Design, Formulation Development and Characterization of Empagliflozin Nanosuspension

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ABSTRACT

To develop empaglifazon nanosuspension by Solvent evaporation technique using ethanol as organic phase then aqueous phase was prepared by dissolving acetate cellulose in water then add poloxamer-188 and sodium lauryl sulphate. Physicochemical properties like melting point, solubility, particle size and shape, *in-vitro* diffusion studies etc. were performed for the prepared nanosuspension formulations. Based on drug excipient compatibility studies such as FTIR images shown that there is no interaction between drug and excipients. XRD studies revealed the crystalline structure of the formulation. A surface characteristic was determined by SEM. *In-vitro* diffusion studies were carried out by Franz diffusion cell, found the ranges around 95% for both pure and optimized formulations. Research indicates that the Empagliflozin nanosuspension is optimal for prolonged and extended release. This nanosuspension has been found to effectively reduce diabetes mellitus when taken orally.

Keywords: Empaglifazon, nanosuspension, franze diffusion cell, solubility, particle size.

INTRODUCTION

Nanosuspensions are colloidal dispersions comprising nanosized drug particles stabilized by submicron-sized surfactants [1]. Pharmaceuticals that are insoluble in both water and lipid environments can benefit from using these additives to help them become more soluble due to the more excellent solubility of the active ingredient in water. There is no matrix ingredient in nanosuspensions manufactured from a water-soluble medicine dispersed in a distribution. Poorly soluble drugs can be delivered intravenously without obstructing blood capillaries thanks to reduced particle size [2]. This process can be used to transform the suspension into solids. In the case of chemicals with poor solubility, permeability, or a combination of the two, this technique is advantageous. Apart from these benefits, liquid formulations provide number of advantages over other type of formulations [3].

MATERIALS AND METHODS

Materials

Empagliflozin received as a gift sample from Hetero Labs, Hyderabad. Cellulose acetate from

Polaxomer-188 procured from Aadhunik Industries Gujarat. Sodium lauryl sulphate bought from Clearsynth Labs Hyderabad. Chloroform, Ethanol, Methanol and other chemicals and reagents purchased from Merck, India.

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METHODOLOGY

Solubility studies

The drug dissolved in organic solvents to know the solubility nature of drug [4].

Determination of melting point

The drug was filled in one side open capillary tubes and placed in melting point apparatus the point at which drug gets dissolved was noticed as melting point [5].

Construction of standard curve

Preparation of stock solution:

Standard stock solution of Empagliflozin were made by properly weighing 100mg of drug and dissolved in 10ml of Ethanol and make up to a 100ml with 6.8 pH phosphate buffer/medium to achieve a concentration of 1000µg/ml (Stock solution). From this 10 ml of the solution was taken and makeup to 100ml with medium to achieve a concentration of 100µg/ml [6].

Determination of maximum wavelength (λ_{max}):

The samples were scanned in a UV spectrophotometer from 200 to 400 nm against methanol as a blank to identify the wavelength corresponding to maximum absorption [7].

Preparation of standard calibration curve:

Calibration standards of 0-10 µg/ml were prepared by pipetting 0, 2, 4, 6, 8, 10, and 12 ml of the 100 µg/ml solution of above prepared solution into a 10ml volumetric flask and absorbance was measured at 224 nm [8].

Methodology

Trial Formulation

Firstly, organic phase was prepared by dissolving 10 mg of drug in 5 ml of ethanol, and then aqueous phase was made by dissolving 100mg of PVA and 10mg of poloxamer-188 in 10ml of water. The aqueous phase was added into organic phase under constant stirring [9].

Table 1: Trial formulation table

Formulation	Drug (mg)	Ethanol (%)	PVA (mg)	Poloxamer 188 (mg)
F1	10	5	10	10
F2	15	5	15	20

Preparation of nanosuspensions

Solvent evaporation technique was used to make empagliflozin nanosuspension. Firstly, organic phase was prepared by dissolving 100mg of empagliflozin in 5ml of ethanol, and then aqueous phase was prepared by dissolving acetate cellulose, poloxamer-188 and sodium lauryl sulphate in water. The organic phase was added to aqueous phase and placed on magnetic stirrer at 500rpm for 30min until complete solution get dissolved. Empagliflozin nanosuspension was finally obtained and stored for future evaluation [10].

Evaluation of nanosuspension

Particle size

Horiba nanoparticle size analyser was used to determine particle size, mean particle size (PS-Z average in nm). Empagliflozin nanosuspension was diluted with twice distilled water to ensure that the particle concentration

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was low enough to avoid double scattering. The data was analysed at a temperature of 25^0 degrees Celsius and an incidence angle of light of 90^0 Celsius [11].

Fourier's Transform Infra – Red Spectroscopy (FTIR):

The drug excipient interaction was determined using FTIR. The background spectrum is also acquired using the potassium bromide (KBr) pellet method. For the maraviroc-coated potassium bromide discs, an electrical KBr press was used. A pneumatic press was used to press about 2 mg of drug into a pellet after triturating it with about 5 mg dry KBr. The IR spectra of the prepared disc were obtained using a Shimadzu 8400S Fourier transform spectrophotometer. Each spectrum is made up of single average scans taken in the 400-4000cm^{-1} range and compared to a background interferogram [12].

X- Ray diffraction (XRD):

Using an X-ray diffractometer with a copper target and a voltage of 49K V with a current of 20 MA, the crystalline state was characterized by X-ray diffraction (XRD) patterns for physical mixes of drug and other excipients in formulation and the manufactured formulation. A scanning rate of 0.30 C/min was used [13].

Scanning Electron Microscopy (SEM):

Surface morphology of the prepared formulation was determined using SEM. Formulation was then coated with carbon film after drying with the appropriate amount of distilled water. Image capture on a scanning electron microscope, the image was stained with 2% phosphotungistic acid. Surface images were captured using microscopy at a 15 accelerating voltage. [14].

***In-vitro* diffusion studies:**

Diffusion studies for nanosuspension: The percentage of drug released from nanosuspension was determined using the dialysis membrane approach One ml of nanosuspension with a pore size of 0.45 m was injected into the dialysis membrane after the membrane's closed or knotted tightly at one end. After filling the dialysis membrane, the ends were knotted together tightlyOnce the dialysis membrane was filled, it was placed in a 100 ml Phosphate Buffer Solution (pH 6.8) [15-17].

Sample was collected at intervals of 0, 1, 2, 4, 6, 8, 12, 16, 20, 24 h from the phosphate buffer solution phase. To keep the sink condition, the same 5 ml of fresh PBS solution were replenished in the receptor compartment. For Empagliflozin, the released drug absorbance was determined using a UV spectrophotometer at 224nm at each time interval [18-19].

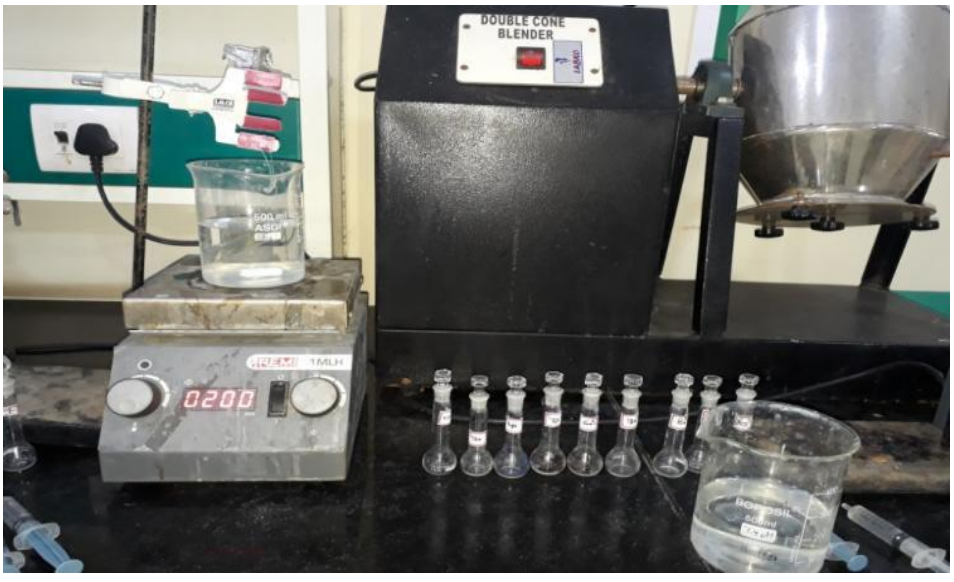

Figure 1: *In-vitro* diffusion studies of nanosuspension

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RESULTS AND DISCUSSION

Solubility study of Empagliflozin

Table 2: Solubility of Empagliflozin in various solvents

Medium	Solubility
Ethanol	Slightly Soluble
Methanol	Slightly soluble
Chloroform	Practically Insoluble
DMSO	Very soluble
Water	Slightly soluble

Melting point Determination:

The melting point of Empagliflozin was observed to be 150°C. The normal value of the melting point of Empagliflozin is 151 to 153 °C that revealed melting point of drug was lying between literatures ranges that indicate purity of the drug.

Calibration curve of Empagliflozin in PH 6.8 buffer:

The 100µg/ml solution of empagliflozin in the Ultraviolet range (200-400 nm) against pH 6.8 the maximum peak observed at the λmax as 224nm. The standard concentrations of Empagliflozin (0-10µg/ml) were prepared in pH 6.8 showed linearity with R^2 value of 0.9237.

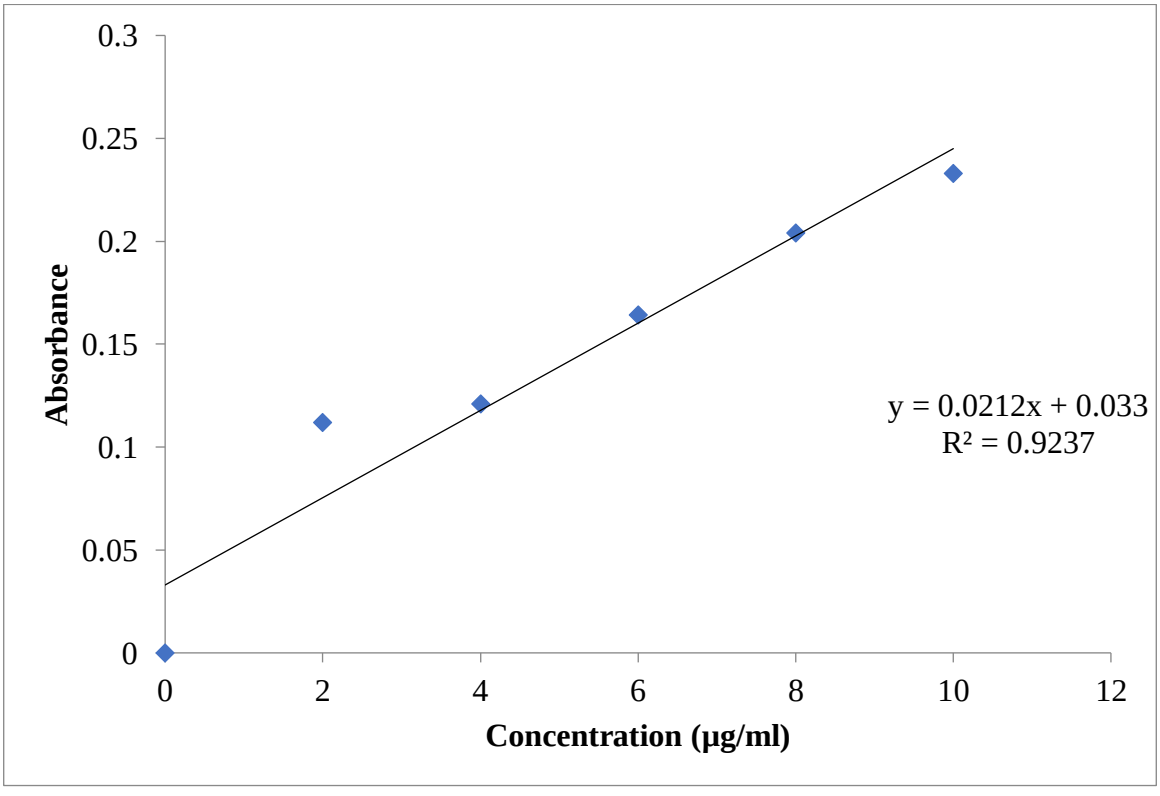

Figure 2: Standard curve of Empagliflozin in pH 6.8 buffer

Drug Excipient Compatibility Studies

The compatibility status of in suspension formulation was investigated using FTIR are shown in figures. In this suspension drug was well persevered with slight changes in terms of bordering or shifting in the temperature of the melt. It is known that the quantity of materials used, especially in drug excipient mixtures could influence the peak shape and enthalpy.

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FTIR studies:

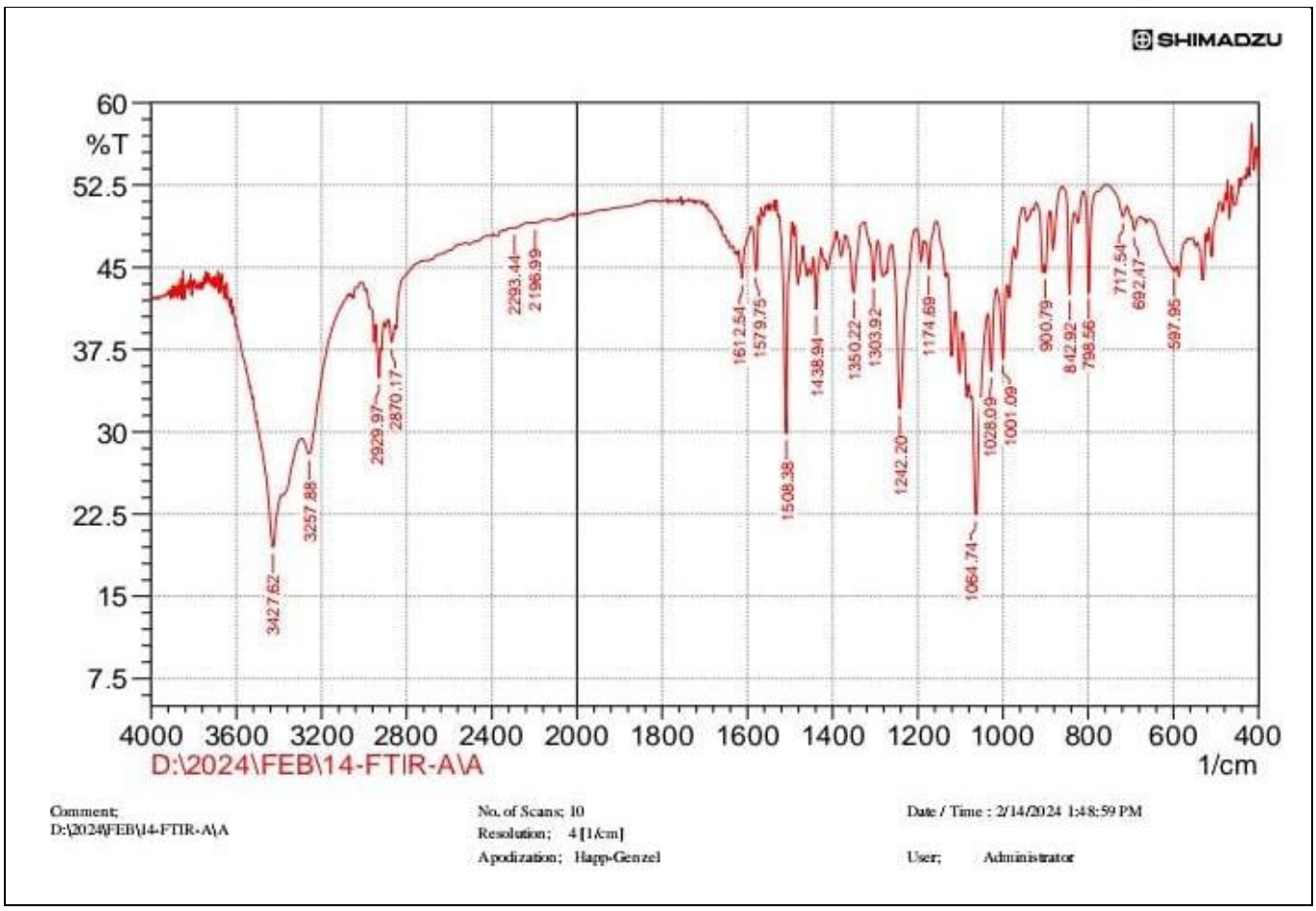

Figure 3: FTIR Spectra of Empagliflozin

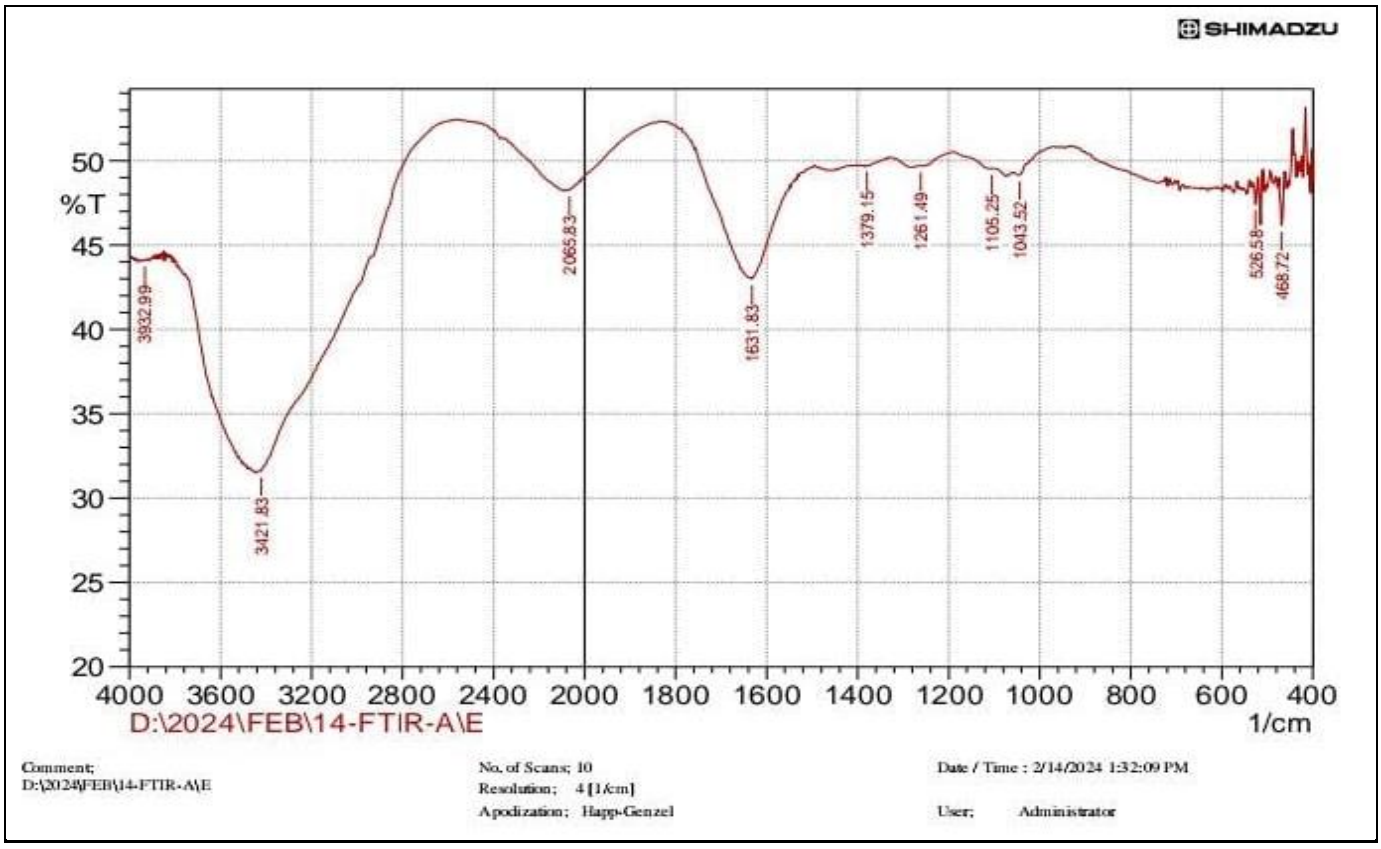

Figure 4: FTIR Spectra of optimized formulation (F2)

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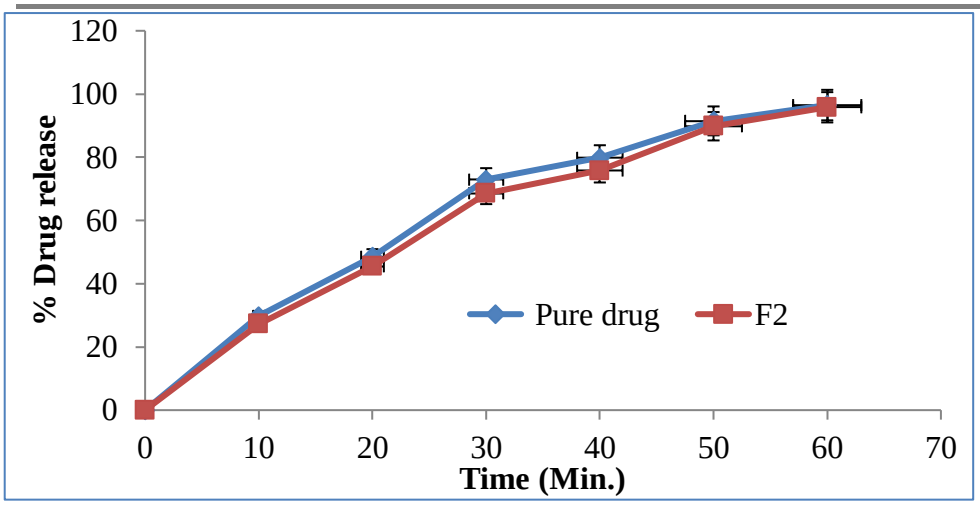

XRD studies:

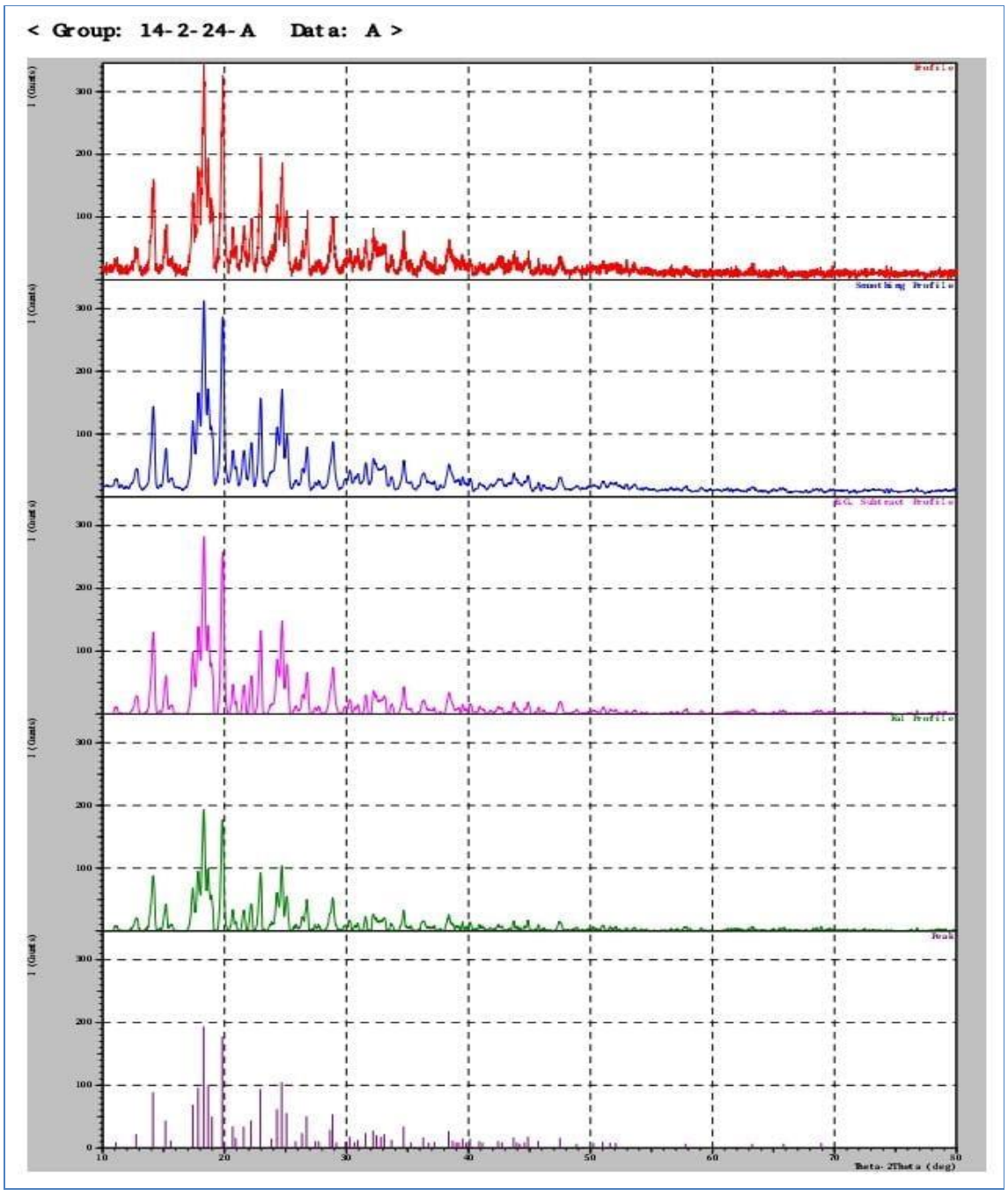

Figure 5: XRD of Empagliflozin

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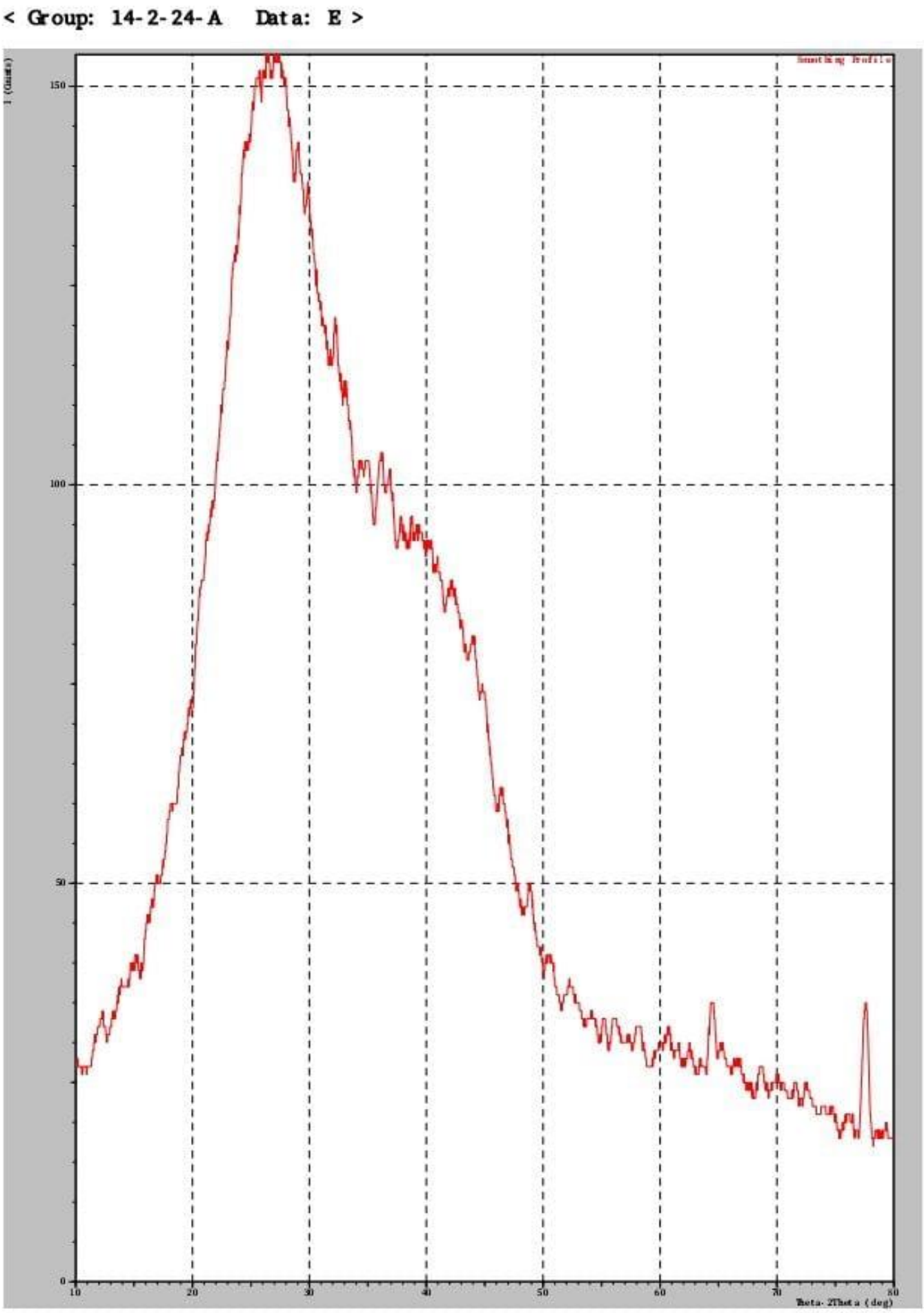

Figure 6: XRD of optimized formulation (F2)

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Scanning Electron Microscopy (SEM) Studies:

The surface characteristic of prepared nanosuspension was studied by SEM. There are some smooth and rough surfaces.

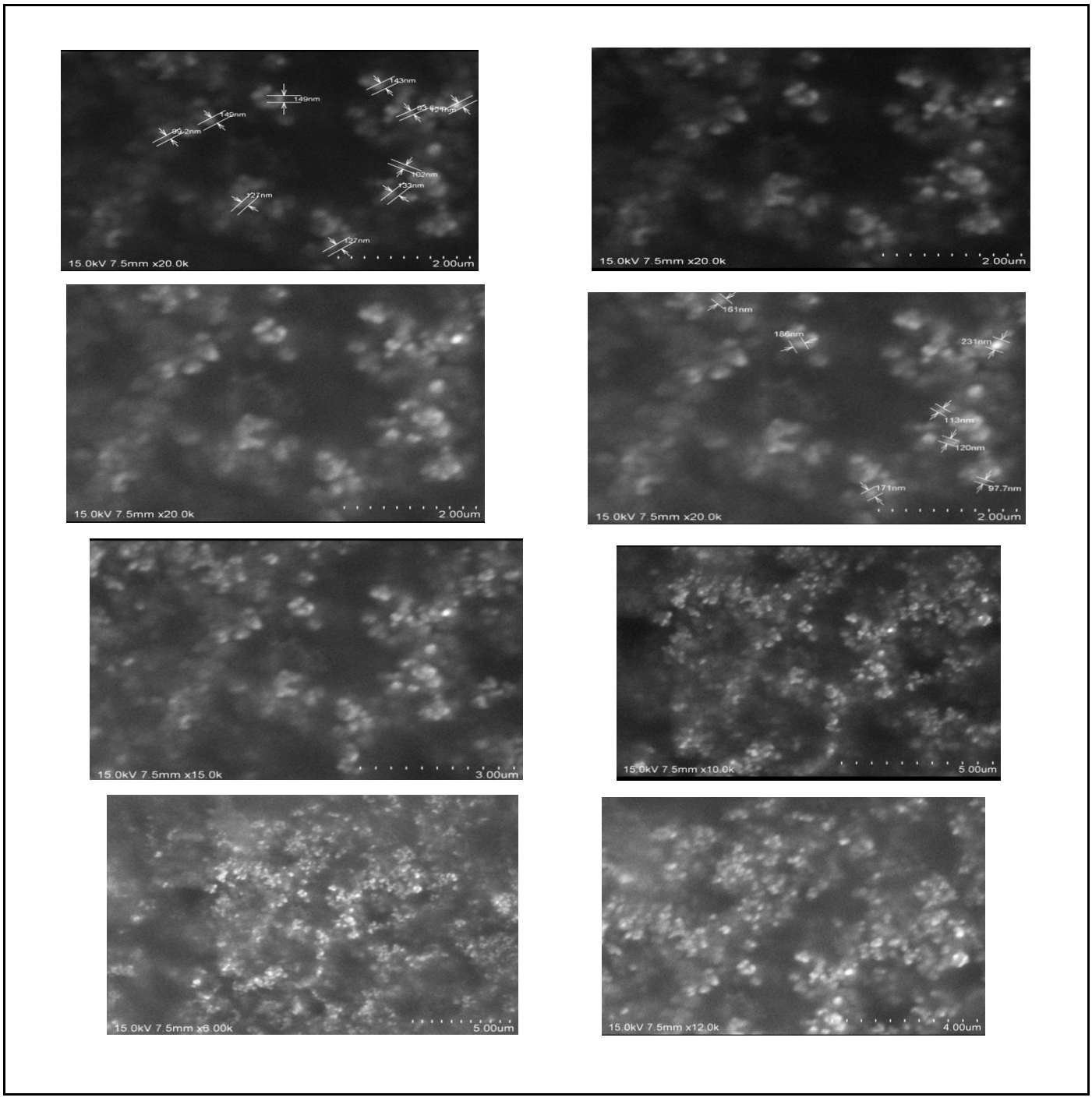

Figure 7: SEM photography of optimized formulation

CONCLUSION

The design and make of nanosuspensions represent a compelling area of research that leverages the advantageous properties of nanocarriers to improve the delivery of pharmaceutical agents. The nanosuspension of empagliflozin was successfully produced by the solvent evaporation method. The prepared nanosuspension exhibits superior *in-vitro* properties. The evidence of results suggests that the prepared nanosuspension provides the best possible extended and prolonged release. The oral administration of this nanosuspension has been found to be effective in decreasing diabetes mellitus. Nonetheless, these findings require further validation through preclinical and clinical investigations.

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