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TO FORMULATION DEVELOPMENT AND EVALUATION OF DAPAGLIFLOZIN EXTENDED RELEASE TABLET

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ABSTRACT

Dapagliflozin is the first novel sodium- glucoseco-transporter-2(SGLT2) asset approved by the European Medicines Agency(EMA) for the treatment of type 2 diabetes. By inhibiting SGLT2, dapagliflozin blocks reabsorption of filtered glucose in the order, adding urinary glucose excretion and reducing blood glucose situations. Its medium of action is independent of pancreatic β cell function and modulation of insulin perceptivity. The results of phase III clinical trials showed that dapagliflozin, at a cure of 5 or 10mg/ day for 24 weeks as monotherapy in preliminarily undressed cases, or as add-on combination remedy with metformin, glimepiride, pioglitazone or insulin- grounded remedy, significantly reduced both HbA1c and fasting tube glucose situations compared with placebo. In addition, dapagliflozin was noninferior to glipizide, in terms of glycemic control after 52 weeks, when used as add- on remedy in cases with type 2 diabetes deficiently controlled with metformin. In utmost clinical trials, dapagliflozin reduced body weight. The combination of both goods(bettered glycemic control and weight loss) is achieved to a lesser extent in treatments that include dapaglifozin. Longer- term extension studies indicated that the efficacity of dapagliflozin on the glycemic control and weight reduction is maintained for over to 2 and 4 times. Dapagliflozin was well permitted. Genital infections and urinary tract infections were more frequent in cases who entered dapagliflozin than in placebo donors. Hypoglycemic occurrences were scarce with dapagliflozin. In conclusion, dapagliflozin is a new option for the operation of type 2 diabetes, particularly when used as add- on remedy. The present study aims to develop and estimate an extended-release (ER) tablet expression of Dapagliflozin, a sodium- glucoseco-transporter 2(SGLT2)

asset, to maintain a sustained remedial effect and enhance patient compliance in diabetes operation. The study focuses on the selection of applicable polymers, excipients, and evaluation parameters to insure optimal medicine release, stability, and bioavailability.

KEYWORDS: Dapagliflozin, Antidiabetic drug, Binder- Gelatin, Sodium Glucose co-transporter inhibitors, extended release tablet.

INTRODUCTION

Antidiabetic drugs are medications used to control blood sugar (glucose) levels in people with diabetes mellitus, a chronic metabolic disorder characterized by high blood sugar. These drugs help manage the disease either by improving the body's sensitivity to insulin, increasing insulin production, slowing glucose absorption from the gut, or promoting glucose excretion through the urine.

There are two main types of diabetes.

1. Type 1 Diabetes — where the body produces little or no insulin.
2. Type 2 Diabetes — where the body becomes resistant to insulin or doesn't produce enough insulin.

Antidiabetic drugs are especially important in Type 2 Diabetes, although insulin therapy is essential for Type 1.

These drugs can be classified as

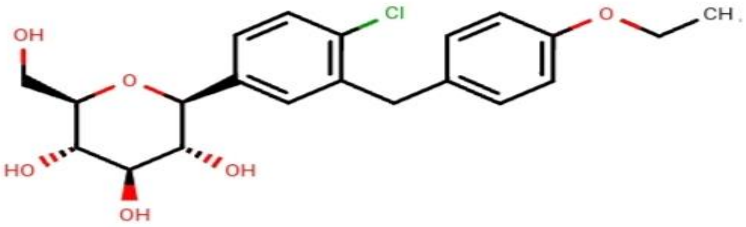
- Oral hypoglycemic agents (e.g., Metformin, Sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors)
- Injectable agents (e.g., Insulin, GLP-1 receptor agonists)

Dapagliflozin is an oral antidiabetic drug that belongs to the class of SGLT2 inhibitors (Sodium-Glucose Co-Transporter 2 inhibitors). It is primarily used in the management of Type 2 Diabetes Mellitus to help control blood glucose levels.

Dapagliflozin works by blocking the SGLT2 protein in the kidneys, which is responsible for reabsorbing glucose back into the blood. By inhibiting this process, dapagliflozin promotes the excretion of excess glucose through urine, thus lowering blood sugar levels independently of insulin action. In addition to its glucose-lowering effect, dapagliflozin has shown benefits in reducing body weight and blood pressure. It is also approved for reducing the risk of hospitalization for heart failure and slowing the progression of chronic kidney disease, even

in some patients without diabetes. It is usually prescribed as monotherapy or in combination with other antidiabetic medications, including metformin or insulin, depending on individual patient needs.

DRUG PROFILE



1. **Drug Class:** Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor

2. **Brand Name:** Farxiga (most common)

3. **Mechanism of Action:** Dapagliflozin lowers blood glucose by inhibiting SGLT2 — a protein located in the proximal renal tubules of the kidneys. SGLT2 is responsible for reabsorbing most of the filtered glucose back into the bloodstream. By blocking thistransporter, dapagliflozin causes excess glucose to be excreted in urine, thereby reducing blood glucose levels. This process is independent of insulin, making it especially useful for patients with insulin resistance.

4. **Indications:** Type 2 Diabetes Mellitus (as monotherapy or combined with other drugs).

Heart failure with reduced ejection fraction (HFrEF).

Chronic Kidney Disease (CKD), even in non-diabetics (some cases).

Reduces risk of hospitalization for heart failure.

5. **Pharmacokinetics**

Absorption: Well absorbed orally.

Bioavailability: ~78%

Peak Plasma Concentration: ~2 hours after dosing.

Half-Life: ~12-13 hours.

Excretion: Mainly via urine (unchanged and as metabolites).

6. **Dosage**

Typically 5 mg to 10 mg once daily taken orally, with or without food

Dose adjustments may be needed in patients with kidney problems.

7. Adverse Effects

Genitourinary infections (due to increased glucose in urine) — common

Increased risk of dehydration and hypotension (due to osmotic diuresis

Risk of ketoacidosis (though rare)

Acute kidney injury (rare but serious)

Increased urination.

8. Contraindications

Severe renal impairment or end-stage renal disease (ESRD)

History of hypersensitivity to dapagliflozin

9. Advantages: Weight loss (because of glucose loss through urine). Blood pressure reduction (mild diuretic effect).Cardiovascular and renal protection — shown in trials (DAPA-HF, DAPA-CKD).

MATERIALS AND METHOD

MATERIALS

1**. Drug**: Dapagliflozin – It is obtained from reliable pharmaceutical source.

2. **Excipients**

a. Polymer: HPMC these is use for release modifier in tablet.

b. Fillers: Lactose. These make up the bulk of tablet and provide structure.

c. Disintegrants: Croscormellose Sodium. These help the tablet break apart after ingestion, allowing for faster drug release.

d. Lubricants: Magnesium Stearate. These prevent sticking during tableting and ensure smooth passage down the throat.

e. Binder: Gelatin these is reduce the risk of tablet breakage.

f. Colourant: Titanium Dioxide these is used as Colourant.

METHOD

- Sieving – All constituents are passed through a 60- mesh sieve to insure a invariant flyspeck size.

- Blending and Mixing – Except for the glidant and lubricant(which will be added latterly), all the constituents are amalgamated and mixed.
- Wet granulation – A water result is used to bind the greasepaint patches together and form wet mass. This is done manually.
- Sieving and drying – The wet millions are passed through a 12- mesh sieve to produce grains of a specific size. These grains are also air- dried for 10 min. Followed by final drying in a charger teetotaler at 45- 50 ° c for 2 hrs.
- Sizing and lubrication- The dried grains are passed through a 16- mesh sieve to achieve the asked final size. also magnesium Stearate, a lubricant is added to ameliorate the inflow of tablet.
- Tablet contraction – The oiled grains are compressed into tablet using a tablet contraction machine with a constant contraction force. Before contraction, the machine die and punches are also waxed with magnesium Stearate to help sticking.
- storehouse- The finished tablet are stored in air tight vessel for farther tesing or use.

Ingredients of Formulation

Sr.No	Ingredients	Role
1	Dapagliflozin	Active Pharmaceutical Ingredient
2	HPMC	Release Modifier
3	Ethyl cellulose	Release Modifier
4	Polyethylene Glycol	Release Modifier
5	Povidone	Binder
6	Microcrystline Cellulose	Excipient
7	Lactose monohydrate	Excipient
8	Magnesium Stearate	Lubricant
9	Croscormelose sodium	Disintegrant
10	Titanium dioxide	Colourant

Different Concentration Of Formulation

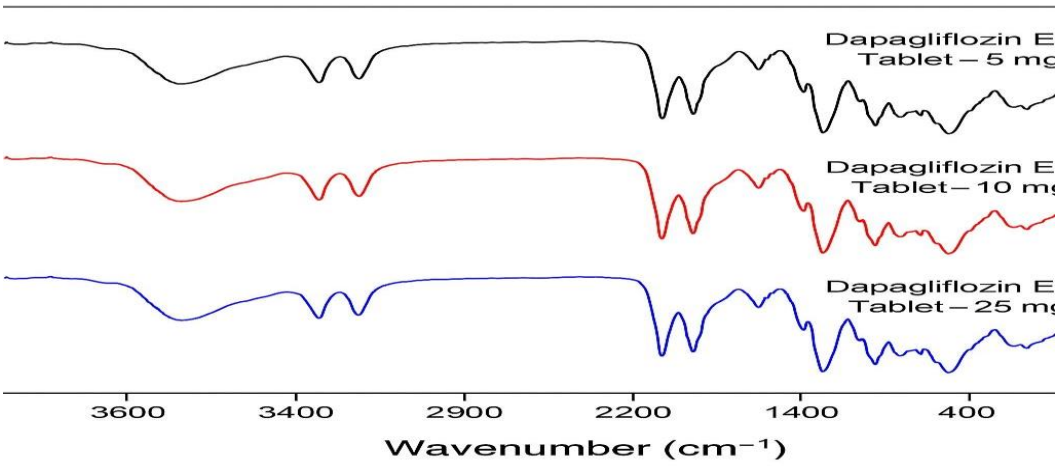
Sr.No.	Ingredients	F1	F2	F3
1	Dapagliflozin	10	5	25
2	HPMC	50	55	35
3	Ethyl cellulose	30	30	30
4	Polyethylene Glycol	10	10	10
5	Povidone	5	5	5
6	Microcrystline Cellulose	90	90	90
7	Lactose monohydrate	40	40	40
8	Magnesium Stearate	3	3	3
9	Croscormelose sodium	7	7	7
10	Titanium dioxide	Optional	Optional	Optional

FTIR

The FTIR spectra shown represent typical absorption bands for Dapagliflozin extended-release (ER) tablets across 5 mg, 10 mg, and 25 mg concentrations. Here's a breakdown of key peaks and their interpretation.

FTIR absorption band of Dapagliflozin

Wavenumber (cm-1)	Functional group	Interpretation
~3400	O-H stretch (hydroxyl)	Presence of hydroxyl group (Dapagliflozin HPMC)
~2900	C-H stretch (aliphatic)	Aliphatic C-H bonds from excipients
~1650	C=C/C=O streach (aromatic/ ketone)	Aromatic or carbonyl group in Dapagliflozin
~1450-1370	C-H bending	Methyl group bending from excipients
~1100-1000	C-O-C stretch	HPMC and lactose related ether functionalities
~900-700	Aromatic C-H bending	Indicative of aromatic rings in Dapagliflozin



SUMMARY

All three spectra (5 mg, 10 mg, 25 mg) show similar patterns, indicating no significant interaction between the drug and excipients.

Characteristic peaks of Dapagliflozin are retained, confirming its structural stability in the ER matrix.

No new peaks or major shifts suggest no chemical incompatibility or degradation.

EXPERIMENTAL WORK

1. Evaluation test for granules

Granule evaluation is a crucial step in the tableting process, ensuring the granules possess the characteristics necessary for forming good quality tablets. Here are some common tests performed on granules.[19,20,21]

2. Evaluation parameters of tablets

Tablets were subjected to following evaluation parameters.

1. **Organoleptic properties:** odour, shape, color, taste was determined
2. **Granule Characterization:** following tests (Angle of repose, Bulk density, Tapped density and Moisture content) were carried out as earlier described for Dapagliflozin on the granules produced prior to compression into tablets.
3. **Compression of Granules into Tablets:** The granules were then mixed with talc and magnesium stearate prior to compression. The granules were compressed into tablets on single punch tablet press using dipunch set of diameter 8 mm at compressional force of 6 metric tons to produce circular tablets. The tablets were kept in air tight containers for 48hr prior to quality control tests.

This test measures the angle formed by a pile of granules when poured freely. A steeper angle indicates indicates poor flow, while a shallower angle indicates good flow. The angle of repose () was calculated as follows:

- Angle of repose ()= tan-1 (2h/d)

3. Bulk Density and Tapped Density

Both bulk density and tapped density are important for understanding the behavior of powders and granules in tableting processes. Here are the formulas for each:

Bulk Density (pb): M/V

Tapped Density (pt): M / Vf.

4. Hausner Ratio

The Compressibility Index and Hausner Ratio are both calculated using the values of bulk density (pb) and tapped density (pt) obtained from the formulas you saw earlier. Here's how they are related:

Compressibility Index (CI): 100 (pt-pb)/pb

Hausner Ratio (H): pt/pb

Evaluation Test for Tablet

3. OTHER TEST

1. Organoleptic property

The organoleptic properties of a tablet refer to the sensory attributes perceived by the consumer upon consumption. These properties include parameter like color uniformity, odor, texture and taste.

2. Size and Shape

size and shape evaluation test are a routine quality control procedure performed on tablets during manufacturing. For thickness, a tolerance of ±5% deviation from the standard value is generally considered acceptable. This ensures consistent tablet weight and drug delivery. Shape is evaluated visually to confirm it matches the intended design, such as round.

3. Hardness Test

This testing plays a vital role in maintaining the quality and consistency of pharmaceutical tablets. This test done by using Monsanto hardness tester Tablet Crushing Strength/Hardness: all tablet passed a test to measure their resistance to breaking under pressure. Acceptable Range: The crushing strength for all tablet fall within an acceptable range of 5kg/cm² to 10kg/cm².

4. Friability Test

It is an important quality control procedure in the pharmaceutical industry that evaluates a tablet's resistance to chipping, cracking, or breaking under physical stress during handling. Transportation and storage. Friability test was done by using rochefriabilator. The friability is expressed as a percentage of the weight lost compared to the initial weight of the sample. Each tablet formulation typically has a predefined acceptable friability limit (usually less than 1%).

4. Official Test

1. Weight Variation Test (U.S.P.)

This test ensures that the weight of individual tablets within a batch is consistent. This consistency is important for maintaining accurate medication dosing.

2. Content uniformity

Content uniformity of a tablet refers to the consistency of the active pharmaceutical ingredient (API) or multiple APIs within individual tablets, as well as across a batch of tablets. It ensures that each tablet in a batch contains the specified amount of active ingredients and meets the required quality standards.

3. Disintegration test

It helps to know about the solubility of active pharmaceutical ingredient in gastric fluid of digestive system. This disintegration rate is essential for ensuring proper drug release and absorption in the body. This test is done by using tablet disintegration machine.

4. Dissolution test

This test is essential for the measurement of rate and extent of drug release form the tables (under standardized condition of temperature and solvent composition) is estimated by basket dissolution test apparatus.

RESULTS

The formulation granules was prepared and Formulation of dapagliflozin extended release tablet were done also evaluated for various parameter and average of results of three formulas are shown in following table 1 evaluation of dapagliflozin granules and table 2 is evaluation of dapagliflozin tablet.

TABLE 1

Test	Result
Appearance	White powder
Solubility	Soluble in methanol, slightly soluble in water
Melting point	78-82°c
PH	6.2
Bulk Density	0.42 g/cm^3
Tapped density	0.52 g/cm^3
Carr's index	19.2%
Hausner ratio	1.24
Angle of repose	28.5° (good flow)

TABLE 2

Batch	F1	F2	F3
Drug content (%)	96.5	97.2	99.1
Hardness (kg/ cm^2)	4.0	4.5	5.0
Disintegration time(min)	10	8	6

Friability (%)	0.72	0.65	0.45
In vitro drug release (%in min)	88.2	90.5	98.4

Dissolution test

Time (min)	% Drug release
5	42.8
10	65.5
20	88.7
30	98.4

All the prepared formulations passed or having nearby observational values as compared to standard values. The values of angle of repose, bulk density, tapped density, hausner ratio and carrs index shows that dapagliflozin granules have good flowability. Table 2. Shows that the all dapagliflozin tablet have good hardness, low friability, also disintegrate and statistically dissolve in standard medium.

CONCLUSION

The formulation and evaluation of Dapagliflozin tablets were successfully carried out with the objective of developing a stable, effective, and fast-dissolving oral dosage form. Preformulation studies confirmed that Dapagliflozin possesses suitable physicochemical properties for tablet formulation.

Among the various formulations developed, the optimized batch demonstrated excellent characteristics, including good hardness, low friability, rapid disintegration, high drug content, and enhanced in-vitro drug release (more than 98% within 30 minutes). The direct compression method proved to be a simple, cost-effective, and efficient approach for the preparation of Dapagliflozin tablets.

Thus, the optimized formulation meets all the necessary quality control parameters and shows promise for further scale-up and commercial production. Future studies including stability testing and in-vivo performance evaluation are recommended to confirm the effectiveness and stability of the final product.

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