Marcovici A and Vlase L (2023), Kinetics of Dapagliflozin 10 Mg Immediate Release Tablet In Healthy Caucasian Volunteers: Does Food Intake Affect Its Disposition in The Body? *Stud. Univ. Babes-Bolyai. Chem.* **68**: 37-48. DOI:10.24193/subbchem.2023.1.03

Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, Belohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett J, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Vinh PN, Schou M, Tereshchenko S, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD, Johanson P, Greasley PJ, Boulton D, Bengtsson O, Jhund PS and McMurray JJV (2020), Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients with Heart Failure with and Without Diabetes. *JAMA* **323**(14): 1353-1368. DOI: 10.1001/jama.2020.1906

Sapra A and Bhandari P (2023), Diabetes. ***In:*** StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551501/.

Scheen AJ (2016), DPP-4 Inhibitor plus SGLT-2 Inhibitor as Combination Therapy For Type 2 Diabetes: From Rationale to Clinical Aspects. *Expert. Opin. Drug. Metab. Toxicol.* **12**(12): 1407-1417. DOI: 10.1080/ 17425255.2016.1215427

Suma Bv Dr and Shenoy P (2019), A New High Performance Thin Layer Chromatographic Method Development and Validation of Dapagliflozin in Bulk and Tablet Dosage Form. *Int. J. Pharm. Sci.* **11**(8): 58-63. DOI: 10.22159/ijpps.2019v11i8.34339

Tanajak P, Sa-Nguanmoo P, Sivasinprasasn S, Thummasorn S, Siri-Angkul N, Chattipakorn SC and Chattipakorn N (2018), Cardioprotection of Dapagliflozin and Vildagliptin in Rats with Cardiac Ischemia-reperfusion Injury. *J. Endocrinol* **236**(2): 69-84. DOI: 10.1530/-JOE-17-0457

Thomas MC (2014), Renal effects of dapagliflozin in patients with type 2 diabetes. *Ther. Adv. Endocrinol. Metab.* **5**(3): 53-61. DOI: 10.1177/2042018814544153

Unnisa A, Chettupalli AK, Al Hagbani T, Khalid M, Jandrajupalli SB, Chandolu S and Hussain T (2022), Development of Dapagliflozin Solid Lipid Nanoparticles as a Novel Carrier for Oral Delivery: Statistical Design, Optimization, *in-vitro* and *in-vivo* Characterization, and Evaluation. *Pharmaceuticals (Basel).* **15**(5): 568. DOI: 10.3390/ph15050568

Vinutha Kommineni KPR and Chowdary SVUMP (2019), Formulation of Dapagliflozin and Saxagliptin Tablets and In vitro Evaluation by RP-HPLC Method. *Asian J Pharm Ana* **9**(2): 93-98. DOI: 10.5958/ 2231-5675.2019.00018.8

WHO (2020), Diabetes. https:// www.who.int/ news-room/-fact-sheets/detail/diabetes.