Nanosuspension of Poorly Soluble Anti-Diabetic Drug for Enhancement of Solubility and Dissolution

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Abstract

Canagliflozin is an anti-diabetic drug used in the adjuvant therapy for type-II diabetes as the inhibitor of sodium-glucose co-transporter-2 in the renal tubules. The poor solubility and permeability of the drug show limitations in the formulation development and therapeutic plasma concentration. The objective of the work was to improve the solubility and dissolution of the BCS class IV drug through surfactant stabilized nanosuspension formulation. Nanoparticles were developed by Nano precipitation-solvent evaporation method using Poly vinyl alcohol and Pluronic as surfactants at 1%, 3% and 5% concentration. Formulation optimized with Pluronic exhibited nano size particles (81-117 nm) with monodisperse nature and high stability zeta potential. The nanosuspension prepared using 1% and 3% Pluronic F127 showed 2-fold and 5-fold increase in the drug dissolution compared to the pure drug aqueous dispersion. The drug and surfactant exhibited mild interactions due to hydrogen bonding and hydrophobic interactions as confirmed by the FTIR and TG-DSC analysis, which favoured the formation of stable nanoparticles. The SEM proved the formation of smooth surface spherical shaped nanoparticles. Hence, the development of Canagliflozin nano-formulation was evidenced be an optimized approach to enhance the dissolution of the drug.

Key words

Canagliflozin, Nanosuspension, Dissolution, Pluronic, Nano-precipitation
Introduction

Dissolution is one of the prime parameters to achieve desired concentration of drug in systemic circulation for desired pharmacological response. More than 40% of therapeutic molecules fall under BCS category II and IV, which exhibits very low solubility in water. Low aqueous solubility and poor dissolution characteristics of water-insoluble drugs are the major challenges faced by the pharmaceutical scientists during formulation development. The drugs must undergo complete dissolution and exist in the form of solution for effective absorption at the required site. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug, particle size reduction, crystal engineering, pharmaceutical salts formation, solid dispersions, use of surfactant, complexation of drugs, use of cosolvents, emulsion formation, microemulsions, micelles, polymeric micelles, pro-drugs, solid state alternation, soft gel technology, drug nanocrystals, nanomorph technology, crystal engineering techniques and so forth.\(^1\) Selection of solubility improving method depends on drug property, site of absorption and required dosage form characteristics.\(^2\)

Among the numerous techniques explored for solubility enhancement purpose, nanoparticles offered the most successful results. Several nanoparticles based products are available in the market and there is a paradigm shift in using approach from simply being solubility enhancement to other novel and specific applications. The nanoparticles for drug delivery have been experimented through top-down, bottom-up and combination technologies.\(^3\) One of the main challenges to effective drug delivery is designing an appropriate nanosuspension preparation with low energy input and erosion contamination.\(^4\) Nanonization provides a plausible pharmaceutical basis for enhancing oral bioavailability and therapeutic effectiveness of poorly soluble compounds by increasing their effective surface area. Novel methods have been reported
recently for the pharmaceutical manufacturing of nanoparticles through wet chemical processes, media milling, high pressure homogenization, gas phase synthesis and form-in-place processes.\(^{(5)}\) Nanosuspension offer the unique advantage of increasing solubility of the native drug resulting in faster drug absorption and hence achieving faster maximum plasma concentration. The colloidal dispersion nanosuspension is generally stabilized by optimum concentration of surfactants and/or polymers. The method selected for optimizing stabilizers, approaches for enhancing stability and other factors influence the stability of nanosuspension.\(^{(6)}\) The key factors for nanosuspension optimization include particle characterization, preparation approach, composition, and excipients of the formulation and sterilization methods.\(^{(7)}\)

Canagliflozin is an oral anti-diabetic drug approved in many countries as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It is an inhibitor of sodium-glucose co-transporter 2 (SGLT2), which is expressed in the proximal renal tubules and responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. By inhibiting SGLT2, Canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion (UGE), lowering elevated plasma glucose concentrations by an insulin-independent mechanism in patients with type 2 diabetes. Urinary glucose excretion induced by Canagliflozin leads to an osmotic diuresis, which can be associated with caloric loss and reduction in weight. Clinical studies have shown no glucose malabsorption with Canagliflozin at the recommended dose of 100 – 300 mg. No deaths, hypoglycemic events, or discontinuations due to adverse events were observed.\(^{(8)}\) In the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, Canagliflozin reduced the rates of major adverse cardiovascular events and the results suggested a renal benefit in patients with type 2 diabetes who were at high risk for cardiovascular events, compared with those
treated with placebo. The main challenge faced in Canagliflozin therapy is due to its poor aqueous solubility and permeability (BCS Class – IV drug). Therefore, the present work focuses on the development of Canagliflozin nanoparticles to enhance the solubility and dissolution property, and thereby improve the therapeutic benefit at possible low dose and reduced side effects.

Materials and Methods

Materials:
Canagliflozin was received as gift sample from Dr Reddys Laboratories, Polyvinyl alcohol (PVA) and Methanol was procured from SRL Chem., Mumbai. Pluronic F127 was purchased from Sigma Aldrich, Mumbai. Distilled water was obtained by double distillation method in-house. All the chemicals were of analytical grade.

Preparation of nanoparticles:
Nano-precipitation by solvent evaporation technique was used to prepare Canagliflozin nanoparticles by experimental optimization method. The surfactants (PVA and Pluronic F127) concentration was varied as 1%, 3% and 5% and three different formulations were prepared for each surfactant (Formulation codes CGF1 – CGF6) as described in Table 1. Methanolic solution of the drug was added drop wise into an aqueous solution of surfactant. The mixture was magnetically stirred for 4 hours to evaporate the solvent, followed by ultra-probe sonication for 20 min at 100 V. The formulation was subjected for centrifugation at 2000 rpm to remove excess of surfactant. The nanoparticles were recovered by centrifuging the supernatant at 15,000 rpm for 15 minutes. The pellet (nanoparticles) was redispersed in distilled water using vortex mixer and the obtained aqueous suspension was used for further analysis. The optimized sample was
selected and lyophilized to obtain free flowing powder and used for the analytical characterization studies. (9)

Table 1: Compositions of Canagliflozin (CGF) Nanosuspension

<table>
<thead>
<tr>
<th>S. No</th>
<th>Constituents</th>
<th>CGF1</th>
<th>CGF2</th>
<th>CGF3</th>
<th>CGF4</th>
<th>CGF5</th>
<th>CGF6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Canagliflozin (mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2.</td>
<td>Polyvinyl alcohol (PVA) (%)</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Pluronic (%)</td>
<td></td>
<td>1</td>
<td>3</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Methanol (mL)</td>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Distilled Water (mL)</td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Drug: Surfactant Ratio</strong></td>
<td>1:1</td>
<td>1:3</td>
<td>1:5</td>
<td>1:1</td>
<td>1:3</td>
<td>1:5</td>
</tr>
</tbody>
</table>

**Determination of pH of nanosuspension:**

The pH of all the formulations was determined at room temperature for ensuring that it wouldn’t cause any irritation or damage to the cells and also for the stability. This was carried out using pH meter fitted with glass electrode. (10)

**Drug Content:**

The drug content present in the formulation was determined by taking 0.1 mL of the formulation and lysed with 1 mL of methanol and made up to 100 mL in volumetric flask using distilled water pH 7. The absorbance of the sample was measured using UV-Vis Spectrophotometer at the λ_{max} of Canagliflozin. The drug content was determined from the calibration curve using the formula (11)

\[
\% \text{ Drug content} = \left( \frac{\text{Absorbance of Test Sample}}{\text{Absorbance of Standard Pure}} \right) \times 100
\]

**Particle size distribution and Zeta potential:**

Mean particle size distribution and zeta potential of the nanosuspension were analyzed using dynamic light scattering method. Analysis was performed with 5mW He-Ne laser at a scattering
angle of 90° at 25°C. Sample was placed in cuvette and diluted to the appropriate concentration using deionised water to avoid multi-scattering phenomena. The reported result of each sample is expressed as mean value.\(^{(12)}\)

**In vitro Dissolution studies:**

The *in vitro* drug dissolution studies were carried out with the help of dialysis membrane for all formulations and pure drug in distilled water as medium to check the enhancement in solubility and dissolution of the drug. About 0.5 mL of each formulation was taken in dialysis bag and both the ends of the bag were tied and immersed in the media. The USP dissolution apparatus (paddle model) was sample basket was filled with 100 mL of distilled water as media and maintained at 37°C and 100 rpm for 6 hours. At periodic time intervals the aliquots of about 5 mL samples were collected and subsequently vessels were refilled with 5 mL of the fresh distilled water media. The collected aliquots were subjected to UV-Visible spectrophotometer analysis at the absorbance maxima wavelength to calculate the concentration of drug released at each time point. The cumulative percentage of drug release was estimated at the end of 6 hours. This study was carried out in triplicate and the results represented as mean with standard deviation.\(^{(9)}\)

**Drug Dissolution Kinetics:**

The drug release pattern of the formulations was studied by kinetic modeling using DD solver software. The models studied were Zero order, First order, Higuchi, KorsmeyerPeppas and Hixon-crowell. The best fitted model was chosen from the highest correlation factor ($R^2$), least
sum of squared residual (SS) and n-value for diffusion process in KorsemeyerPeppas kinetics obtained, to understand the mechanism of release of the drug from the formulation. Each model followed different mode of kinetic analysis based on which the release pattern was calculated.\(^{13}\)

**Morphological studies:**

Surface morphology of the optimized nanoparticles was studied by scanning electron microscopy (SEM). Nano formulations were freeze dried and placed on blank double sided sticker tap on metal stub and coated with platinum under reduced pressure. The coated nanoparticles were introduced into the sample holder and scanning carried out at 25kV.\(^{14}\)

**Fourier Transform Infrared Spectroscopy (FTIR):**

The compatibility between the drug and excipient used in the nanoparticles was determined using FTIR by comparing the spectrum of pure drug and freeze dried nanoparticles formulation. About 2 mg of the sample was taken and made into pellet by mixing with IR grade Potassium Bromide (KBr) and compressed in a hydraulic press. Then the IR spectrum was obtained between wave number 4000 cm\(^{-1}\) to 400 cm\(^{-1}\). This spectrum was used to identify the characteristic functional groups present in the samples.\(^{15}\)

**Thermogravimetric analysis and Differential scanning calorimetry (TGA-DSC):**

TGA-DSC analysis was carried out for pure drug and freeze dried nanoparticle formulation. The change in mass of the sample with respect to temperature was analyzed using TGA by subjecting it to controlled temperature in the range of 10\(^\circ\)C per min to 600\(^\circ\)C. In DSC, thermal changes occurring in the nature of the sample irrespective of the mass of sample was studied. About 2-4
mg of the sample was taken in the sample holder of the furnace, which was maintained at 30ºC to 600ºC to get the output changed in the TG and DSC thermogram.\(^{(16)}\)

**Results and Discussion:**

**Physicochemical Characterization of the Nanoparticles:**

The formulated Canagliflozin nanosuspensions (using Pluronic or PVA surfactants) exhibited maximum drug content in the range of 97 – 100 % (Table 2), which confirmed the chemical stability of the drug in the formulations. The average size of the particles in Pluronic based nanosuspension was found to be within 80-117 nm with minimum polydispersity index value as 0.1, which indicated monodisperse narrow size distribution of the particles in the suspension. In case of PVA based suspension, the particle size ranged above 1000 nm (1 - 2.2 µm) with PDI values between 0.8 – 1. Hence, the particles were highly polydisperse in nature. The zeta potential of Canagliflozin-Pluronic nanosuspension was found to be significantly increasing as +3.65, +4.55 and +11.6 with increase in the surfactant concentration as 1%, 3% and 5%, respectively. This phenomenon could be attributed to the enhancement of the physical stability of the nanoparticles in presence of optimum concentration of the surfactant.\(^{(17)}\)

**Table 2: Physico-chemical Characterization studies of Canagliflozin Nanosuspensions**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation Code</th>
<th>Drug Content (%)</th>
<th>Average Particle Size (nm)</th>
<th>Poly Disperstiy Index (PDI)</th>
<th>Zeta Potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CGF1</td>
<td>97.5 ± 0.65</td>
<td>81.94</td>
<td>0.132</td>
<td>+3.65</td>
</tr>
<tr>
<td>2</td>
<td>CGF2</td>
<td>99.4 ± 0.85</td>
<td>117.5</td>
<td>0.122</td>
<td>+4.55</td>
</tr>
<tr>
<td>3</td>
<td>CGF3</td>
<td>100.6 ± 0.61</td>
<td>117.2</td>
<td>0.138</td>
<td>+11.6</td>
</tr>
<tr>
<td>4</td>
<td>CGF4</td>
<td>98 ± 2.02</td>
<td>1320</td>
<td>0.847</td>
<td>+1.43</td>
</tr>
<tr>
<td>5</td>
<td>CGF5</td>
<td>96.9 ± 6.38</td>
<td>1924</td>
<td>1</td>
<td>+1.62</td>
</tr>
<tr>
<td>6</td>
<td>CGF6</td>
<td>100.7 ± 1.56</td>
<td>2270</td>
<td>0.954</td>
<td>+2.97</td>
</tr>
</tbody>
</table>
Figure 1: Particle size distribution of Canagliflozin-Pluronic 1% nanosuspension (NF1)
Figure 2: Zeta Potential of Canagliflozin-Pluronic 1% nanosuspension (NF1)

<table>
<thead>
<tr>
<th>Z-Average (d.nm)</th>
<th>117.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDI</td>
<td>0.122</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.938</td>
</tr>
</tbody>
</table>

Result quality: Good

Figure 3: Particle size distribution of Canagliflozin-Pluronic 3% nanosuspension (NF2)

<table>
<thead>
<tr>
<th>Zeta Potential (mV)</th>
<th>4.55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeta Deviation (mV)</td>
<td>6.51</td>
</tr>
<tr>
<td>Conductivity (mS/cm)</td>
<td>0.334</td>
</tr>
</tbody>
</table>

Result quality: Good
Figure 4: Zeta potential of Canagliflozin-Pluronic 3% nanosuspension (NF2)

<table>
<thead>
<tr>
<th>Size (d.nm)</th>
<th>% Intensity</th>
<th>St Dev (d.nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-Average</td>
<td>117.2</td>
<td></td>
</tr>
<tr>
<td>Pdi</td>
<td>0.136</td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.974</td>
<td></td>
</tr>
</tbody>
</table>

Result quality: Good

Figure 5: Particle size distribution of Canagliflozin-Pluronic 5% nanosuspension (NF3)

<table>
<thead>
<tr>
<th>Mean (mV)</th>
<th>Area (%)</th>
<th>St Dev (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeta Potential (mV)</td>
<td>11.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Zeta Deviation (mV)</td>
<td>6.25</td>
<td>0.00</td>
</tr>
<tr>
<td>Conductivity (mS/cm)</td>
<td>0.0805</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Result quality: Good
Figure 6: Zeta Potential of Canagliflozin-Pluronic 5% nanosuspension (NF3)

<table>
<thead>
<tr>
<th>Size (d.nm)</th>
<th>% Intensity</th>
<th>St Dev (d.nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1320</td>
<td>385.6</td>
<td>57.84</td>
</tr>
</tbody>
</table>

Pdi: 0.847

Intercept: 0.601

Result quality: Refer to quality report

Figure 7: Particle size distribution of Canagliflozin-PVA 1% nanosuspension (NF4)

<table>
<thead>
<tr>
<th>Mean (mV)</th>
<th>Area (%)</th>
<th>St Dev (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.43</td>
<td>100.0</td>
<td>3.27</td>
</tr>
<tr>
<td>3.18</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0.374</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Result quality: Good
Figure 8: Zeta Potential of Canagliflozin-PVA 1% nanosuspension (NF4)

**Z-Average (d.nm):** 1924  
**Pd1:** 1.000  
**Intercept:** 0.819  

**Peak 1:** 323.5  
**Peak 2:** 0.000  
**Peak 3:** 0.000  

**Result quality:** Refer to quality report

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Figure 9: Particle size distribution of Canagliflozin-PVA 3% nanosuspension (NF5)

**Zeta Potential (mV):** -1.62  
**Zeta Deviation (mV):** 4.36  
**Conductivity (mS/cm):** 0.318  

**Peak 1:** -1.63  
**Peak 2:** 0.00  
**Peak 3:** 0.00  

**Mean (mV):**  
**St Dev (mV):**  
**Area (%):**  

**Result quality:** Good
Figure 10: Zeta Potential of Canagliflozin-PVA 3% nanosuspension (NF5)

Z-Average (d.nm): 2270  
Pdi: 0.954  
Intercept: 0.874  

Result quality: Refer to quality report

Figure 11: Particle size distribution of Canagliflozin-PVA 5% nanosuspension (NF6)

Zeta Potential (mV): 2.07  
Zeta Deviation (mV): 3.50  
Conductivity (mS/cm): 0.102  

Result quality: Good

Figure 12: Zeta Potential of Canagliflozin-PVA 5% nanosuspension (NF6)
In vitro drug dissolution studies:

The in vitro drug dissolution of the prepared nanosuspension was compared to the drug release from pure drug aqueous dispersion using distilled water media to check the improvement in the solubility profile of the drug. The pure aqueous dispersion showed only 7% of drug dissolution at the end of 6 hours. The nanosuspension prepared using 1% Pluronic F127 showed double the amount of drug dissolution (around 17%) compared to the pure drug. An increase in the concentration of surfactant to 3% had shown 5 folds increase (around 36%) in the cumulative drug dissolution at end of 6 hours study.\textsuperscript{(18)} The improvement in dissolution of the drug in presence of Pluronic is attributed to the micelle aggregation of the amphiphilic tri-block-co-polymer in aqueous environment above its critical micelle concentration level, which encapsulates the hydrophobic drug and enhances the solubility.\textsuperscript{(19)} However, further increase in the Pluronic F127 concentration as 5% did not show significant changes in the drug dissolution profile. This could be due to saturation solubilization level of the drug in this surfactant.
In case of the PVA based formulations, a significant increase in the dissolution of the drug was observed due to the hydrophilic nature of the surfactant and the micron sized particles.\(^{(20)}\) An increase in the concentration of the surfactant as 1%, 3% and 5% had shown increase in the dissolution rate to reach the cumulative drug concentration of 13%, 20% and 24% at the end of 6 hours study. This increase in the dissolution is approximately 2 to 3 fold, as compared to the pure drug sample.

The higher dissolution of the drug in Pluronic based formulations compared to PVA suspensions could be due to the particle size distribution, wherein the former exhibited monodisperse nanosized particles and the later showed polydisperse micron sized particles. The significant reduction in the size of the particles to nano scale range enhanced the effective surface area to contact the dissolution media, which ultimately resulted in improved solubility and higher dissolution rate of the drug in Pluronic based nanosuspensions.\(^{(21)},(22)\)
**Drug release kinetics:**

The drug dissolution data of pure sample and the formulated nanosuspensions was fitted to various kinetic models to study the mechanism of drug release from the particles. The highest correlation factor \( R^2 \) value and least sum of squared residual (SS value) in the Korsemeyer-Peppas kinetics clearly indicated the drug dissolution due to diffusion mechanism. The n-value of 0.4-0.5 in pure drug and PVA based formulations depicted the drug release by Fickian diffusion mechanism. Whereas, in case of Pluronic based nanosuspensions, the drug release phenomenon followed Anamolous non-Fickian transport mechanism. This could due to the nano size particles in the formulation, which supported higher drug dissolution through the diffusion process.\(^{(13)}\)

<table>
<thead>
<tr>
<th>Kinetics Model</th>
<th>Parameters</th>
<th>Pure Drug</th>
<th>1% PVA</th>
<th>3% PVA</th>
<th>5% PVA</th>
<th>1% Pluronic</th>
<th>3% Pluronic</th>
<th>5% Pluronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation Code</strong></td>
<td>( R^2 )</td>
<td>CGF1</td>
<td>CGF2</td>
<td>CGF3</td>
<td>CGF4</td>
<td>CGF5</td>
<td>CGF6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SS</td>
<td>17.304</td>
<td>54.937</td>
<td>125.002</td>
<td>92.735</td>
<td>31.551</td>
<td>123.723</td>
<td>80.003</td>
</tr>
<tr>
<td>First</td>
<td>( R^2 )</td>
<td>0.583</td>
<td>0.599</td>
<td>0.618</td>
<td>0.832</td>
<td>0.901</td>
<td>0.925</td>
<td>0.949</td>
</tr>
<tr>
<td></td>
<td>( K_1 )</td>
<td>0.015</td>
<td>0.028</td>
<td>0.044</td>
<td>0.051</td>
<td>0.036</td>
<td>0.079</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>SS</td>
<td>16.304</td>
<td>49.555</td>
<td>106.622</td>
<td>72.810</td>
<td>24.894</td>
<td>76.740</td>
<td>55.488</td>
</tr>
<tr>
<td>Higuchi</td>
<td>( R^2 )</td>
<td>0.981</td>
<td>0.966</td>
<td>0.965</td>
<td>0.979</td>
<td>0.977</td>
<td>0.971</td>
<td>0.937</td>
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### Table

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>$SS$</td>
<td>0.724</td>
<td>4.153</td>
<td>9.910</td>
<td>9.000</td>
<td>5.811</td>
<td>29.812</td>
<td>68.366</td>
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<tr>
<td><strong>Korsemeyer-Peppas</strong></td>
<td>$R^2$</td>
<td>0.998</td>
<td>0.983</td>
<td>0.982</td>
<td>0.981</td>
<td>0.992</td>
<td>0.988</td>
</tr>
<tr>
<td>$SS$</td>
<td>0.074</td>
<td>2.051</td>
<td>4.975</td>
<td>8.395</td>
<td>2.012</td>
<td>12.744</td>
<td>25.105</td>
</tr>
<tr>
<td>$n$</td>
<td>0.407</td>
<td>0.404</td>
<td>0.403</td>
<td>0.532</td>
<td>0.613</td>
<td>0.620</td>
<td>0.709</td>
</tr>
<tr>
<td><strong>Hixson-Crowell</strong></td>
<td>$R^2$</td>
<td>0.575</td>
<td>0.585</td>
<td>0.597</td>
<td>0.818</td>
<td>0.893</td>
<td>0.912</td>
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<tr>
<td>$K_{HC}$</td>
<td>0.005</td>
<td>0.009</td>
<td>0.014</td>
<td>0.016</td>
<td>0.012</td>
<td>0.025</td>
<td>0.024</td>
</tr>
<tr>
<td>$SS$</td>
<td>16.634</td>
<td>51.307</td>
<td>112.523</td>
<td>79.003</td>
<td>26.984</td>
<td>90.324</td>
<td>61.865</td>
</tr>
</tbody>
</table>

**SEM Analysis:**

The SEM images of the Canagliflozin freeze dried nanoparticles displayed smooth spherical nanoparticles. The irregular shaped flake like structures of the pure drug was converted into monodisperse nanoparticles by the Nano precipitation method. The size of the particles was comparable to be range analyzed by the zeta sizer. This solid state transition of the material could favor the increase in solubility by reducing the crystallinity of the pure drug.\(^{(23)}\)

![SEM image of pure Canagliflozin](image)

**Figure 15:** SEM image of pure Canagliflozin
Fourier Transform Infra – Red (FTIR) Analysis:

The FTIR spectrum of the formulated optimum nanoparticles was compared to the pure drug to identify the chemical stability and the interactions with added excipients. The FTIR graph of pure Canagliflozin displayed the characteristic peaks at 3367 cm\(^{-1}\) for \(-\text{OH}\) stretching, 2902 cm\(^{-1}\) for aromatic C-H stretching, 1600 cm\(^{-1}\) for aromatic C-C=C symmetric stretching, 1508 cm\(^{-1}\) for C-C=C asymmetric stretching, 1285 cm\(^{-1}\) for C-O stretching, 808 cm\(^{-1}\) for C-S stretching, 1438 cm\(^{-1}\) and 1051 cm\(^{-1}\) for C-F stretching. Hence, the purity and identity of the drug was confirmed with its chemical structure. In case of the nanoparticles formulation, the peaks of the drug were observed at 3430 cm\(^{-1}\), 2970 cm\(^{-1}\), 1633 cm\(^{-1}\), 1508 cm\(^{-1}\), 1280 cm\(^{-1}\), 809 cm\(^{-1}\), 1467 cm\(^{-1}\) and 1060 cm\(^{-1}\) for its specified functional groups, respectively. The peaks were slightly shifted from its original values in the nanoparticles compared to the pure sample due to the hydrogen bonding and hydrophobic interactions caused by the presence of surfactant during the formation of the
matrix nanoparticles. The mild interactions between the drug and the excipient favored the formation of stable nanoparticles with negligible chemical interactions.\cite{24}

Figure 17: FTIR of Pure Canagliflozin
Thermogravimetric - Differential Thermal Analysis (TG-DTA):

The TG-DTA thermogram of the formulated nanoparticles was compared with the pure drug to study the stability and changes in thermal behavior. The DTA curve of pure Canagliflozin exhibited a sharp endothermic peak at 70°C due to its characteristic melting point, followed by shallow exothermic bend up to 400°C due to uptake of the heat energy. The drug was decomposed at 420°C, showing a sharp exothermic peak. At corresponding temperature, the TG curve showed the sudden decline in the weight of the sample from initial 100% to less than 10%, which confirmed the thermal decomposition of the drug. In case of the nanoparticles, the DTA curve with endothermic peak at 68°C (identity melting point) confirmed the presence of drug without significant alterations. When the nanoparticles sample started decomposition at 420°C,
an endothermic peak was observed due to the higher heat flow (mW) required for the decomposition of the drug in nanoparticles compared to the pure drug, which could be attributed to the presence of surfactant in the freeze dried nanoparticles sample. Also, the TG thermogram ensured the percentage weight loss of the drug by thermal decomposition. Hence, the incorporation of drug in surfactant stabilized nanoparticles could be suitable for preventing the degradation of drug and improving its stability.\(^{(25)}\)

**Figure 19: TG-DSC Thermogram of Pure Canagliflozin**
Conclusion

The nanosuspension formulations prepared using Pluronic and PVA clearly demonstrated improvement in the dissolution of the drug. The nanoparticles were formed with smooth surface and spherical shape, high zeta potential surface charge colloidal stability, uniform drug content, negligible drug-excipient interactions and optimum thermal stability. Effective drug loading and enhanced drug release from the nanoparticles was favored by nanoparticle formation and diffusion process, respectively. Therefore, the design of optimized nanoparticles of Canagliflozin was found to be a successful approach to improve the dissolution and thereby, the therapeutic effect.
Acknowledgement

References