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Development and Evaluation of Fast Dissolving Tablets of Emapagliflozin by Enhancing Dissolution Rate and Bioavailability

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A B S T R A C T
A suitable analytical method based on UV-Visible spectrophotometry was developed to identify Empagliflozin, with a maximum absorbance (λmax) at 257 nm in 0.1N HCL. A direct compression method was established for the manufacture of mouth disintegrating tablets (MDTs) of Empagliflozin, employing super disintegrants such as Sodium Starch Glycolate (SSG), Crospovidone, and Croscarmellose Sodium. The prepared MDTs were evaluated for parameters including hardness, friability, weight variation, and drug content, all of which were found to be within permissible limits. An in vitro drug release study indicated that the F-6 formulation exhibited the best performance, achieving 99% drug release within 30 minutes. Notably, formulations containing Crospovidone demonstrated superior release profiles compared to others. This investigation successfully developed MDTs of Empagliflozin that release the drug within 30 minutes, meeting the objective of creating effective tablets with minimal excipients and a straightforward manufacturing process.
Keywords: Empagliflozin, Crospovidone, Sodium Starch Glycolate, mouth disintegrating tablets.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Among all oral dosage forms, tablets are the most favored due to their ease of administration, compactness, and flexibility in manufacturing. Additionally, solid dosage forms are advantageous because of their high stability, easy transportation, and precision in administration. However, a common issue with solid forms is dysphagia, which affects children, the elderly, and individuals with conditions like nausea, vomiting, aphthous stomatitis due to chemotherapy, Parkinson's disease, motion sickness, unconsciousness, and mental disabilities. This is particularly concerning for pediatric and geriatric patients[1-4]. To address this, orodispersible tablets (ODTs) have been developed. These tablets dissolve quickly and completely in the mouth, turning into a liquid in less than a minute upon contact with saliva. ODTs combine the benefits of solid and liquid dosage forms, offering high patient compliance and ease of administration. They also reduce first-pass metabolism, have a rapid onset of action, and exhibit higher bioavailability. However, they can lack strength and present taste-masking challenges. ODTs prepared by the direct compression method generally rely on super disintegrants such as crospovidone and croscarmellose sodium. Empagliflozin, a sodium glucose co-transporter 2 (SGLT-2) inhibitor, is a novel oral hypoglycemic agent used alongside diet and exercise to improve glycemic control in adults with type 2 diabetes. By inhibiting SGLT-2, empagliflozin

promotes the excretion of glucose through the kidneys, reducing hyperglycemia, and aiding in weight loss and blood pressure reduction[5,6].

Empagliflozin stimulates the release of natural insulin, helping control high blood sugar, which in turn prevents heart disease, strokes, kidney disease, blindness, circulation problems, and sexual dysfunction[7]. Its mechanism involves blocking potassium channels in the beta cells of the islets of Langerhans, leading to increased calcium and insulin release. In the pharmaceutical field, β-cyclodextrins are versatile crystalline complexing agents that enhance the bioavailability, solubility, and stability of drugs while masking their color and taste. In this study, the solubility of empagliflozin was enhanced by complexing it with β-cyclodextrin. Given the relatively poor oral absorption of empagliflozin from standard tablets (which takes nearly 3 hours), efforts were made to improve its absorption by formulating it as an ODT. The objective was to develop ODTs of empagliflozin and study the effects of different super disintegrants on tablet properties. ODTs are emerging as prominent new drug-delivery systems, dissolving or disintegrating in the oral cavity within a minute without the need for water or chewing. This study aimed to enhance the safety and efficacy of the drug molecule, improve patient compliance, solve swallowing difficulties, expedite the onset of action, and provide a stable dosage form [8-10].

2. Materials and methods

Empagliflozin was obtained as a gift sample from Pharma Train (Hyderabad). Crospovidone and croscarmellose sodium were purchased from Nihal Pharma, Hyd. Microcrystalline Cellulose, mannitol, magnesium stearate, talc, methanol, potassium chloride, silica gel G were obtained from SD Fine Chemicals, Mumbai.

Preparation of Oral Disintegrating Tablets

Direct compression method:

Mouth disintegrating tablets of Empagliflozin were prepared by direct compression method. All the ingredients were powdered separately and passed through # 40 mesh sieve separately. The drug and directly compressible excipient were mixed by adding small portion of each at a time and blending it to get a uniform mixture and keptaside. Then the other ingredients were mixed in geometrical order, in an inflated polyethylene pouch magnesium stearate and talc were added last and mixed for further two minutes and the tablets were compressed using 6 mm flat round punches to get tablets of 75 mg weight.

Pre-formulation studies:

- Angle of repose
- Bulk and tapped density
- Hausner ratio
- Compressible index etc.

Manufacture of tablets

Evaluation of tablets

- Weight variation
- Hardness
- Friability
- Disintegration time
- Content uniformity
- In vitro dispersion time
- In-Vitro dissolution Studies
- Release kinetics

In vitro Dissolution Study:

900 ml of 0.1N HCL was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 370C±0.50C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 30mins at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium were analyzed spectrophotometrically at λ_{max}=257 nm using a UV-spectrophotometer (Lab India).

Release Kinetics:

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and it is practically evident in case of matrix system. As a model dependent approach the dissolution data are fitted to three popular release models such as zero order, first order, diffusion equations which have been described in the literature. The order of drug release from matrix system was described by zero order kinetics or first order kinetics. The mechanism of drug release from matrix system was studied by Higuchi equation.

A. Zero Order Release:

It defines a linear relationship between the fraction of drug release

Q=KoT

Q=Fraction of drug release at time t.

A plot of fraction drug release against time will be linear if the release obeys zero order release kinetics.

B. First order release kinetics:

Wagner assuming that the exposed surface area of the tablet decreased exponentially with time during dissolution process suggested that drug release from most slow release tablets could be described adequately by apparent first order kinetics.

The equation used is

Log (1-Q)= -K1T

Thus a plot of logarithm of fraction of drug remained against time will be linear if the release obeys first order kinetics.

Table No – 1: Formulation of Mouth Disintegrating Tablets of Empagliflozin

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Empagliflozin	10	10	10	10	10	10	10	10	10	10
SSG	20	40	60							
Crospovidone				20	40	60				60
CCS							20	40	60	

Mannitol	60	60	60	60	60	60	60	60	60	60
Lactose	-	-	-	-	-	-	-	-	-	67
MCC pH 102	71	69	67	71	69	67	71	69	67	-
Aspartame	5	5	5	5	5	5	5	5	5	5
Pipperment flavour	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1
Megnesium stearate	1	1	1	1	1	1	1	1	1	1
Total weight (mg)	169	187	205	169	187	205	169	187	205	205

Table No – 2: Dissolution Parameters

Parameter	**Details**
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCL
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	2, 4, 6, 8, 10, 15, 20 and 30mins
Analytical method	Ultraviolet Visible Spectroscopy
Λmax	257 nm

3. Results and Discussion

Table No 3 : Standard Calibration Graph Values of Empagliflozin in 0.1 N HCL

Concentration (µg/ml)	**Absorbance**
0	0
2	0.141
4	0.26
6	0.372
8	0.507
10	0.64

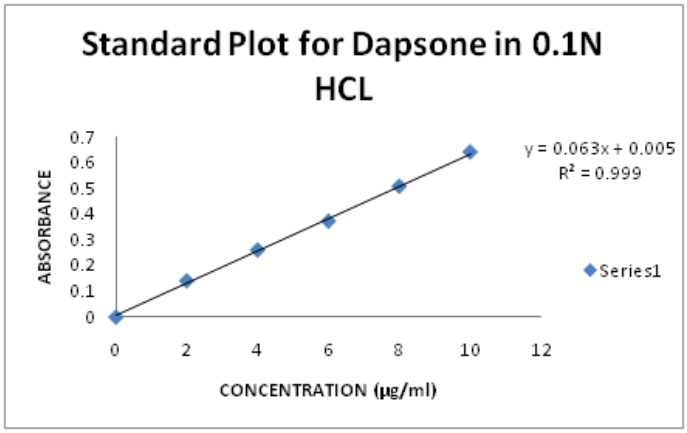

Figure No. 1: Standard Calibration Curve of Empagliflozin in 0.1 N HCL

A) Pre Compression studies:

Table No. 4: Pre Compression Studies of EmpagliflozinOral Disintegrating Tablets

Formulation code	**Bulk density (Kg/cm^3)**	**Tapped density (Kg/cm^3)**	**Cars index**	**Hausners ratio**	**Angle of repose (˚)**
F1	0.40	0.48	16	1.2	32.73
F2	0.39	0.48	18	1.23	34.96
F3	0.50	0.58	13	1.16	28.58

F4	0.44	0.50	12	1.1	27.92
F5	0.37	0.41	9.75	1.1	25.35
F6	0.37	0.41	9.75	1.1	33.14
F7	0.36	0.39	7.6	1.0	27.03
F8	0.41	0.45	8.8	1.0	31.85
F9	0.39	0.48	18	1.23	28.96
F10	0.41	0.45	8.8	1.0	27.85

B) Post Compression Studies:

Table No – 5: Post Compression Studies For Oral Disintegrating Tablets of Empagliflozin

Batch	Hardness (kg/cm2)	Friability (%)	Drug Content (%)	Thickness (mm)	Disintegration Time (sec)	Wetting Time (sec)	In vitro dispersion time	Weight variation	Water absorption ratio
F1	3.1	0.45	99.12	2.5	30	45	29	pass	61.3
F2	2.9	0.62	100.73	2.8	25	42	34	pass	69.8
F3	3.3	0.71	99.74	2.6	20	35	25	pass	73.4
F4	2.5	0.32	98.98	2.5	31	31	32	pass	86.2
F5	2.8	0.51	99.67	2.6	27	36	31	pass	84.12
F6	2.8	0.52	99.83	2.8	25	43	33	pass	93.4
F7	2.9	0.38	101.32	2.8	31	41	36	pass	64.3
F8	3.2	0.48	100.87	2.5	26	36	33	pass	74.8
F9	3.5	0.63	99.74	2.7	24	48	39	pass	76.1
F10	3.0	0.54	99.86	2.6	32	39	28	pass	82.3

In-vitro dissolution studies of empagliflozin tablets:

Table No –6: Dissolution Data of Oral Disintegrating Tablets of Empagliflozin

Time points (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	**0**	0	0	0	0
2	17	22	23	25	30	**34**	21	28	29	32
4	25	32	34	34	44	**50**	28	36	34	48
6	30	44	46	49	61	**69**	34	48	49	64
8	48	55	58	68	75	**80**	53	60	62	75
10	60	69	72	86	84	**89**	64	74	75	81
15	85	89	91	97	94	**96**	88	90	91	93
20	99	97	99	98	99	**98**	100	98	97	98
30	99	96	99	98	99	**99**	99	99	99	99

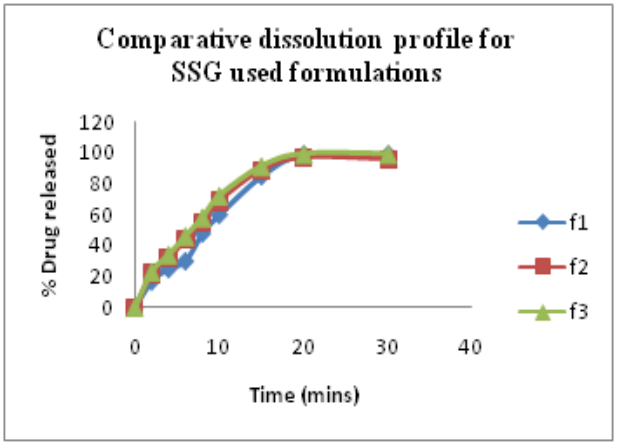

Figure No – 2: Comparative dissolution profiles for SSG used Formulations

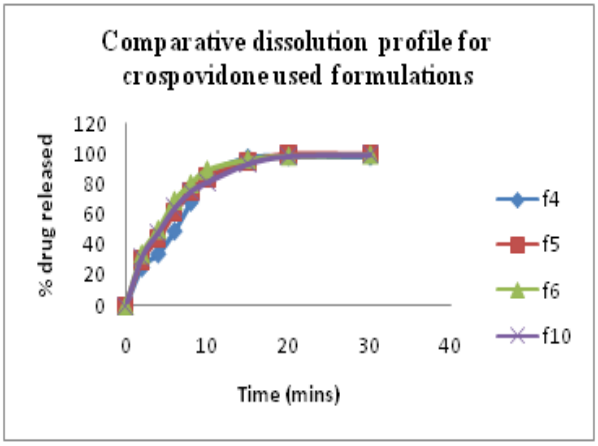

Figure No – 3: Comparative dissolution profiles for Crospovidone used Formulations

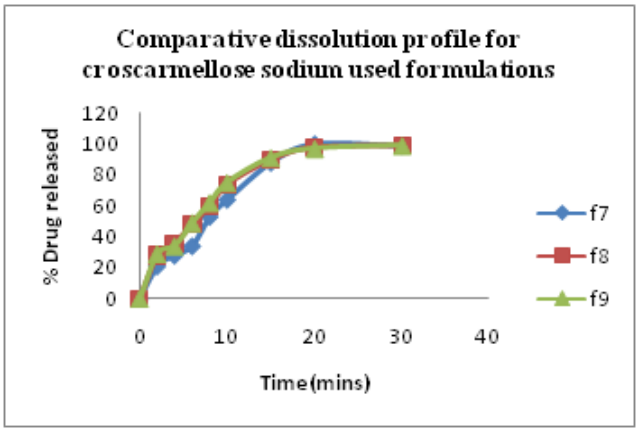

Figure No – 4: Comparative dissolution profiles for Croscarmellose sodium used Formulations

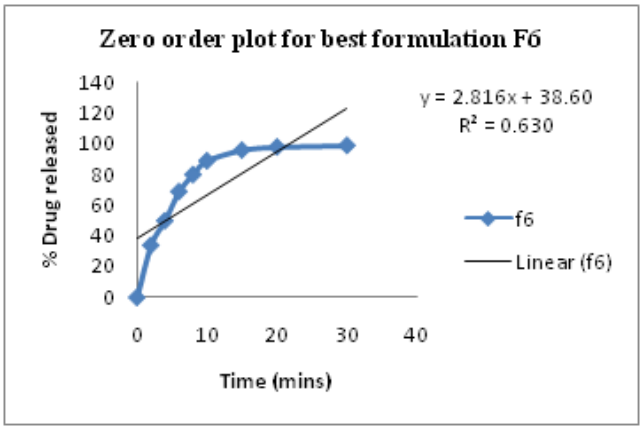

Figure No – 5: Zero order plot for best formulation F6

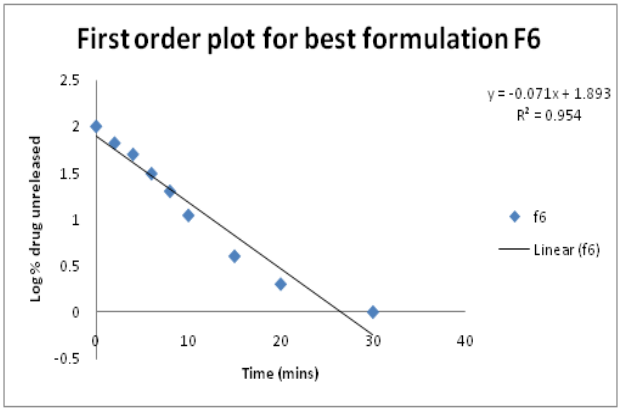

Figure No – 6: First order plot for best formulation F6

Discussion

A UV-Visible spectrophotometric analytical method was developed for Empagliflozin, identifying a maximum absorbance (λmax) at 257 nm in 0.1N HCL. A direct compression method was established to manufacture mouth disintegrating tablets (MDTs) of Empagliflozin, using super disintegrants such as Sodium Starch Glycolate (SSG), Crospovidone, and Croscarmellose Sodium. The MDTs were evaluated for hardness, friability, weight variation, and drug content, all of which met permissible limits. In vitro drug release studies revealed that the F-6 formulation achieved 99% drug release within 30 minutes, with formulations containing Crospovidone showing superior release profiles.

4. Conclusion

The study successfully developed mouth disintegrating tablets of Empagliflozin using a direct compression method. The tablets met all evaluation parameters and demonstrated efficient drug release, with the F-6 formulation being the most effective. This investigation achieved the objective of creating MDTs with minimal excipients and a simple manufacturing process, ensuring rapid drug release within 30 minutes.

5. References

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