International Journal of Medical Toxicology & Legal Medicine **Volume 26, No. 1 and 2, 2023**
e-ISSN: 0974-4614
p-ISSN: 0972-0448

Design And Characterization Of Dapagliflozin Nano-Particles

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Received: 11.01.2023 Revised: 08.02.2023 Accepted: 16.03.2023

ABSTRACT
The development of sustained-release Dapagliflozin (DPZ) nanoparticles marks a significant advancement in the management of type 2 diabetes mellitus, particularly for patients requiring long-term glycemic control. This study meticulously evaluated the physicochemical properties, in vitro drug release profiles, and stability of DPZ-loaded nanoparticles, aiming to enhance therapeutic efficacy and patient compliance. In summary, the development of DPZ nanoparticles, along with the utilization of polymeric nanoparticles and stimuli-responsive systems, represents a promising strategy to enhance the oral bioavailability and therapeutic efficacy of this poorly soluble drug. These advancements in drug delivery technologies hold significant potential for improving the treatment of conditions such as diabetes.

Keywords: Dapagliflozin, Sustained-release, Nanoparticles, enhance patient compliance.

1. INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder characterized by elevated blood glucose levels, affects millions worldwide and poses significant health and economic burdens. Type 2 diabetes mellitus (T2DM), the most prevalent form, is often managed through lifestyle interventions and pharmacotherapy. Dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, has emerged as an effective oral anti-diabetic drug by promoting glucose excretion through urine, thereby reducing hyperglycemia. However, its conventional formulations often require frequent dosing due to a short half-life, leading to challenges in patient compliance and maintaining consistent therapeutic levels. Sustained-release drug delivery systems, particularly nanoparticle-based formulations, offer a promising approach to overcome these limitations. Nanoparticles enhance drug solubility, bioavailability, and controlled release, ensuring prolonged therapeutic effects and reduced dosing frequency. By encapsulating Dapagliflozin in nanoparticles, it is possible to achieve sustained drug release, improve pharmacokinetic profiles, and enhance patient adherence, which is critical for managing chronic conditions like diabetes. In vitro evaluation of such formulations provides critical insights into their physicochemical properties, drug release kinetics, and stability, serving as a foundation for further in vivo studies. This study focuses on the formulation and in vitro evaluation of sustained-release Dapagliflozin nanoparticles, aiming to optimize their therapeutic efficacy for T2DM management. The investigation includes nanoparticle synthesis, characterization, and assessment of drug release profiles under simulated physiological conditions, with the goal of developing an effective and patient-friendly drug delivery system [1, 2].

2. MATERIALS AND METHODS

Table.2.1:List of Chemicals

S.No.	Chemicals	Brand
1	Dapagliflozin (mg)	Mediseller A Unit of Medicare Chandni Chowk, New Delhi
2	Sodium Caprate (mg)	Aggarwal Mercantiles Janakpuri, New Delhi
3	Tween-20(ml)	NKBR College of Pharmacy and Research Centre Meerut
4	Poly Lactic-co-glycolic acid (mg)	Aggarwal Mercantiles Janakpuri, New Delhi
5	Methanol(ml)	NKBR College of Pharmacy and Research Centre Meerut
6	Final Volume H2O	NKBR College of Pharmacy and Research Centre Meerut

Table.2.2:List of Equipments Used

S.No.	Equipments	Manufacturer
1	UV-Visible double beam Spectrophotometer	ShimadzuUV1700
2	Electronic Balance	Sortorius Single Pan
3	Magnetic Stirrer	Remiequipment, Mumbai.
4	pH meter	ElicoL1120
5	Brookfield Viscometer	LVII model
6	FTIR	PerkinElmer
7	Optical microscope	Nikon U.S
8	AFM	Commercial Nanoscope III Digital Instruments, Veeco,
9	TEM	Topcon, Paramus, NJ
10	Cooling centrifuge	Remi

2.1 Preformulation Studies

Preformulation may be described as a stage of development process during which the researches characterize the physical, chemical and mechanical properties of the drug substance to form effective, stable and safe dosage form. Hence, pre- formulation studies are essential to characterize the drug for proper designing of the drug delivery system. The pre- formulation studies which were performing in this project include.

2.1.1 Description

Organoleptic characters of drug was observed and recorded by using descriptive terminology [3].

2.1.2 Melting Point

Capillary tube, which is sealed at one end is charged with sufficient amount of dry powder to form a column in the bottom of the tube 2.5 mm to 3.5 mm, and packed down as closely as possible by moderate tapping on a solid surface. The apparatus is operated according to the standard operating procedure. The block is heated until the temperature is about 30°C below the expected melting point. The capillary tube is inserted into the heating block, and the heating is continued at a rate of temperature increased of about 1°C to 2°C per minute until melting is completed [4].

2.1.3 Solubility Studies

The spontaneous interaction of two or more substance to form a homogenous molecular dispersion is called as solubility. 10mg of drug was a suspended separately in 10ml of different solvents at room temperature in tightly closed tubes and shaken. The solubility profiles of two drugs in various solvents are shown in the table (2.3) [5].

Table.2.3: Solubility Profile I.P. 1996

Descriptive term	Parts of solvent required for 1 part of solute.
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10, 000
Practically insoluble of Insoluble	Greater than or equal to 10,000

2.1.5. Identification of Drug Sample

2.1.5.1. Finding the absorption maxima (λ max)

The absorption maxima were found for drug identification. Ultraviolet visible spectrophotometry has been used to obtain specific information on the chromophoric part of the molecules. Organic molecules in solutions when exposed to light in the visible/ultraviolet region of the spectrum absorb light of particular wavelength on the type of electronic transition associated with the absorption. Calibration of the drug was performed using different media such as 0.1 N hydrochloric acid (pH-1.2) and phosphate buffer (pH-7.4). The λ max of the drug was observed by scanning the drug solutions between 200–800 nm using double beams UV-Visible Spectrophotometer. The standard calibration curve was plotted using concentration vs absorbance to get the linearity and regression factor [6].

2.1.7 Fourier transforms infrared (FTIR) spectral analysis

The FTIR study was done using Fourier Transform Infrared spectrophotometer (Shimadzu, 8400S, Japan). The test samples were mixed with KBr, pressed into a disk and scanned from 400–4000 cm^{-1} [7].

2.1.7.1 Differential Scanning Calorimetry

The physical state characteristics of Dapagliflozin entrapped nano-particles were characterized by Differential Scanning Calorimetry (DSC-60, Shimadzu, Japan). Each sample was selected in standard aluminum pans with lids and purged with air at a flow rate of 40ml/min. The heat flows were recorded in the range of 30-300°C under inert nitrogen atmosphere [8].

2.2 Method of preparation of Dapagliflozin loaded Nanoparticles

2.2.1 Solvent dispersion (Nano-precipitation)

The nanoparticles are prepared by dissolving the Dapagliflozin in organic phase Methanol along with the Poly (lactic-co-glycolic acid) polymer (PLGA), Sodium Caprate and added to the aqueous solution containing Tween-20 which acts as an emulsifier. The solution of organic phase was added in dropwise into aqueous phase under homogenization at 11,000 rpm. The dispersion was kept under magnetic stirring for 4 hrs at room temperature. The solution is kept under reduced pressure for about 2–3 min. This process forms nanoparticles loaded with drug [9].

Table 2.4 Preparation of Dapagliflozin loaded Nanoparticles

S.No.	Ingredients	BatchNo					
		F1	F2	F3	F4	F5	F6
1	Dapagliflozin (mg)	100	100	100	100	100	100
2	Sodium Caprate(mg)	1	1.5	2	1	1.5	2
3	Tween-20(ml)	2	2	4	2	2	4
4	Poly Lactic-co-glycolic acid (mg)	25	50	75	25	50	75
5	Methanol(ml)	1	2	3	1	2	3
6	Final Volume H2O	100	100	100	100	100	100

2.3 Evaluation of Dapagliflozin Nano-particles

2.3.1 Particle Size

The cuvettes provided by Biophysics require approx 70 µL sample volume. Material must be highly mono-disperse and stable. It is advisable to filter or spin down samples before loading to remove any highly-scattering large aggregates or dust particles (NB: scattering is proportional to (diameter), therefore large particles will dominate the data, even at very low relative concentrations). Particle size was calculated using Malvern Zeta Sizer [10].

2.3.2 Zeta Potential

Zeta potential is the measurement of attraction or repulsion in between particles. Its measurement brings details about the dispersion mechanism which is used to measure electrostatic dispersion. The zeta potential calculation is an important limitation across a various range of industries incorporates pharmaceuticals, brewing, medicine, ceramics, and water treatment. For colloidal stability, the repulsive forces between two particles should be ascendant. Zeta potential is a useful index of magnitude for interaction between colloidal particles. In general, the colloidal systems stability is determined using measurements based on zeta potential [11].

2.3.3 Determination of pH

The digital pH meter is used to find out the pH value of a formulated topical gel. The values of prepared formulations are between the ranges of 4-8 that ignores the chance of skin irritation [12].

2.3.4 Spread Ability

The assessment of spread capacity, two glass slides were taken, and the prepared gel was compressed in between the two glass slides to steady stability by applying weight and leaves it for 6min. The value of Spreadability is gathered by determining the time taken for the two glass slides to get separated [13].

2.3.5 Percentage Yield

The practical yield of each sample is determined by weighing the empty container and the container along with the gel formulation and subtraction of empty container with the container along with the gel. The expression “uniformity of dosage unit” is explained as the substances degree of uniformity among dosage units. The content uniformity test depends on the assay of the active medicament. 2 mg of the nanoparticles is taken and dissolved in 100 ml of phosphate buffer of pH 6.8. The above solution is allowed to stand for 30 min followed by gentle stirring to enhance the solubility of the drug. Then, it is treated, and the absorbance of the solution was identified spectrophotometrically at 291 nm using phosphate buffer pH 6.8 as blank [14].

2.3.6 Viscosity Estimation

Alteration in viscosity of the product displaysadjustment instability and efficacy of the product. Uniformity of formulation lies on the ratio of the solid fraction to liquid fraction which constructs gel structure. The viscosity of nanoparticles was acquired using Brook- Field viscometer DE-V model using spindle no 61 and spindle speed of 50rpm at 37°C [15].

2.3.7 In vitro drug Release Study

Franz-diffusion cells equipment is used to study the in vitro drug release using various formulations. The specific quantity of formulation was applied on the membrane positioned between the donor and receptor chambers with an available diffusion area. Fill the receptor chamber with phosphate buffer pH 6.8 and is blended repeatedly with a tiny magnetic bead, the speed of 50 rpm is continued at the temperature at 37°C ± 2°C. At different meantime, the samples were taken and then it is exchanged with the same volume of phosphate buffer pH 6.8 to maintain the volume of dissolution medium. In all cases, sink conditions are seen. The obtained samples were analyzed spectrophotometrically at 291 nm [16].

2.4 Stability Study

The concentration of an active ingredient of all formulation may fall with upraise in the temperature and time. This assists in drop in the potency of the product. Stability study in various temperatures ought to be dispensed to anticipate the formulation stability. Stability studies are strenuous at regulating the outcome of aging and storage under divers circumstance on the formulated gel. Stability studies take place to detect whether any chemical breakdown of nanoparticles formulations take place or not. The chief formulation was kept at 30±2°C and 40±2°C at RH 65±5 and75±5 RH for 2 months in a glass vial. After 1 or 2 months, the samples were repeatedly tested for the drug content and in vitro release studies [17].

3. RESULTS AND DISCUSSION

3.1. Preformulation Study

3.1.1. Organoleptic Properties

Table.3.1: Identification tests of Dapagliflozin

Parameter	Reported value	Observed value
Appearance	Crystalline	Crystalline
Colour	White	White
Odour	Sweet	Sweet

3.1.2. Melting Point

The melting point was determined by melting point apparatus and the melting point was found to be.

Table.3.2: Melting point of Dapagliflozin

Parameter	Standard	Observed
Melting Point	98-100℃	99℃

3.1.3. Solubility

Solubility of Dapagliflozin was checked in various solvents.

Table.3.3: Determination of drug solubility in various solvents

S.No.	Solvent	Descriptive Term
1	Methanol	Soluble
2	Water	Slightly Soluble
3	Dimethyl Formamide	Soluble
4	**Dimethyl Sulfoxide**	Soluble
5	Tetra hydrofuran, acetone	Soluble
6	*Phenolic*	Soluble

3.1.4. Identification of Drug Sample

3.1.4.1. Finding the absorption maxima (λmax)

The absorbance for various concentrations measured at 291 nm is as follows:

Table.3.4: Standard Graph of Dapagliflozin in 0.1 N hydrochloric acid Solution

S.No.	Conc.(µg/ml)	Abs.at 291nm
1	0	0
2	5	0.408
3	10	0.582
4	15	0.654
5	20	0.764
6	25	0.822

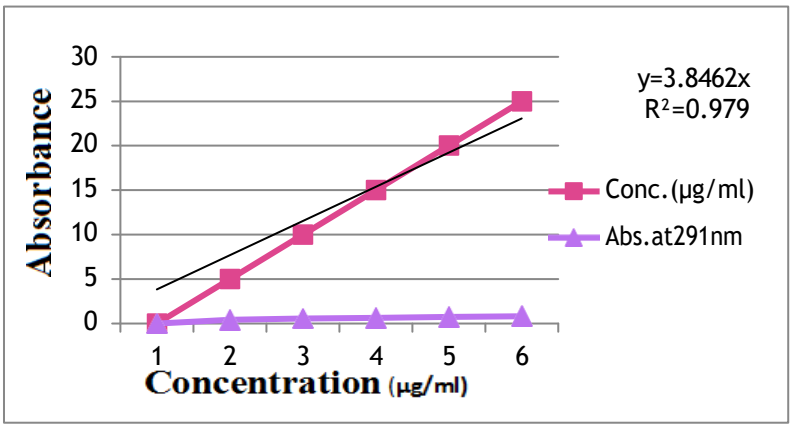

Fig.3.1: Standard Graph of Dapagliflozin in 0.1N hydrochloric acid Solution

3.1.4.2. Determination of Absorption Maximum (λ max)of Dapagliflozin

Determination of Dapagliflozin λ-max was done for accurate quantitative assessment of drug dissolution rate.

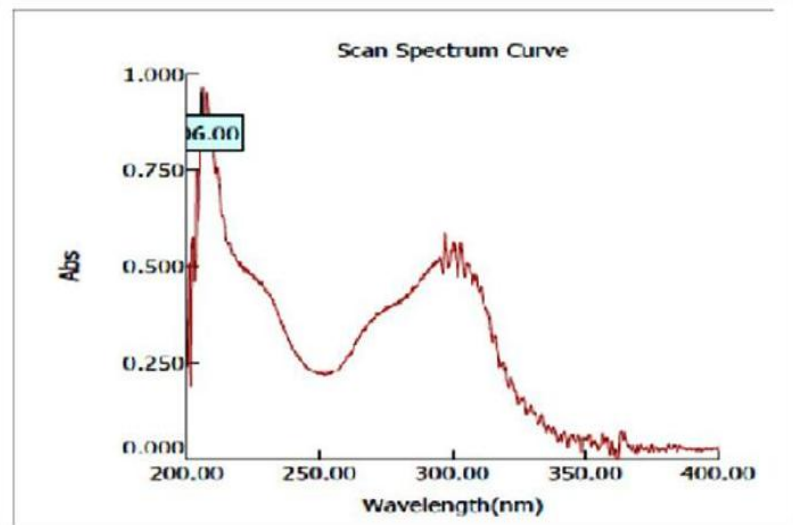

Fig.3.2: Absorption Maximum (λ max) of Dapagliflozin

3.1.4.3 FTIR Study

3.1.4.3.1 IR Spectra of Pure Drug

The FTIR spectrums of Pure Drug with different polymers were used in formulation was showed in Figures.

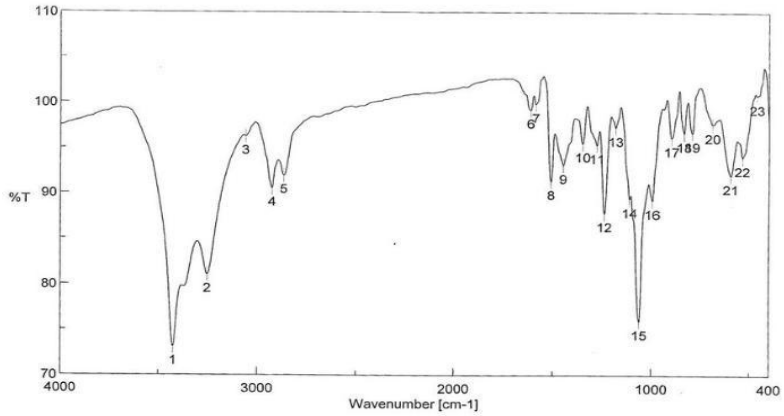

Fig.3.3: FTIR spectrum of Dapagliflozin

Table.3.5:Interpretation of IR spectra of pure drug

S.No.	Functional Group	Range(cm-1)	Observed Frequency(cm- 1)
1	O=C=stretching	1690-1760	1720.25
2	C4H4O stretching	1700-1680	1420.85
3	C-H bend Alkane	1500-1378	1268.64
4	C-O-C stretching	1060-1650	1246.78
5	C-F Bending	1060-1760	1128.40
6	C-H Aromatic Bending	610-1260	710.58

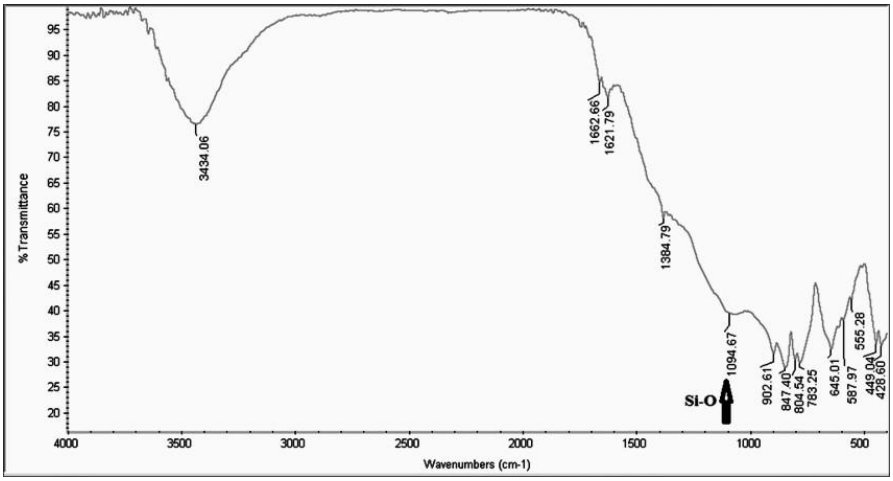

Fig. 3.4: FTIR spectrum of pure drug + Tween-20

Table.3.6:Interpretation of IR Spectra of Pure Drug+Tween-20

S.No.	Functional Group	Observed Frequency (cm-1)
1	O=C=stretching	1718.20
2	C4H4O stretching	1430.80
3	C-H bend Alkane	1286.64
4	C-O-C stretching	1240.56
5	C-F Bending	1117.39
6	C-H Aromatic Bending	710.56

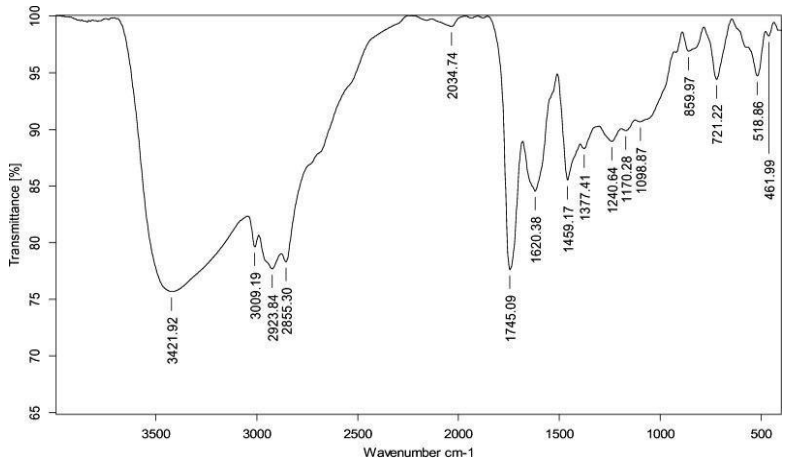

Fig.3.5: FTIR spectrum of pure drug + Sodium Caprate

Table.3.7:Interpretation Spectra of Pure Drug+Sodium Caprate

S.No.	Functional Group	Observed Frequency(cm-1)
1	O=C=stretching	1717.19
2	C4H4O stretching	1429.86
3	C-H bend Alkane	1244.60
4	C-O-C stretching	1237.27
5	C-F Bending	1145.36
6	C-H Aromatic Bending	712.54

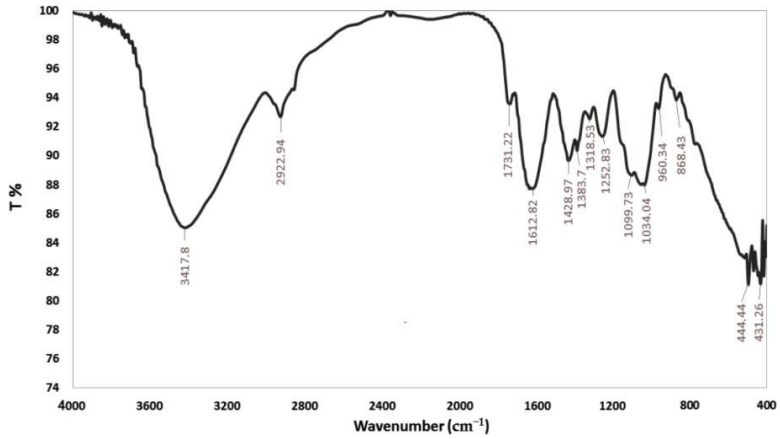

Fig.3.6: FTIR spectrum of Carbopol 934P

Table.3.8: Interpretation Spectra of Pure Drug+Carbopol 934P

S.No.	Functional Group	Observed Frequency (cm-1)
1	O=C=stretching	1607.17
2	C4H4O stretching	1309.84
3	C-Hbend Alkane	1190.59
4	C-O-C stretching	1132.05
5	C-F Bending	1007.28
6	C-H Aromatic Bending	725.42

Discussion of FTIR Spectrum

The IR spectrum of the formulation showed that there was no significant evidence for interaction between drug and the polymer. Peaks of both drugs as well as formulation were observed are same. So this clearly suggest that the drug has not undergone any interaction with the polymer in the formulation, as there was no any shift in the positions of the characteristic absorption bands of drug in the formulation.

3.2. Differential Scanning Calorimetry(DSC)

Two endothermic peaks were visible in the optimized batch at 174.44°C because of Poly Lactic-co-glycolic acid and 200.71°C because of Dapagliflozin. Pure Dapagliflozin endothermic peak was discovered at 207.04°C. The endothermic peak of Dapagliflozin in drug-loaded nanoparticle was somewhat different from that of pure Dapagliflozin. The drug's amorphous rather than crystalline shape might be the cause of this. The medication and the polymers were compatible, according to DSC testing. Fig.3.7 displays the optimized batch's Thermogram.

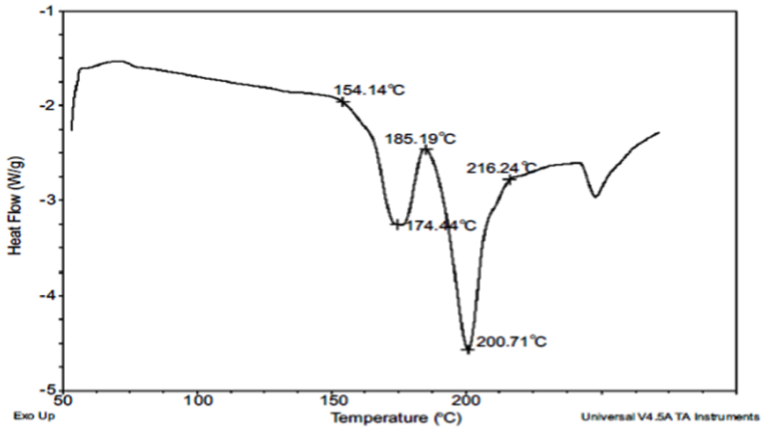

Fig.3.7:DSC thermo grams of Dapagliflozin and Lactic-co-glycolic acid

3.3 Evaluation of Dapagliflozin Nano-particles

Table.3.9: Evaluation Parameters of Nanoparticles

Formulation Code	Particle Size (nm)	Zetapotential (mV)	Determination of pH	Spread Ability	Percentage Yield
F1	264.06	4.42	6.9	13.8	90.23
F2	255.42	3.53	6.4	14.2	93.56
F3	298.21	5.87	6.5	12.6	94.88
F4	234.76	3.98	5.9	13.10	95.45
F5	278.22	4.10	6.8	14.6	94.55
F6	286.14	5.24	6.6	14.01	97.36

Formula Code	Viscosity(cp)
F1	3220
F2	3332
F3	4320
F4	4850
F5	5920
F6	5030

The mean average viscosity was found to be 4000 to 6000 cp; F6 batch shows highest viscosity in Table 3.9.

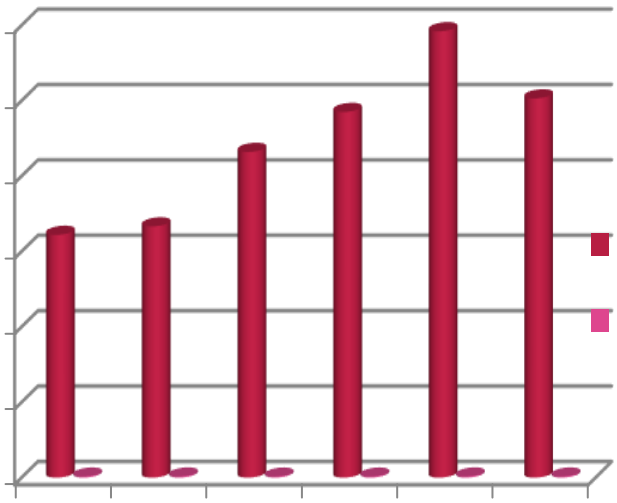

Fig.3.8:A Diagram matically Representation of Viscosity(cp) & Spreadibility

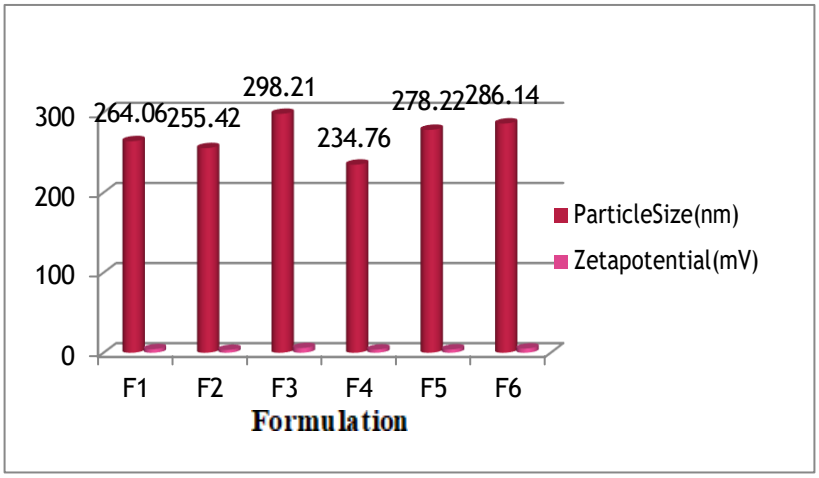

Fig.3.9:A Diagrammatically Representation of Particle size and Zetapotential

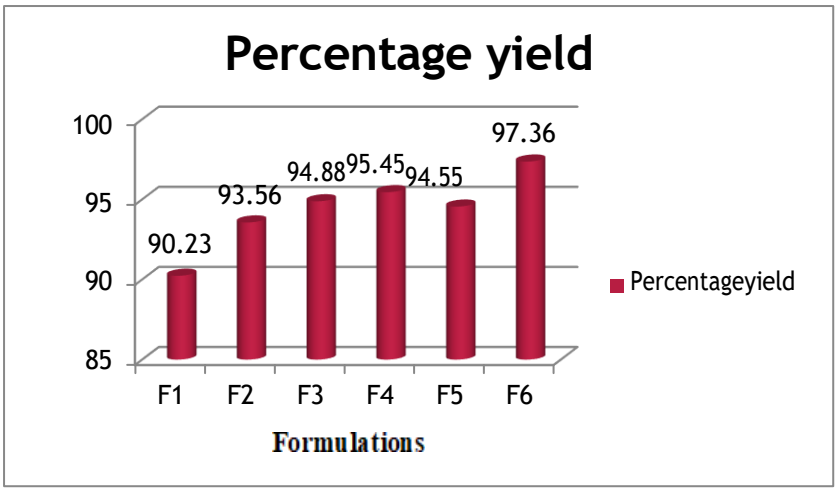

Fig.3.10: A Diagrammatically Representation of % yield

3.4. In-Vitro Drug Release Studies:

Table.3.10:Release studies F1-F6

Time/Hrs	**%Release Drug**					
Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
1	26.56	25.55	21.46	22.52	24.85	26.78
2	34.78	33.04	28.52	30.13	29.58	33.47
3	42.25	41.56	35.32	40.49	37.44	42.89
4	48.52	46.78	46.70	48.21	45.98	52.43
5	55.48	52.65	53.46	57.16	53.43	62.25
6	68.89	64.44	63.24	66.29	67.78	75.67
8	75.34	73.13	72.76	74.90	76.38	80.96
9	84.45	80.54	79.92	82.87	84.62	87.13
10	94.21	92.12	90.32	94.56	94.24	97.90

Point are communicate as mean ± standard deviation (n=3)

Discussion

The in vitro release studies of Nanoparticles were carried out for a period of 10hours in phosphate buffer of pH 7.4 as a dissolution medium. The drug release of F1, F2, F3, F4, F5, and F6 were 94.21%, 92.12%, 90.32%, 94.56%, 94.24% and 97.90% at the end of 10hrs.

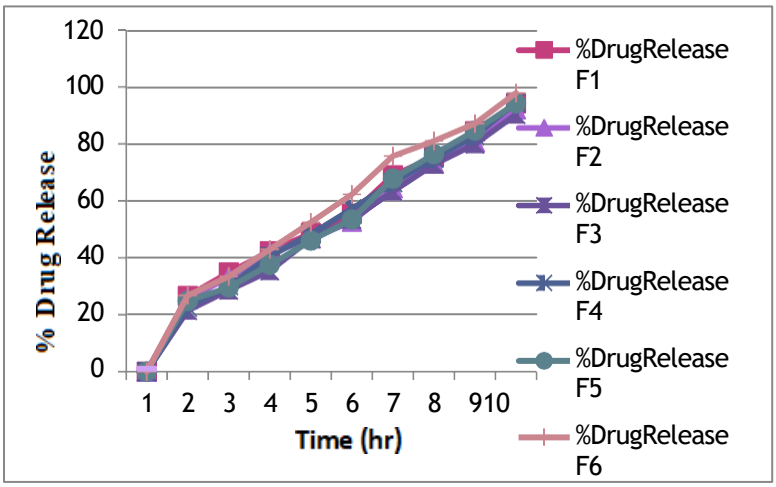

Fig.3.11: A Diagrammatically Representation of % Release Drug

3.5. Stability Studies

The 6-month stability data for optimized nanoparticles stored at refrigerated temperature showed insignificant increase in particle size from 286.14 nm to 290.18 nm, while storage under room temperature conditions showed a slight increase from 286.14 nm to 293.87 nm, respectively. The nanoparticles stored at 40° ± 2°C showed an increase in the size of particles from 289.30 nm and 297.50 nm, respectively. Nanoparticles at the refrigerator conditions shows better stability as compared to room temperature and 40°C conditions which may be attributed to the aggregation of nanoparticles with a rise in temperature [Table 3.11].

Table.3.11: Physical stability data of optimized Nanoparticles for the 6-month stability study

S.No.	Storage Temp. Condition	Initial Particle Size	Particle Size nm		
			2months	4months	6months
1	4°C	286.14	286.14	287.50	290.18
2	Roomtemp.	-	288.10	289.14	293.87
3	40°C		289.30	290.42	297.50

4. CONCLUSION

The development of sustained-release Dapagliflozin Nanoparticles represents a significant advancement in the management of diabetes mellitus, particularly for patients requiring long-term glycemic control. This study meticulously evaluated the physicochemical properties, in vitro drug release profiles, and stability of Dapagliflozin-loaded Nanoparticles, aiming to enhance therapeutic efficacy and patient compliance. The nanoparticles stored at 40° ± 2°C showed an increase in the size of particles from 289.30 nm and 297.50 nm, respectively. Nanoparticles at the refrigerator conditions shows better stability as compared to room temperature and 40°C conditions which may be attributed to the aggregation of nanoparticles with a risein temperature. In summary, the development of Dapagliflozin Nanoparticles, along with the utilization of polymeric Nanoparticles and stimuli-responsive systems, represents a promising strategy to enhance the oral bioavailability and therapeutic efficacy of this poorly soluble drug. These advancements in drug delivery technologies hold significant potential for improving the treatment of conditions such as diabetes.

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