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FORMULATION AND EVALUATION OF EMPAGLIFLOZIN IR TABLETS

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ABSTRACT

An analytical method using UV-Visible spectrophotometry was developed to assess Empagliflozin; identifying a λmax of 257 nm in 0.1N HCl. Mouth-dissolving tablets of Empagliflozin were successfully formulated using direct compression with excipients including sodium starch glycolate (SSG), Crospovidone, and Croscarmellose sodium. The tablets were evaluated for hardness, friability, weight variation, and drug content, all of which fell within acceptable limits. Among the various formulations, F-6 demonstrated the optimal performance with a 99% drug release within 30 minutes. The formulation utilizing Crospovidone exhibited the most effective release profile. This study achieved its goal of developing mouth-dissolving tablets of Empagliflozin with a minimal amount of excipients and a simple manufacturing process, ensuring rapid drug release and enhanced patient compliance.

INTRODUCTION:

An ideal dosage regimen in drug therapy aims to promptly achieve and maintain the desired therapeutic drug concentration in plasma throughout treatment via specific doses and frequencies. Oral administration, particularly through tablets and hard gelatin capsules, is the most popular and convenient method due to its natural, safe, and flexible nature. However, many individuals, including the elderly, children, and patients with certain conditions, have difficulty swallowing these forms. Mouth-dissolving tablets (MDTs) address this issue by disintegrating rapidly in the mouth without water, ensuring optimal convenience And faster therapeutic response across various drug categories. MDTs offer several advantages, such as ease of administration without water, suitability for patients with swallowing difficulties, rapid onset of action, and increased bioavailability. Nonetheless, they may exhibit limitations like insufficient mechanical strength and potential for unpleasant taste if not properly formulated. Techniques like freeze-drying, tablet molding, spray drying, sublimation, direct compression, cotton candy process, and mass-extrusion are utilized in MDT formulation, with several patented technologies (e.g., Zydis, DuraSolve, OraSolve, Flash Dose, Wow Tab, Flash Tab,

Oraquick, Quick-Dis, and Nano Crystal) enhancing their effectiveness. The disintegration mechanism of super disintegrants in MDTs involves processes such as swelling, capillary action, repulsion forces, deformation, and gas release, facilitating rapid disintegration and dissolution in the mouth.

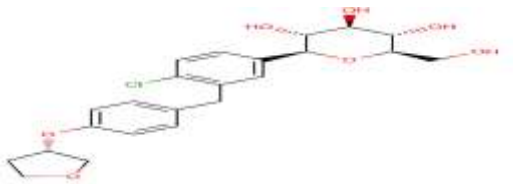

Figure No .1.Structure of Empagliflozin

Empagliflozin, a selective sodium-glucose co-transporter-2 (SGLT2) inhibitor, is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. SGLT2 co-transporters are crucial for glucose reabsorption in the kidneys. Inhibiting SGLT2 reduces renal glucose reabsorption, lowers the renal threshold for glucose, and increases urinary glucose excretion, thereby reducing hyperglycemia, aiding weight loss, and lowering blood pressure. Empagliflozin's IUPAC name is (1S)-1,5-anhydro-1-(4-chloro-3-{4-[(3S)-tetrahydrofuran-3-yloxy]benzyl}phenyl)-D-glucitol, with a molecular formula of C23H27ClO7 and a molecular weight of 450.91 g/mol. It is a white to yellowish, non-hygroscopic powder with very slight solubility in water and varying solubility in organic solvents like methanol and ethanol. Pharmacokinetic studies indicate that peak plasma concentrations are achieved at 1.5 hours post-oral administration, with a distribution volume of 73.8 L and an 86.2% plasma protein binding rate. Empagliflozin is primarily metabolized by glucuronidation via UGT2B7, UGT1A3, UGT1A8, and UGT1A9, without significant interaction with cytochrome P450 isoforms. It is eliminated mainly through feces (41.2%) and urine (54.4%), with a terminal elimination half-life of approximately 12.4 hours.

2. MATERIALS AND METHODS:

2.1. MATERIALS: The preparation of empagliflozin mouth-dissolving tablets involves a variety of ingredients sourced from reputable suppliers. The active pharmaceutical ingredient, empagliflozin, is supplied by Pharma Train. Excipients such as sodium starch glycolate, croscarmellose sodium, mannitol, lactose, Avicel PH102, aspartame, magnesium stearate, and talc are procured from SD Fine Chemicals, Mumbai. Crosprovidone and peppermint flavor are supplied by Nihal Pharma, Hyderabad. The manufacturing process utilizes several key pieces of equipment. An electronic weighing balance from Scale-Tec ensures accurate measurement of ingredients. A Roche Friabilator from Electrolab, Mumbai, tests tablet friability. Compression of tablets is performed using a CMD (Cadmach) compression machine. The Pfizer hardness tester from Mumbai measures tablet hardness, while the LABINDIA UV 3000+ UV spectrophotometer is used for analytical purposes. The Electrolab TDT-08L dissolution apparatus evaluates the dissolution profile of the tablets. Finally, Vernier calipers (model CD-6”CS) are employed for precise measurement of tablet dimensions.

2.2. METHODOLOGY: Analytical Method Development and Preparation of Oral Disintegrating Tablets

Preparation of 0.1 N Hydrochloric Acid (pH 1.2) 8.5 ml of concentrated hydrochloric acid was diluted to 1000 ml with distilled water.

Determination of λmax of Empagliflozin in 0.1N HCL: A working standard of 100 mg empagliflozin was dissolved in 10 ml methanol and diluted to 100 ml with 0.1N HCL to obtain a 1000 µg/ml solution.

Further dilutions were made to 100 µg/ml and 10 µg/ml. The 10 µg/ml solution was scanned between 200-400 nm to determine the λmax, which was found to be 257 nm.

Construction of Calibration Curve: A 1000 µg/ml stock solution of empagliflozin was prepared similarly. From this, 100 µg/ml solution was obtained and further diluted to concentrations of 2, 4, 6, 8, and 10 µg/ml. Absorbance was measured at λmax = 257 nm.

Preparation of Mouth-Disintegrating Tablets: Empagliflozin mouth-dissolving tablets were prepared using the direct compression method. Ingredients included empagliflozin, sodium starch glycolate (SSG), crospovidone, croscarmellose sodium (CCS), mannitol, lactose, MCC pH 102, aspartame, peppermint flavor, talc, and magnesium stearate. Tablets were compressed using 6 mm flat round punches, each weighing 75 mg.

EVALUATION OF TABLETS: The formulated Tablets were evaluated for the following quality control studies & In vitro dissolution studies

Pre formulation studies:

Angle of Repose:

The angle of repose is the maximum angle between the surface of a pile of powder and the horizontal plane. It was determined using the funnel method, where a accurately weighed powder blend was placed in a funnel. The funnel height was adjusted so that the tip just touched the apex of the powder blend. The blend was allowed to flow freely through the funnel onto a surface, forming a cone. The angle of repose (q) was calculated using the formula

$$q = \tan^{-1}(h/r)$$

Where h is the height and r is the radius of the cone base. This angle is indicative of the flow properties of solids, reflecting inter-particle friction and resistance to movement.

Density:

Bulk Density (BD): Measure the mass of powder and its bulk volume without compaction to calculate bulk density using the formula Db = M / V0.

Tapped Density (TD): Measure the mass of powder and its volume after tapping to minimum volume using a tap density tester. Calculate tapped density using Dt = M / Vf.

3. Carr's Index: Calculate compressibility index to assess powder blend compressibility using the formula: Compressibility index (%) = [(Tapped density - Bulk density) / Tapped density] x 100.

4. Hausner's Ratio: Calculate Hausner's Ratio to evaluate powder flowability using the formula: Hausner's Ratio = Tapped density / Bulk density.

Post compression Parameters:

General Appearance: Evaluate tablets for shape, color, texture, and odor.

Average Weight/Weight Variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$\textbf{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

$$\textbf{\%weight variation} = \frac{\text{average weight - weight of each tablet}}{\text{Average weight}} \times 100$$

Thickness: Measure tablet thickness using a Vernier caliper (n=3).

Hardness Test: Measure tablet hardness using a Monsanto hardness tester (n=3) to assess tablet strength.

Friability Test: Determine friability by weighing 20 tablets before and after tumbling in a friabilator. Calculate friability as percentage loss in weight:

$$\%Friability = [(W1 - W2) / W1] \times 100$$

Wetting time: Five circular tissue papers were placed in a petridish of 10cm diameter. Ten millimeters of water was added to the petridish. A tablet was carefully placed on the surface of the tissue paper in the petridish at 25^0C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicates of six. Wetting time was recorded using a stopwatch.

***In- Vitro* Dispersion Time:** In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of 0.1N HCL. Tablets from each formulation were randomly selected and in vitro dispersion time was performed.

Water absorption ratio(%):A piece of tissue paper folded twice was placed in a small petridish (Internal diameter=6.5 cm) containing 6ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured. The water absorption ratio (R) wasw determined using the following equation.

$$Water\ absorption\ ratio\ (R) = \frac{Wa - Wb}{Wb} * 100$$

Where, Wb is the weight of the tablet before water absorption and Wa is the weight of the tablet after absorption.

Assay: To determine the Empagliflozin content, ten tablets were weighed and powdered. A portion of the powder equivalent to 100 mg of Empagliflozin was transferred to a 100 ml volumetric flask. To this, 10 ml of methanol was added, and the mixture was shaken vigorously for 15 minutes to extract the drug. The volume was then adjusted to the mark with 0.1N HCl, and the solution was filtered. From this prepared solution, 0.1 ml was diluted in a 10 ml volumetric flask with 0.1N HCl. The Empagliflozin content was determined by measuring the absorbance at 257 nm using UV spectrophotometry. The drug content was calculated using a standard calibration curve. The mean percentage of drug content was derived from three independent determinations. The quantity of drug in the portion was calculated using the formula:

Assay = test absorbance/standard absorbance*standard concentration/sample concentration*purity of drug/100*100

***In-Vitro* Dissolution Study**: Dissolution studies were performed using the USP-II apparatus (Paddle method). A total of 900 ml of 0.1N HCl was placed in the dissolution vessel, which was equilibrated to 37±0.5°C. A tablet was placed in the vessel and the apparatus was operated at 50 rpm for 30 minutes. At specific time intervals (2, 4, 6, 8, 10, 15, 20, and 30 minutes), 5 ml of the dissolution medium was withdrawn filtered, and replaced with 5 ml of fresh medium to maintain sink conditions. The samples were analyzed using UV spectrophotometry at a wavelength of 257 nm. The parameters for the dissolution study are summarized in Table 5.

Release Kinetics: The release kinetics of the drug from the matrix system were analyzed by fitting the dissolution data to several release models: zero-order, first-order, and diffusion models.

A. Zero-Order Release: It defines a linear relationship between the fractions of drug release

Table No.1. Formulation Composition

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 2: Angle of Repose Limits

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Table 3: Compressibility Index Limits

Scale of Flow ability (USP29-NF34)

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Table No .4: Weight Variation Tolerance For Uncoated Tablets
Acceptance criteria for tablet weight variation (USP 29-NF 34)

Average weight of tablet(mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Table No – 5: 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

Table No 6: 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

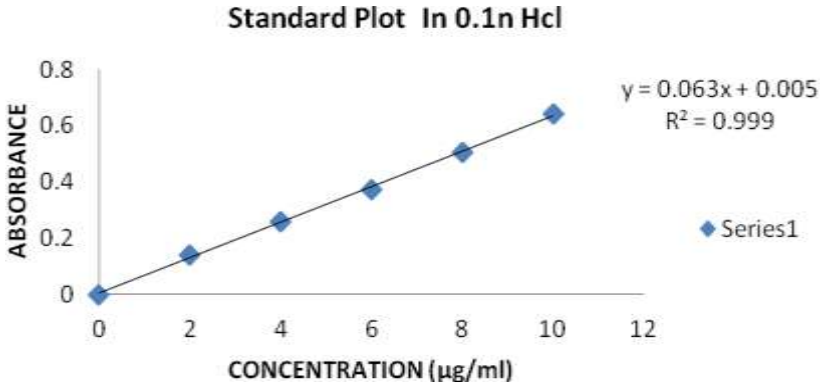

Figure No .2: Standard Calibration Curve ofEmpagliflozin in 0.1 N HCL

II) EVALUATION OF BLEND

A) Pre Compression studies

Table No – 7: Pre Compression Studies of Empagliflozin Oral 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 – 8: Post Compression Studies For OralDisintigrating 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	100.7	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	101.3	2.8	31	41	36	pass	64.3
F8	3.2	0.48	100.8	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

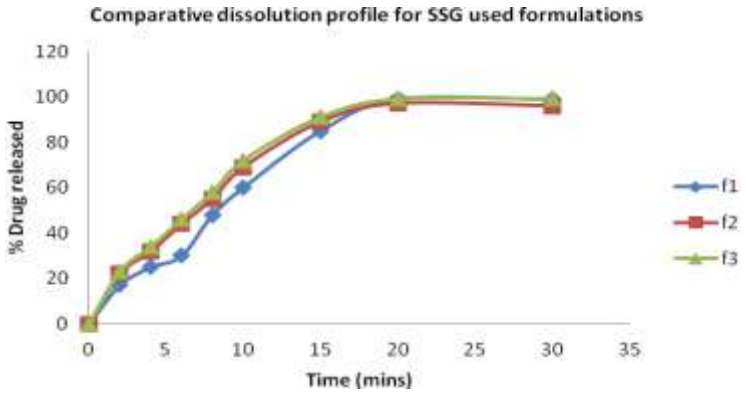

Figure No .3: Comparative dissolution profiles for SSG used Formulations

***IN VITRO* DISSOLUTION STUDIES OF Empagliflozin TABLETS:**

Table No 9: 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

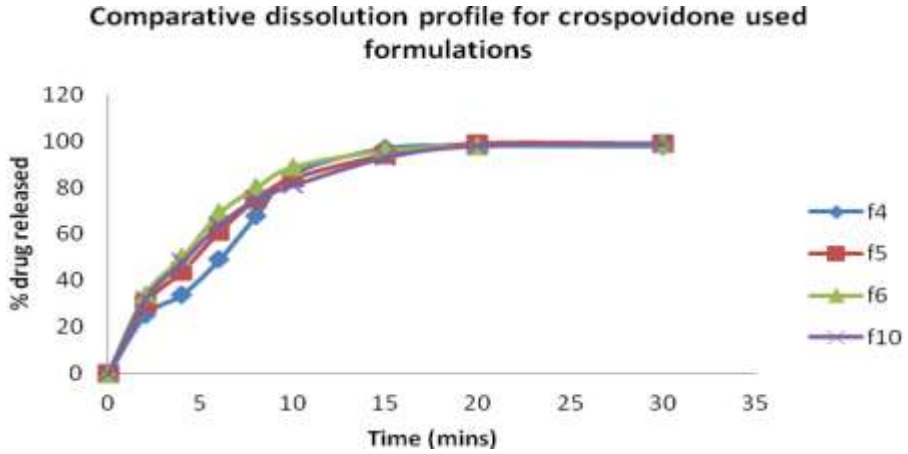

Figure No .4: Comparative dissolution profiles forCrospovidone used Formulations

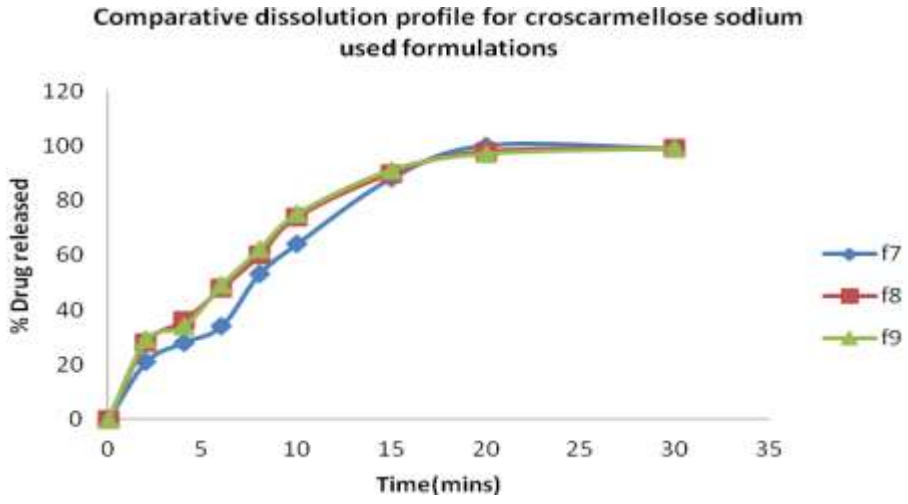

Figure No .5: Comparative dissolution profiles for Croscarmellose sodium used Formulations

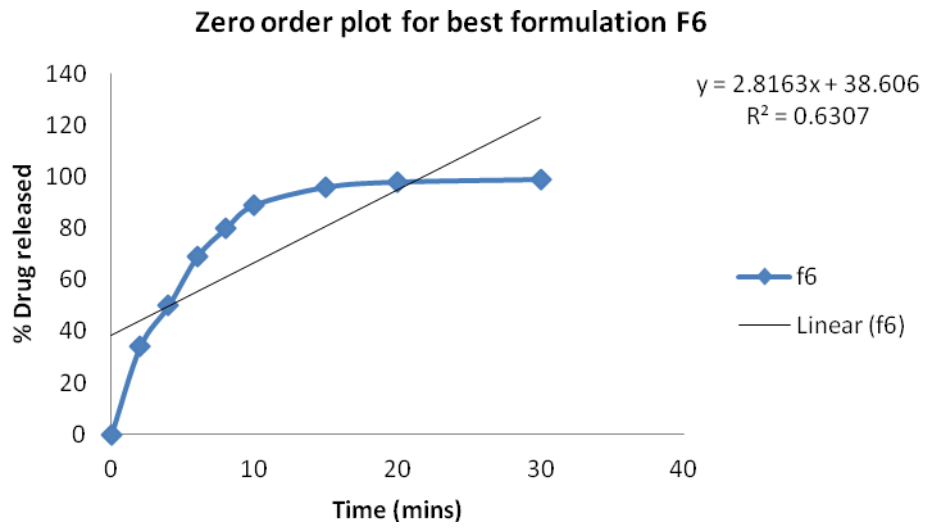

Figure No .6: Zero order plot for best formulation F6

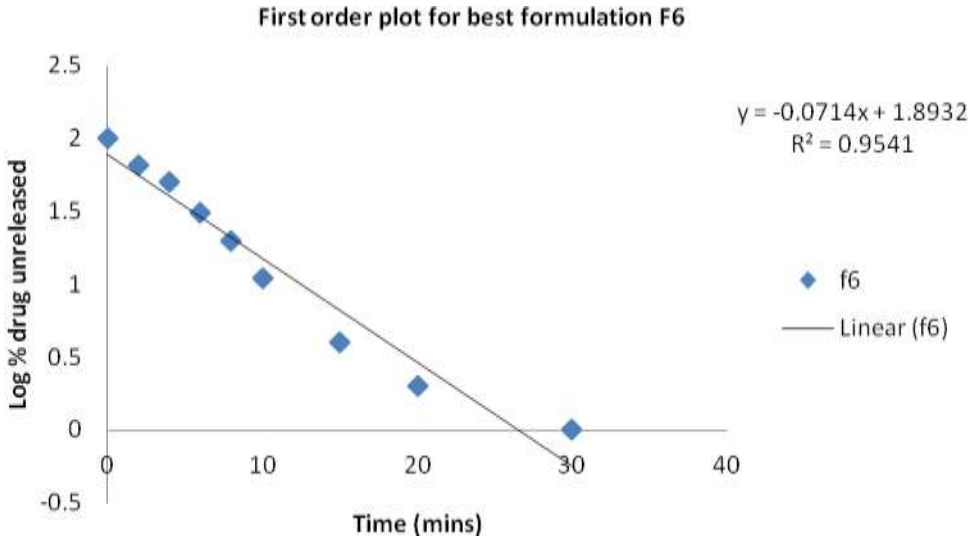

Figure No .7: First order plot for best formulation

$$Q=KoT$$

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 proposed that as the exposed surface area of the tablet decreases exponentially over time during the dissolution process, drug release from slow-release tablets often follows Apparent first-order kinetics. The relationship is described by the equation:

$$\log_{10}(1-Q)=-K1T \backslash \log(1 - Q) = -K\_1 T \log(1-Q)=-K1T$$

In this model, a linear plot of the logarithm of the fraction of drug remaining versus time indicates that the release kinetics conform to first-order behavior.

3. RESULTS AND DISCUSSION

1. Construction of Standard Calibration Curve ofEmpagliflozinin0.1 N HCL:

The absorbance of the solution was measured at 257nm, using UV spectrometer with 0.1N HCL as blank. The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml. Standard plot of Empagliflozin by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown fig.

4. CONCLUSION:

A Suitable analytical method for Empagliflozin was developed using UV-Visible spectrophotometry, with a λmax identified at 257 nm in 0.1N HCl. The direct compression method was successfully utilized to manufacture mouth disintegrating tablets of Empagliflozin, employing excipients such as SSG, Crospovidone, and Croscarmellose sodium. The evaluation parameters, including hardness, friability, weight variation, and drug content, were within permissible limits for all formulations. An in vitro drug release study revealed that formulation F-6 exhibited the best performance, achieving 99% drug release within 30 minutes. Notably, the formulation with Crospovidone demonstrated superior release characteristics compared to others. Thus, the developed mouth disintegrating tablets of Empagliflozin effectively release the drug within 30 minutes using a minimal amount of excipients and a straightforward manufacturing process, meeting the study's objectives.

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