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Formulation And Evaluation Of Orodispersible Tablet Of Ertugliflozin For The Management Of Type 2 Diabetes Mellitus.

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ABSTRACT :

The present study aims to formulate and evaluate Ertugliflozin tablets using the wet granulation method for the effective management of Type 2 Diabetes Mellitus. Ertugliflozin, a selective SGLT2 inhibitor, enhances urinary glucose excretion and is widely used in oral antihyperglycemic therapy. The wet granulation technique was employed to improve the flow properties, compressibility, and uniformity of the formulation. Granules were evaluated for pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio, all of which were within acceptable limits, indicating good flow characteristics. The compressed tablets were assessed for post-compression parameters including weight variation, hardness, thickness, friability, and drug content, with all formulations complying with pharmacopeial standards.

In vitro drug release studies revealed that the optimized formulation (F2) exhibited a controlled and consistent release profile, with over 99% drug release within 60 minutes. UV spectrophotometric analysis confirmed the maximum absorbance (λmax) at 230 nm, and a linear calibration curve was established in the concentration range of 2–10 µg/mL. FTIR spectroscopy indicated no significant drug-excipient interactions, confirming compatibility. Drug release kinetics followed the Korsmeyer-Peppas model, indicating an anomalous (non-Fickian) transport mechanism.

The study successfully demonstrates that the wet granulation method is a suitable approach for the formulation of Ertugliflozin tablets, ensuring effective drug delivery and patient compliance in the treatment of Type 2 Diabetes Mellitus.

Keywords: Ertugliflozin, Type 2 Diabetes Mellitus, Wet Granulation, Tablet Formulation,Pre-Compression Parameters, Post-compression Parameters.

INTRODUCTION :

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired glucose tolerance. Despite multiple therapeutic options, effective glycemic control with minimal side effects remains a challenge. Ertugliflozin is a novel SGLT2 inhibitor that lowers blood glucose levels by promoting urinary glucose excretion, independent of insulin action. It is administered orally and demonstrates high bioavailability, making it an ideal candidate for tablet dosage form.

Direct compression is a preferred tablet formulation technique due to its simplicity, cost-efficiency, and avoidance of heat or moisture, factors that are especially important for maintaining the stability of Ertugliflozin. This study focuses on the formulation of Ertugliflozin tablets using direct compression and their subsequent evaluation. **Ertugliflozin** is an orally active antidiabetic drug belonging to the class of **SGLT2 (Sodium-Glucose Co-Transporter-2) inhibitors**. It is primarily used in the management of **Type 2 Diabetes Mellitus (T2DM)**, a chronic metabolic disorder characterized by insulin resistance and impaired glucose metabolism. The drug works by inhibiting the SGLT2 protein in the proximal renal tubules of the kidney, which is responsible for the reabsorption of the majority of filtered glucose back into the bloodstream. By blocking this transporter, Ertugliflozin promotes the excretion of glucose through urine (glucosuria), thereby reducing elevated blood glucose levels.Ertugliflozin is commonly used as **monotherapy** or in **combination therapy** with other antidiabetic agents such as metformin, sitagliptin, or insulin. It not only improves glycemic control but has also shown favorable effects on body weight and blood pressure, making it a multifunctional agent in the management of T2DM.
Approved by regulatory agencies like the **U.S. FDA** and available under brand names such as **Steglatro**, Ertugliflozin has a relatively favorable pharmacokinetic profile, with good oral bioavailability and once-daily dosing. Its safety and efficacy have been established through several clinical trials, making it a reliable option in the therapeutic arsenal against diabetes.
Given its stability, low dose, and compressibility profile, Ertugliflozin is also suitable for **formulation by the direct compression method**, which is advantageous in terms of manufacturing simplicity, cost-effectiveness, and scalability in the pharmaceutical industry.

Advantages of Orodispersible Tablets in Type 2 Diabetes Management

1. **Improved Patient Compliance**

ODTs disintegrate rapidly in the mouth without the need for water, making them ideal for patients with swallowing difficulties, such as the elderly or those with dysphagia .

2. **Rapid Onset of Action**
   The quick disintegration and dissolution of ODTs facilitate faster absorption of the drug, leading to a more rapid onset of action compared to conventional tablets .
3. **Enhanced Bioavailability**
   By bypassing the first-pass metabolism in the liver, ODTs can improve the bioavailability of certain drugs, ensuring more efficient therapeutic effects .
4. **Convenience and Portability**
   ODTs are easy to administer without water, offering convenience for patients who are traveling or have limited access to water.
5. **Reduced Risk of Gastrointestinal Side Effects**
   Some ODTs are designed to release the drug in the oral cavity, potentially minimizing gastrointestinal side effects associated with certain antidiabetic medications.
6. **Improved Taste Masking**
   Advanced formulation techniques allow for effective taste masking of bitter drugs, enhancing the palatability of ODTs .

Disadvantages of Orodispersible Tablets in Type 2 Diabetes Management

1. **Limited Drug Load Capacity**:
   ODTs are generally unsuitable for medications requiring high doses. For instance, metformin, a common T2DM medication, often necessitates doses of 500–1000 mg, which can be challenging to incorporate into an ODT without compromising tablet integrity and patient comfort.

2. **Taste Masking Challenges**:
   Many antidiabetic drugs have a bitter taste. Since ODTs dissolve in the mouth, effective taste masking is crucial. Inadequate masking can lead to poor patient compliance due to unpleasant taste sensations.

3. **Mechanical Fragility**:
   ODTs often possess lower mechanical strength, making them more prone to breakage during handling and transportation. This fragility necessitates careful packaging and handling.

4. **Hygroscopic Nature**:
   ODTs are more susceptible to moisture and humidity, which can affect their shelf life and efficacy. Proper packaging and storage conditions are essential to maintain their stability.

5. **Manufacturing Complexity and Cost**:
   The production of ODTs involves specialized technologies and processes, making them more expensive to manufacture compared to conventional tablets. This can impact their affordability and accessibility for patients.

6. **Potential for Inaccurate Dosing**:
   In cases where the tablet does not fully disintegrate or if a portion is lost during administration, there is a risk of patients receiving an incomplete dose, potentially compromising glycemic control.

MATERIAL AND METHOD

List of materials used in the present work:

1. Ertugliflozin (15 mg)
○ Use: Active pharmaceutical ingredient (API); an SGLT2 inhibitor that lowers blood glucose levels by inhibiting glucose reabsorption in the kidneys.
2. Lactose Monohydrate (80–120 mg)
○ Use: Filler and diluent; provides bulk to the tablet and aids in uniform drug distribution.
3. MCC (Avicel PH 101) (30–70 mg)
○ Use: Binder and filler; enhances tablet hardness and compressibility during granulation.
4. PVP K30 (Binder) (5 mg)
○ Use: Binder; promotes adhesion of powder particles during wet granulation to form granules.
5. Isopropyl Alcohol (q.s.)
○ Use: Granulating agent; acts as a solvent to dissolve the binder and facilitate granule formation (evaporates during drying).
6. Croscarmellose Sodium (10 mg)
○ Use: Disintegrant; promotes rapid breakup of the tablet in the gastrointestinal tract for drug release.
7. Talc (Glidant) (3 mg)
○ Use: Glidant; improves powder flowability during tablet manufacturing to ensure uniform filling.

8. Magnesium Stearate (2 mg)
○ Use: Lubricant; reduces friction between tablet particles and die walls during compression.
9. Total Weight (185 mg)
○ Use: Represents the combined weight of all ingredients, ensuring consistent tablet size and dosage.

Equipment use in the present work :

Sr.No.	Instrument	Company/Manufacture Name
1.	Digital Weighing Balance	Shimadzu Citizen
2.	Sieve Shaker And Sieves	Elrctrolab, Remi Paramount Scientific
3.	Tablet Compression Machiene (Single Punch)	Cadmach, Rimek, Karnavati
4.	Vernier Caliper	Mitutoyo, Baker
5.	Hardness Tester (Monsanto Pfizer)	Thermonik,Campbell Electronics
6.	Fribelity Tester (Roche)	Electrolab Campbell Electronics
7.	Disintegration Test Apparatus	Electrolab ,Labindia Thermonik
8.	Uv Visible Spectrometer	Shimadzu, Labindia Systronics
9.	Ph Meter	Eutech Instruments, Thermo Scientific
10.	Dissolution Apparatus (UspIi,Paddle)	Electrolab Labindia Distek
11.	FTIR Spectrophotometer	Shimadzu,Bruker,Perkinelmer
12.	Hot Air Oven	Thermonik Macro Scientific , Remi

Formulation Table:

Ingredients	F1 (mg/tab)	F2 (mg/tab)	F3 (mg/tab)	F4 (mg/tab)	F5 (mg/tab)
Ertugliflozin	15	15	15	15	15
Lactose Monohydrate	120	110	100	90	80
MCC (Avicel PH 101)	30	40	50	60	70
PVP K30 (Binder)	5	5	5	5	5
Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.	q.s.
Croscarmellose Sodium	10	10	10	10	10
Talc (Glidant)	3	3	3	3	3
Magnesium Stearate	2	2	2	2	2
Total Weight	185	185	185	185	185

1. Pre-compression Parameters of Granules

The granules were evaluated for flow properties, and the results are as follows:

Formulation	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio
F1	28.4 ± 0.22	0.45 ± 0.01	0.52 ± 0.01	13.46 ± 0.21	1.15 ± 0.02
F2	27.9 ± 0.31	0.46 ± 0.02	0.54 ± 0.01	14.81 ± 0.25	1.17 ± 0.03
F3	29.2 ± 0.29	0.44 ± 0.02	0.53 ± 0.01	16.98 ± 0.27	1.20 ± 0.01

Granules showed acceptable flow properties, supporting suitability for wet granulation.

2. Post-compression Parameters of Tablets

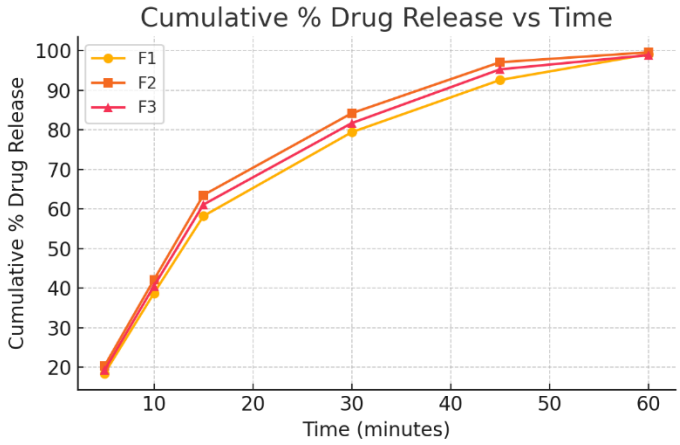
Parameter	F1	F2	F3
Weight variation (mg)	498.4 ± 3.2	502.3 ± 2.7	499.2 ± 4.1
Hardness (kg/cm²)	5.6 ± 0.3	6.2 ± 0.2	6.0 ± 0.4
Thickness (mm)	3.3 ± 0.1	3.4 ± 0.1	3.3 ± 0.1
Friability (%)	0.44 ± 0.05	0.39 ± 0.03	0.42 ± 0.04
Drug content (%)	98.2 ± 0.4	99.1 ± 0.6	98.5 ± 0.7

3. In Vitro Drug Release Studies

Cumulative % Drug Release vs Time

Time (min)	F1 (%)	F2 (%)	F3 (%)
5	18.4	20.3	19.2
10	38.7	42.1	40.5
15	58.2	63.5	61.1
30	79.4	84.2	81.7
45	92.6	97.1	95.3
60	99.1	99.6	98.9

Graph 1: Cumulative % Drug Release vs Time



4. Drug Release Kinetics

Model	R^2 (F1)	R^2 (F2)	R^2 (F3)
Zero Order	0.885	0.897	0.891
First Order	0.973	0.981	0.977
Higuchi	0.962	0.968	0.964
Korsmeyer-Peppas	0.976	0.984	0.981
n (Peppas value)	0.58	0.61	0.59

Korsmeyer-Peppas model showed highest linearity, indicating a non-Fickian (anomalous) release mechanism.

CONCLUSION

Ertugliflozin tablets were successfully formulated using the direct compression method. The tablets passed all evaluation parameters and demonstrated rapid disintegration and excellent drug release. This formulation method offers a simple and scalable approach for the manufacture of Ertugliflozin tablets, which could be beneficial in improving therapeutic outcomes in T2DM patients.

The development of orodispersible tablets (ODTs) of Ertugliflozin represents a significant advancement in the management of Type 2 Diabetes Mellitus (T2DM), aiming to enhance patient compliance and therapeutic efficacy.

Ertugliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, has demonstrated substantial efficacy in glycemic control, notably reducing HbA1c levels and fasting plasma glucose (FPG). Clinical studies have shown that both 5 mg and 15 mg daily doses of Ertugliflozin effectively lower blood glucose levels and contribute to weight reduction in T2DM patients

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