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Nanosuspension Of Poorly Soluble Anti-Diabetic Drug For Enhancement Of Solubility And Dissolution

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ABSTRACT

As an inhibitor of sodium-glucose co-transporter-2 in the renal tubules, tolbutamide is an anti-diabetic medication used in the adjuvant therapy for type-II diabetes. "Limitations in formulation development and therapeutic plasma concentration are evidenced by the drug's poor solubility and permeability. The research aimed to develop a surfactant-stabilized nanosuspension formulation that would increase the drug's solubility and dissolving rate in the body. Poly vinyl alcohol and Pluronic were used as surfactants in 1%, 3%, and 5% concentrations to create nanoparticles by the nanoprecipitation-solvent evaporation process. Nano-sized (81-117 nm), monodisperse, and zeta-potential-stable particles were seen in Pluronic-optimized formulations. In comparison to the pure drug aqueous dispersion, the nanosuspension generated with 1% and 3% Pluronic F127 increased drug solubility by a factor of 2 and 5, respectively. FTIR and TG-DSC studies indicated that the drug and surfactant displayed weak interactions due to hydrogen bonding and hydrophobic interactions, which facilitated the creation of stable nanoparticles. The SEM confirmed the creation of spherical nanoparticles with smooth surfaces. As a result, it is clear that developing Tolbutamide nanoformulation was an optimised method to improve drug dispersion

Keywords- Tolbutamide, Nanosuspension, Dissolution, Pluronic, Nanoprecipitation

INTRODUCTION

How well a medicine dissolves is crucial to ensuring that it enters the bloodstream at the correct concentration and has the desired impact on the body. More than forty percent of pharmaceuticals fall into BCS categories II and IV, which have very low solubility in water. Low water solubility and poor dissolving capabilities of the drugs are the primary challenges faced by pharmaceutical chemists during formulation design. The drugs must be totally dissolved and exist as a solution in order to be absorbed properly at the correct site. Poorly soluble drugs can have their solubility improved through a variety of techniques, including chemical and physical alterations to the drug itself, particle size reduction, crystal engineering, the formation of pharmaceutical salts, solid dispersions, the use of surfactant, the complexation of drugs, the use of cosolvents, emulsion formation, microemulsions, micelles, polymeric micelles, pro-drugs, solid state alternation, soft gel technology, drug nanocrystals, nanomorph Choosing Soluble Materials The medicine's characteristics, the site of absorption, and the intended attributes of the dosage form all play a role in choosing the best approach to making the drug better.[2]

By increasing the native drug's solubility, nanosuspension helps speed up drug absorption and get the drug to its maximum plasma concentration more quickly. Stabilising the nanosuspension of a colloidal dispersion often involves using surfactants and/or polymers at the optimum concentration. The method used for optimising stabilisers, approaches to improving stability, and other factors all have an impact on the nanosuspension's overall stability.[3] One of the main challenges to effective drug delivery is designing an appropriate nanosuspension preparation with low energy input and erosion contamination.[4] Boosting the effective surface area through nanonization is a plausible pharmacological basis for boosting the oral bioavailability and therapeutic efficacy of poorly soluble drugs. Wet chemical procedures, media milling, high pressure homogenization, gas phase synthesis, and form-in-place techniques have all been reported as

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novel strategies for the pharmaceutical manufacture of nanoparticles in recent years.[5] Increased native drug solubility from nanosuspension facilitates rapid absorption and rapid achievement of maximum plasma concentration. Typically, the colloidal dispersion nanosuspension is stabilised by using the optimum concentration of surfactants and/or polymers. The stability of a nanosuspension depends on a variety of factors such as the method used to optimise stabilisers, approaches to enhancing stability, and others.[6] Particle characterization, preparation process, formulation composition, excipients, and sterilising techniques are just few of the factors that contribute to optimal nanosuspension.[7]

In addition to a good diet and regular physical activity, the oral anti-diabetic medicine tolbutamide has been shown to enhance glycemic control in people with type 2 diabetes mellitus. Specifically, it prevents glucose from being reabsorbed from the tubular lumen after being filtered by binding to sodium-glucose co-transporter 2 (SGLT2). Proximal renal tubules are rich in SGLT2 expression. Tolbutamide reduces reabsorption of filtered glucose and decreases the renal threshold for glucose (RTG), resulting in an increase in urine glucose excretion (UGE), hence lowering high plasma glucose concentrations in people with type 2 diabetes. Because of the increased excretion of glucose in the urine brought on by tolbutamide-induced osmotic diuresis, weight loss and calorie deficits may be linked to this drug. Clinical studies have not shown that the recommended dose range of 100–300 milligrammes of tolbutamide results in glucose malabsorption. No withdrawals were made due to adverse effects, and no deaths or hypoglycemic episodes were reported.8Tolbutamide 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, according to the Tolbutamide Cardiovascular Assessment Study (CANVAS) Programme. Tolbutamide's (a BCS Class - II drug) low water solubility and permeability is the biggest obstacle to its therapeutic application. Therefore, the goal of this research is to develop nanoparticles of Tolbutamide with improved solubility and dissolving characteristics in order to provide therapeutic effectiveness at a potentially low dose while decreasing adverse effects

MATERIALS AND METHODS:

Materials:

Polyvinyl alcohol (PVA) and methanol were purchased from SRL Chem. in Mumbai, while tolbutamide was provided as a free sample by Ananth Pharmaceuticals Pvt Limited in Maharastra. Sigma Aldrich in Mumbai was where we made our buy for Pluronic F127. The water used in-house was distilled using a twofold distillation process. All of the compounds were laboratory-quality.

Preparation of nanoparticles:

Tolbutamide nanoparticles were prepared using an evaporation of solvent nanoprecipitation approach for experimental optimisation. Each surfactant (PVA and Pluronic F127) was formulated in three distinct ways (Formulation codes CGF1 through CGF6), with concentrations of 1%, 3%, and 5% (Table 1). A surfactant aqueous solution was slowly infused with a methanolic solution of the medication. After evaporating the solvent for 4 hours with magnetic stirring, the liquid was sonicated for 20 minutes with an ultra-probe at 100 V. Centrifugation at 2,000 rpm was used to separate the surfactant from the formulation. After centrifuging the supernatant at 15,000 rpm for 15 minutes, the nanoparticles were extracted. We resuspended the pellet (nanoparticles) in distilled water using a vortex mixer, and then analysed the resulting aqueous suspension. In order to employ the optimised sample in the characterisation analyses, it was lyophilized to create a free-flowing powder.[9]

Table 1: Compositions of Tolbutamide Nanosuspension

	Constituents	CGF1	CGF2	CGF3	CGF4	CGF5	CGF6
1.	Tolbutamide (mg)	100	100	100	100	100	100
2.	Polyvinyl alcohol (PVA) (%)	1	3	5			
3.	Pluronic (%)				1	3	5
4.	Methanol (mL)	5					

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5.	Distilled Water (mL)	10					
	Drug: Surfactant Ratio	1:1	1:3	1:5	1:1	1:3	1:5

Determination of pH of nanosuspension:
To avoid irritating or damaging the cells, and to ensure the formulations' stability, the pH was measured at room temperature. A pH metre with a glass electrode was used for this.[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 Tolbutamide. The drug content was determined from the calibration curve using the formula.[11]

$$\% \text{ Drug Content} = (\text{Absorbance of test sample}/\text{Absorbance of Standard Pure}) \times 100$$

Particle size distribution and Zeta potential:
Dynamic light scattering was used to analyse the zeta potential and mean particle size distribution of the nanosuspension. The study was conducted with a 5mW He-Ne laser at 25 degrees Celsius and a scattering angle of 90 degrees. Prior to being placed in the cuvette, the sample was diluted with deionized water to reduce the likelihood of multi-scattering occurrences. The data are shown as the mean for each sample.[12]

In vitro Dissolution studies:
Improved solubility and dissolution tests were conducted in vitro utilising a dialysis membrane and distilled water as the dissolution medium for both the formulations and the pure medicine. About 0.5 mL of each formulation was placed in a dialysis bag before being immersed in its corresponding medium. A sample was dissolved in 100 mL of distilled water at 100 rpm for 6 hours using the USP dissolution device (paddle model). Aliquots of 5 mL were taken at regular intervals and replaced with new media containing 5 mL of distilled water. Analysing the aliquots with a UV-Visible spectrophotometer at the absorbance maximum wavelength allowed us to calculate the concentration of medication released at each time point. The estimated cumulative percentage of drug release was computed after 6 hours. The study was conducted three times, and the data is presented as a mean + SD.[9]

Drug Dissolution Kinetics:
The drug release characteristics of the formulations were analysed using kinetic modelling with DD solver software. We looked into the zero-order and first-order variants of the Hixon-crowell, Korsmeyer-Peppas, and Higuchi models. For the diffusion process in Korsemeyer Peppas kinetics, we compared the models obtained by calculating the correlation coefficient (R2), sum of squared residual (SS), and n-value. Each model's release pattern was calculated using a different kinetic analysis method.[13]

Morphological studies:
Scanning electron microscopy (SEM) was used to examine the surface morphology of the optimised nanoparticles. Using low pressure, platinum was coated onto freeze-dried nanoformulations that had been glued to a blank, double-sided sticker that had been taped to a metal counterfoil. The coated nanoparticles were placed in the sample holder, and 25kV scanning was done.[14]

Fourier Transform Infrared Spectroscopy (FTIR):
FTIR was used to determine whether or not the drug and excipient used in the nanoparticles were compatible by comparing the spectra of the pure drug with those of the freeze dried nanoparticles formulation. About 2 mg of the sample was compressed using IR grade Potassium Bromide (KBr) to form a pellet. The infrared spectrum followed, covering wavelengths from four thousand to four hundred. Using this spectrum, we could identify the presence or absence of specific functional groups in each sample.[15]

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

TGA-DSC analysis was performed on both the unadulterated medicine and the freeze-dried nanoparticle formulation. The thermal analysis of a sample's mass as it is heated from room temperature to 600 degrees Celsius at a rate of 10 degrees Celsius per minute was performed using TGA. DSC examines the thermal changes in the sample's nature regardless of the sample's size. After placing 2-4 mg of the sample in the sample holder, we adjusted the furnace temperature from 30 degrees Celsius to 600 degrees Celsius to compare the results of the TG and DSC thermograms.[16]

RESULTS AND DISCUSSION:

Physicochemical Characterization of the Nanoparticles:

Tolbutamide nanosuspensions were successfully made using Pluronic or PVA surfactants, with maximum drug content ranging from 97 to 100% (Table 2). This data demonstrates the chemical stability of the drug in the formulations. Using a polydispersity index as small as 0.1, the average size of particles in a Pluronic-based nanosuspension was determined to be 80-117 nm, showing a narrow monodisperse size range. Particle size was found to be more than 1000 nm (1 - 2.2 m) in PVA-based suspensions, with PDI values falling between 0.8 and 1. As a result, the particles had a lot of variation. The zeta potential of a Tolbutamide-Pluronic nanosuspension was found to be significantly greater as surfactant concentration was increased from 1% to 3% to 5%, respectively, yielding values of +3.63, +4.55, and +11.6. This might be because the surfactant's optimum concentration makes the nanoparticles more physically stable.[17]

Table 2: Physico-chemical Characterization studies of Tolbutamide Nanosuspensions

S. No.	Formulation Code	Drug Content (%)	Average Particle Size (nm)	Poly Dis100persity Index (PDI)	Zeta Potential (mV)
1	CGF1	97.5 ± 0.65	81.94	0.132	+3.65
2	CGF2	99.4 ± 0.85	117.5	0.122	+4.55
3	CGF3	100.6 ± 0.61	117.2	0.138	+11.6
4	CGF4	98 ± 2.02	1320	0.847	+1.43
5	CGF5	96.9 ± 6.38	1924	1	+1.62
6	CGF6	100.7 ± 1.56	2270	0.954	+2.97

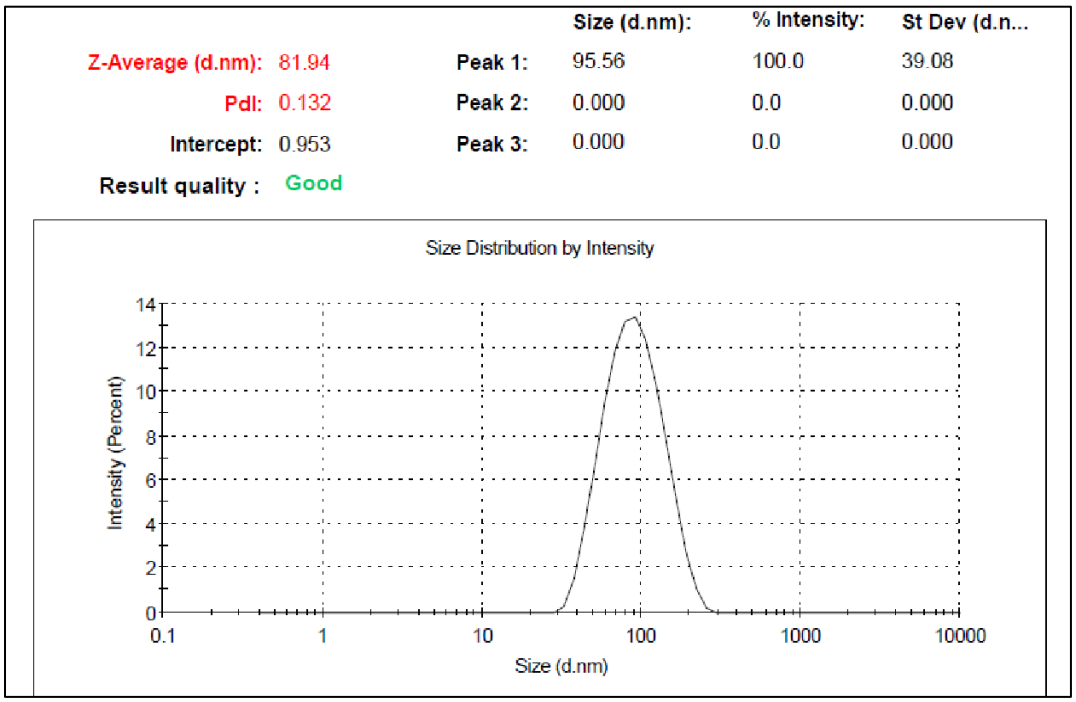

Figure 1: Particle size distribution of Tolbutamide-Pluronic 1% nanosuspension (NF1)

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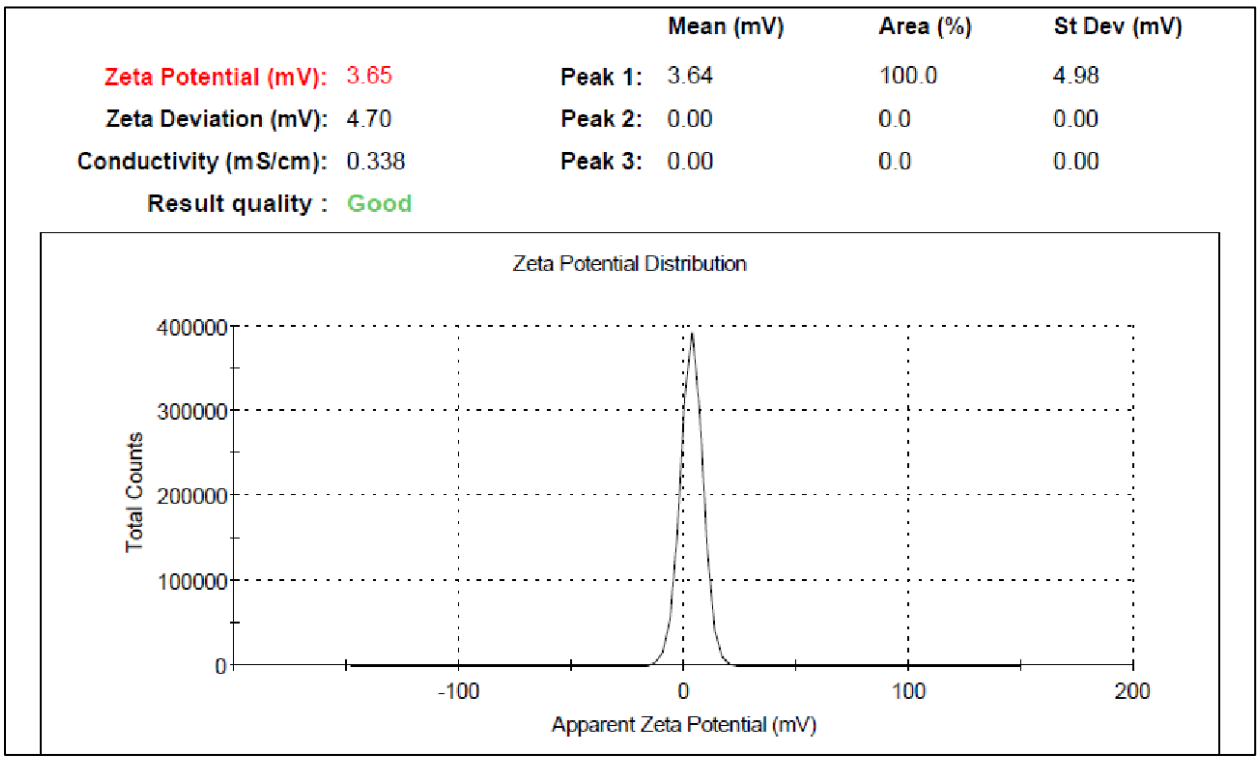

Figure 2: Zeta Potential of Tolbutamide -Pluronic 1% nanosuspension (NF1)

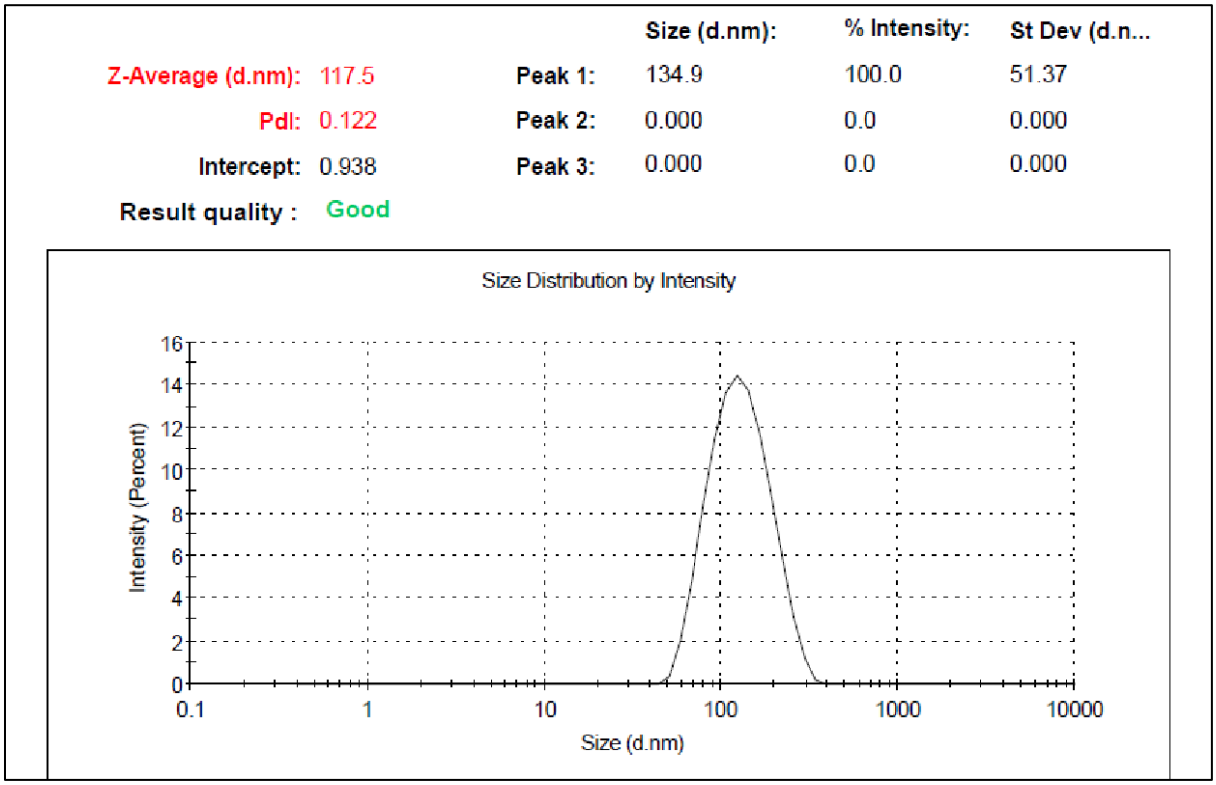

Figure 3: Particle size distribution of Tolbutamide -Pluronic 3% nanosuspension (NF2)

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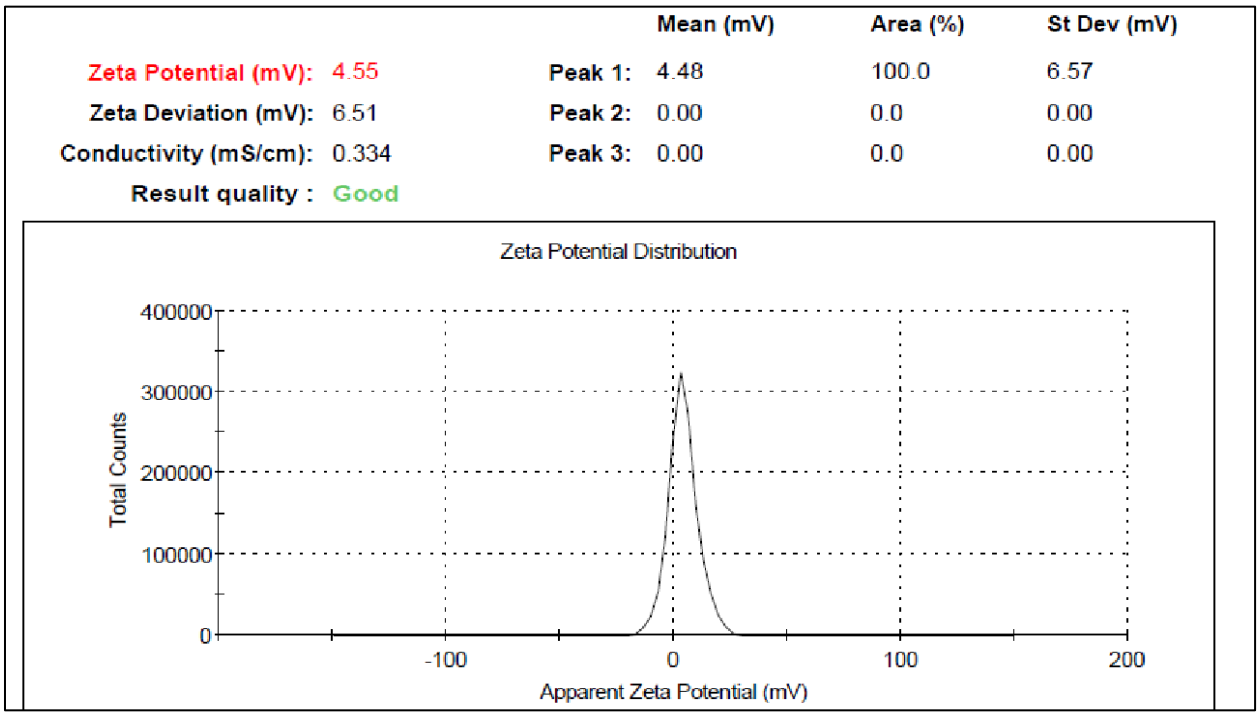

Figure 4: Zeta potential of Tolbutamide -Pluronic 3% nanosuspension (NF2)

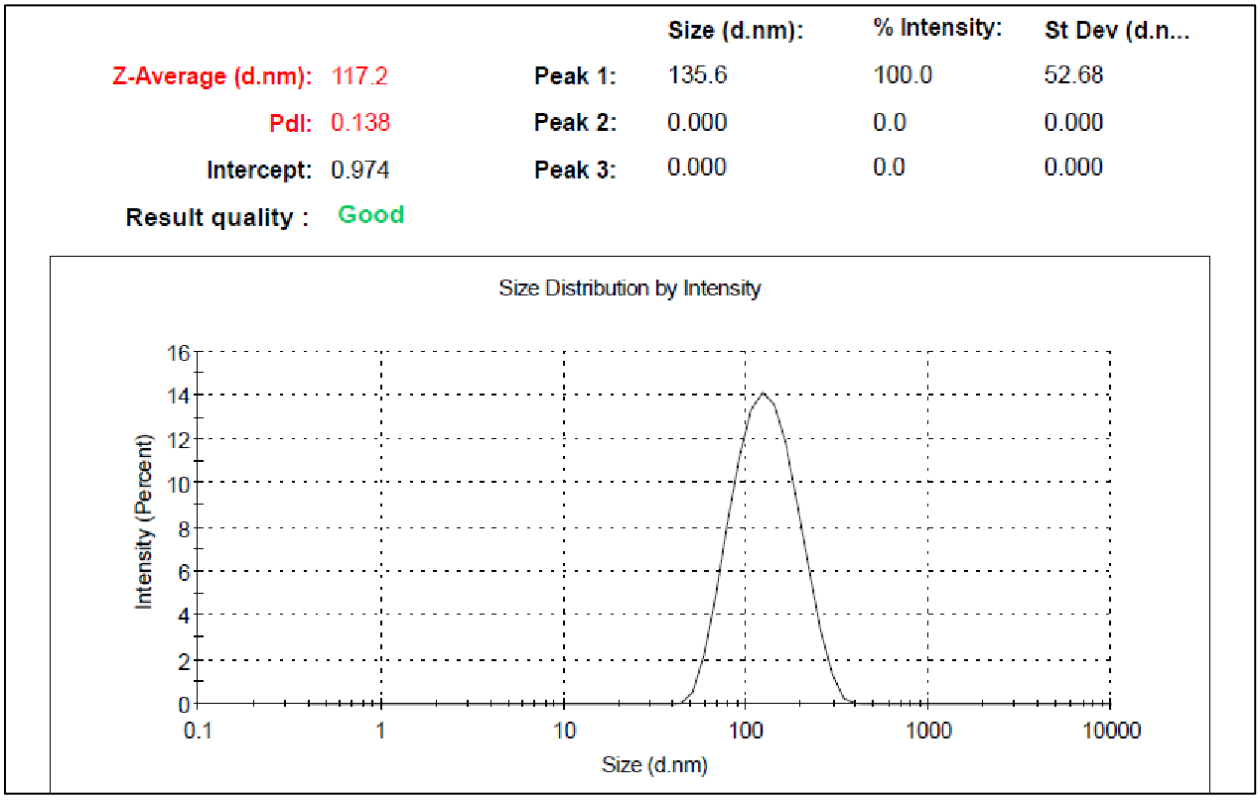

Figure 5: Particle size distribution of Tolbutamide -Pluronic 5% nanosuspension (NF3)

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		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): 11.6	Peak 1:	11.6	100.0	6.29
Zeta Deviation (mV): 6.25	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm): 0.0805	Peak 3:	0.00	0.0	0.00
Result quality : Good				

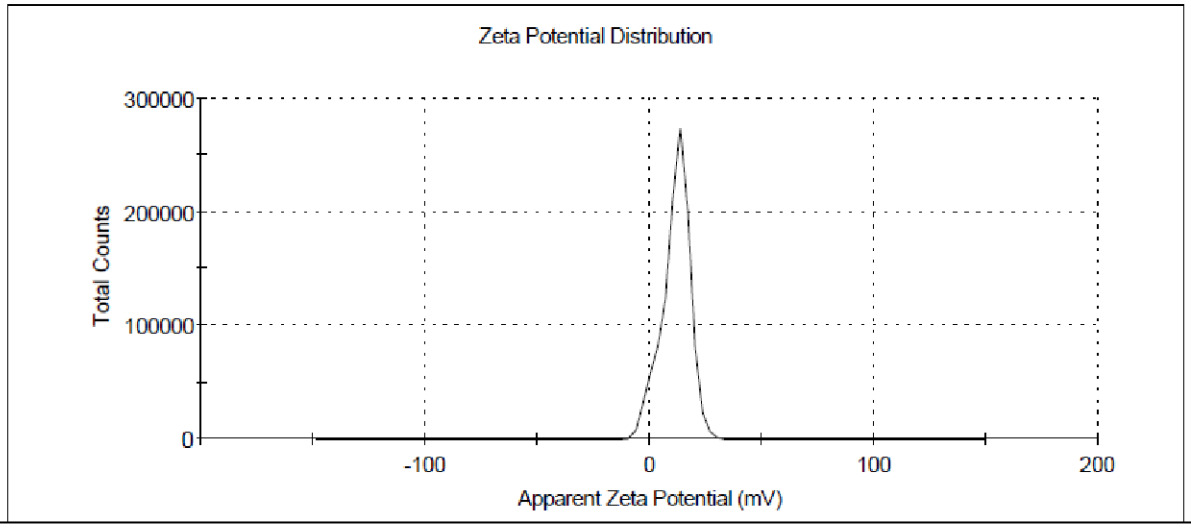

Figure 6: Zeta Potential of Tolbutamide -Pluronic 5% nanosuspension (NF3)

		Size (d.nm):	% Intensity:	St Dev (d.n...)
Z-Average (d.nm): 1320	Peak 1:	385.6	100.0	57.84
PdI: 0.847	Peak 2:	0.000	0.0	0.000
Intercept: 0.691	Peak 3:	0.000	0.0	0.000
Result quality : Refer to quality report				

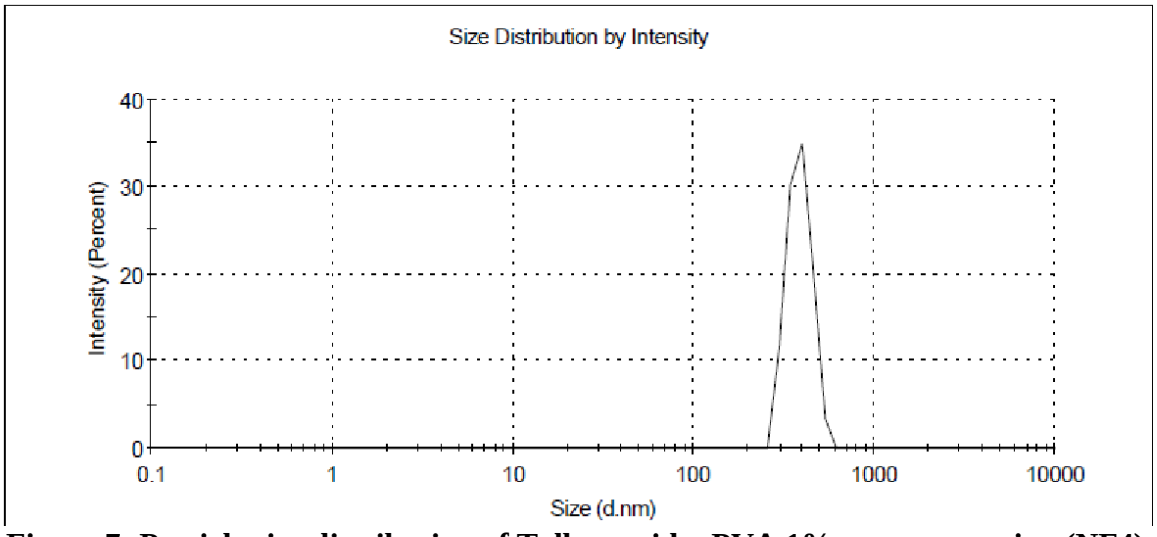

Figure 7: Particle size distribution of Tolbutamide -PVA 1% nanosuspension (NF4)

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		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	-1.43			
Zeta Deviation (mV):	3.18	Peak 1:	-1.45	100.0	3.27
Conductivity (mS/cm):	0.374	Peak 2:	0.00	0.0	0.00
Result quality :	Good	Peak 3:	0.00	0.0	0.00

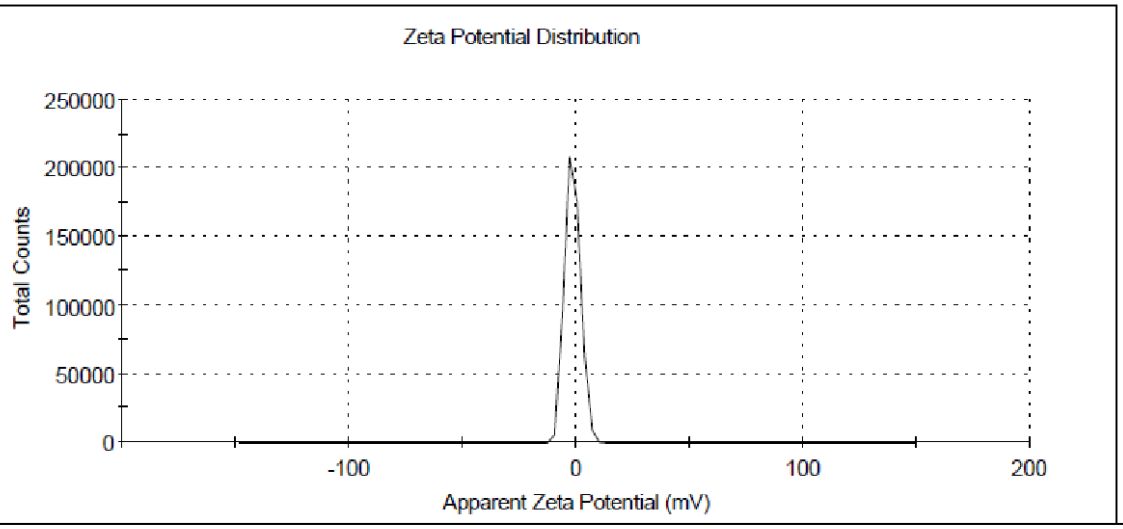

Figure 8: Zeta Potential of Tolbutamide -PVA 1% nanosuspension (NF4)

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	1924			
PdI:	1.000	Peak 1:	323.5	100.0	27.86
Intercept:	0.819	Peak 2:	0.000	0.0	0.000
Result quality :	Refer to quality report	Peak 3:	0.000	0.0	0.000

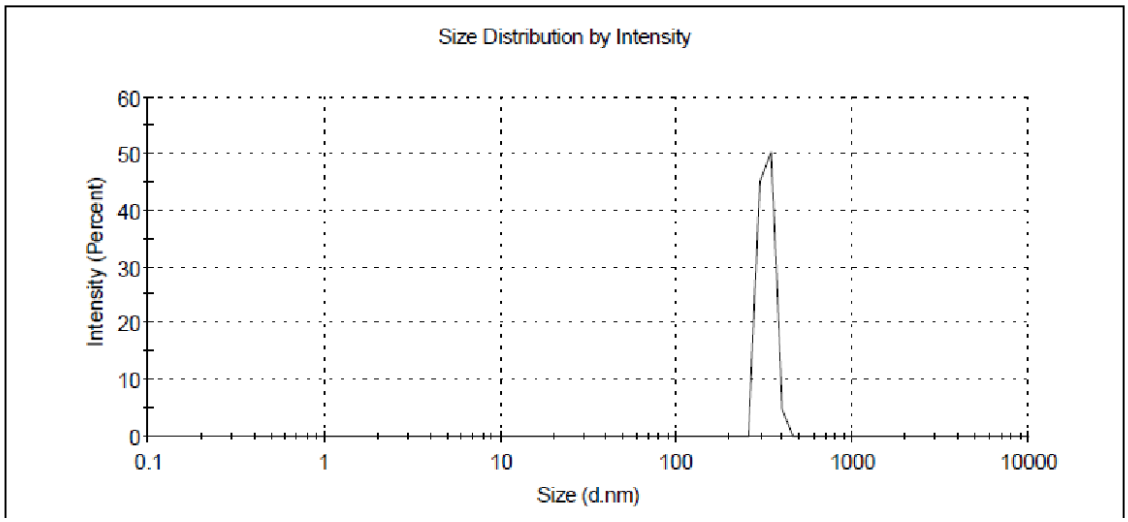

Figure 9: Particle size distribution of Tolbutamide -PVA 3% nanosuspension (NF5)

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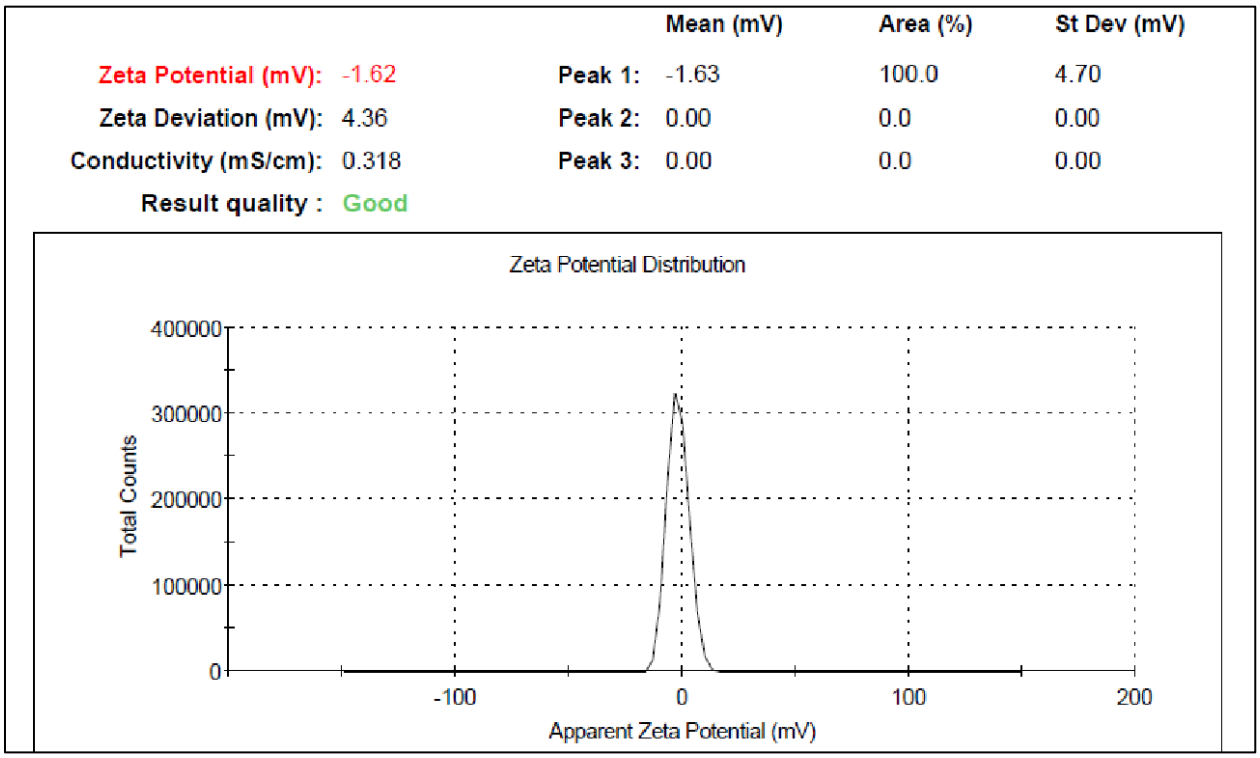

Figure 10: Zeta Potential of Tolbutamide -PVA 3% nanosuspension (NF5)

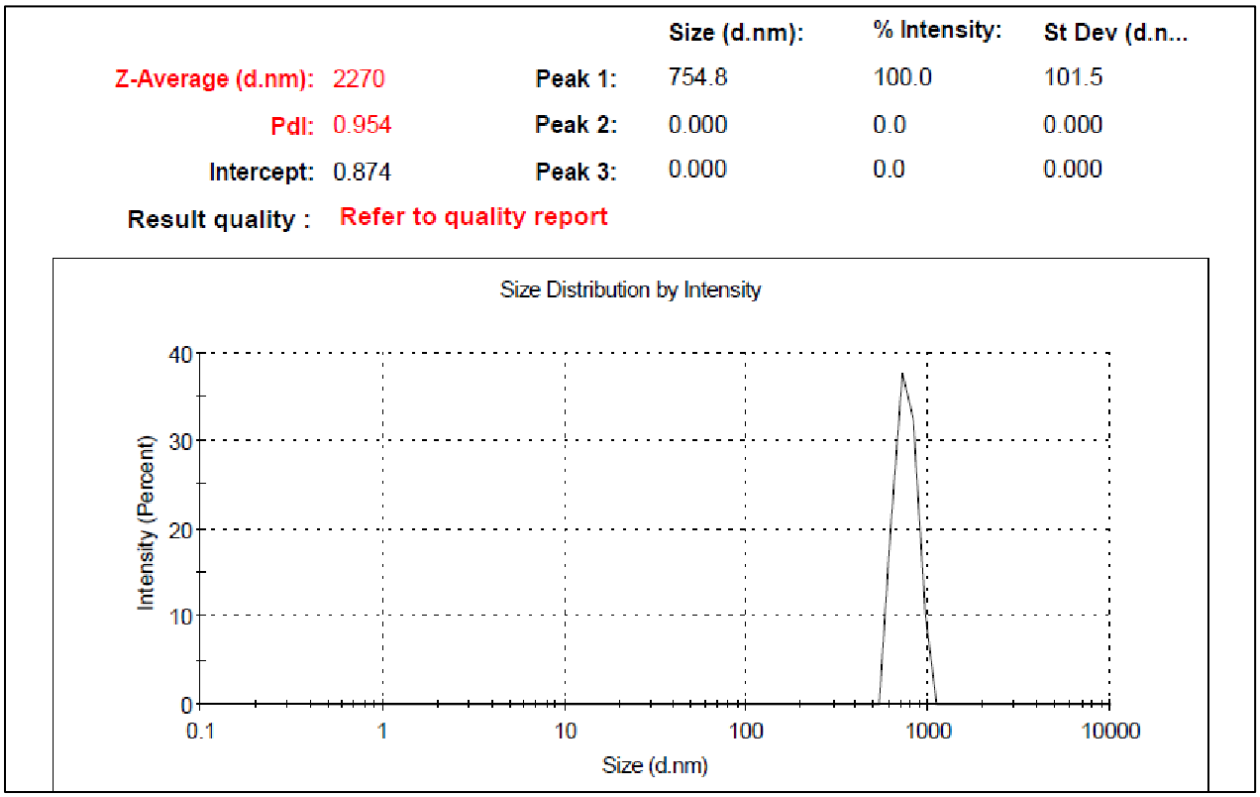

Figure 11: Particle size distribution of Tolbutamide -PVA 5% nanosuspension (NF6)

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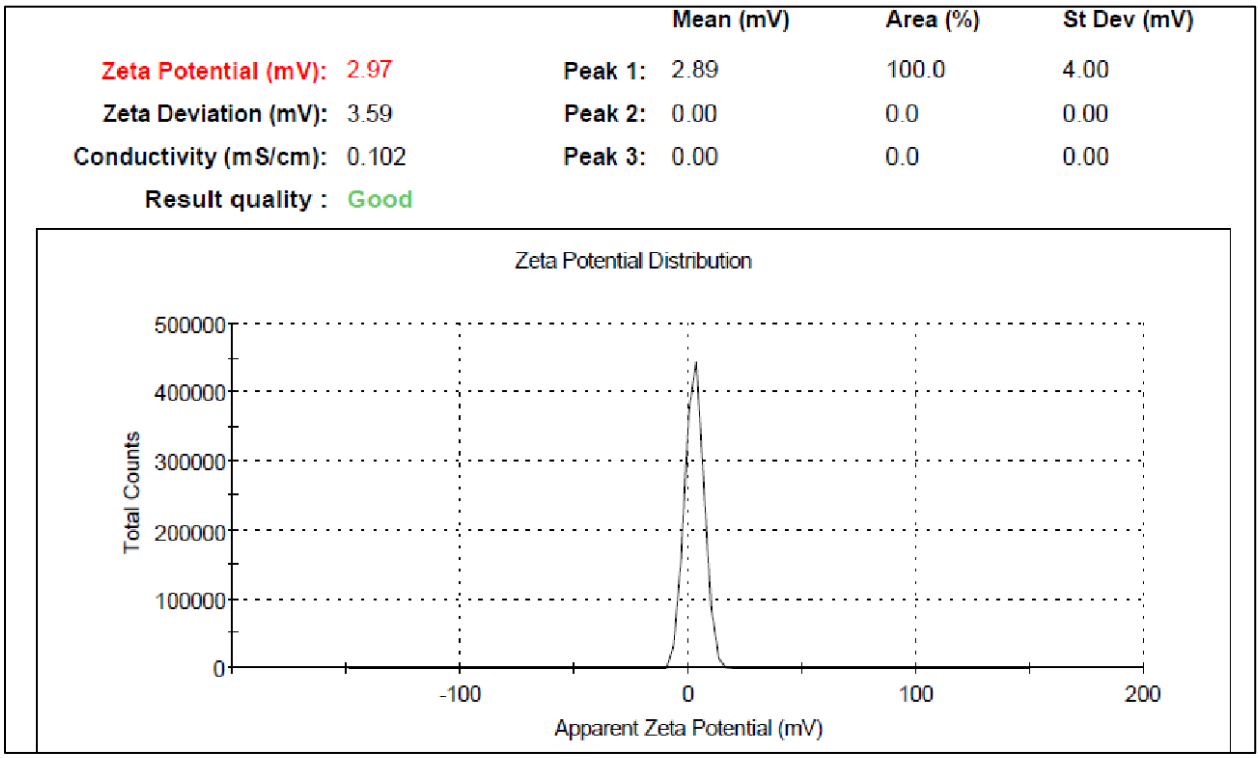

Figure 12: Zeta Potential of Tolbutamide -PVA 5% nanosuspension (NF6)

In vitro drug dissolution studies:

The produced nanosuspension was put through in vitro drug dissolving assays, with findings compared to the drug release from pure drug aqueous dispersion in distilled water media, to determine if the medication's solubility profile has improved. The pure aqueous dispersion only managed to dissolve 7% of the drug after 6 hours. The drug solubility in the 1% Pluronic F127 nanosuspension was roughly double that in the pure drug (around 17%). At the end of the 6-hour study, the surfactant concentration was increased to 3%, resulting in five times (about 36%) greater cumulative drug dissolution.[18] Above its critical micelle concentration threshold, Pluronic's amphiphilic tri-block-co-polymer aggregates into micelles in an aqueous environment, encapsulating the hydrophobic medicine and improving its solubility[19] However, the medication dissolving profile did not noticeably change even after increasing the Pluronic F127 concentration to 5%. The drug's saturation solubilization level in this surfactant may be to blame.

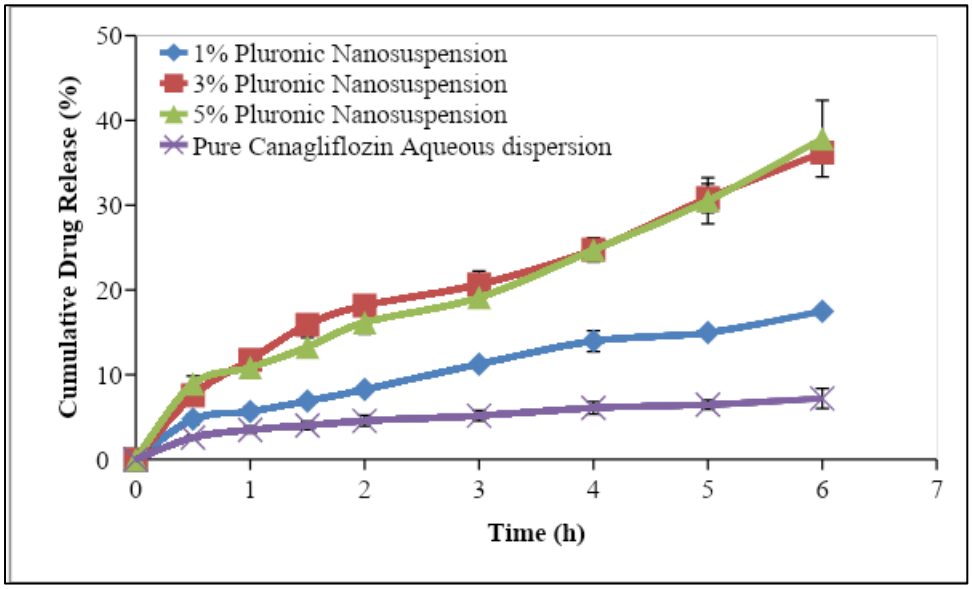

Figure 13: *In vitro* dissolution studies of Calibration-Pluronic F127 Nanosuspensions

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PVA-based formulations with a micron-sized particle size and a hydrophilic surfactant significantly increased drug solubility.20When the surfactant concentration was 1%, 3%, or 5%, the cumulative drug concentration was 13%, 20%, and 24%, respectively, at the end of the 6-hour study. This improvement in solubility is around a factor of two to three when compared to a sample of the medication in its purest form.

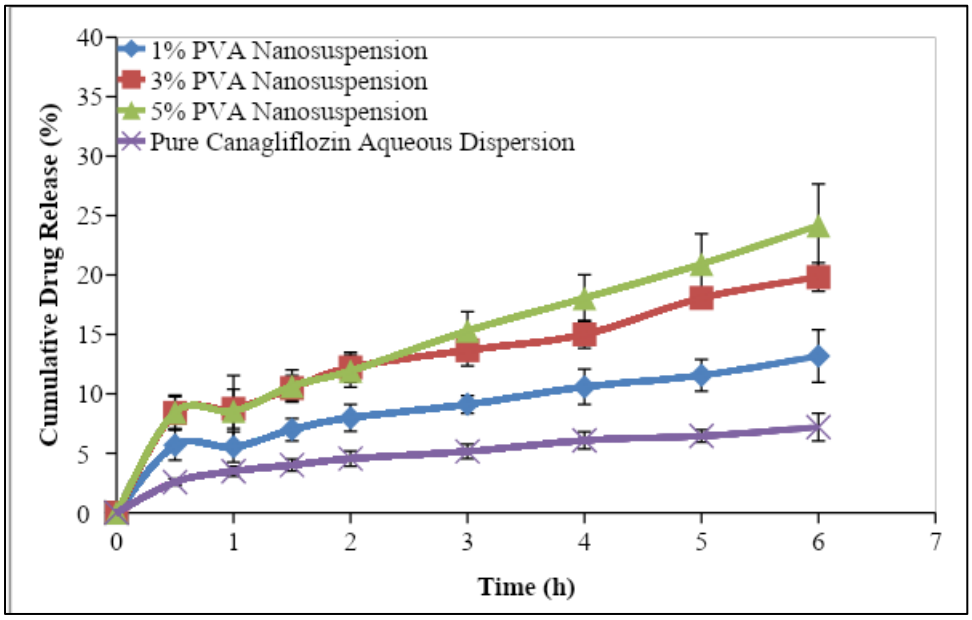

Figure 14: *In vitro* dissolution studies of Calibration-PVA Nanosuspensions

Pluronic-based formulations have a monodispersenano sized particle distribution, whereas PVA suspensions have a polydisperse micron sized one, which may explain why the drug dissolves more quickly in the former. Due to the drug particles being drastically decreased in size to the nano scale range, the effective surface area to touch the dissolution media is much increased, resulting in better solubility and dissolution rates in pluronic-based nanosuspensions.[21,22]

Drug release kinetics:

Several kinetic models were used to fit the dissolving data of pure drug samples and the generated nanosuspensions, illuminating the mechanism of drug release from the particles. The diffusion mechanism was unmistakably established as the cause of drug dissolution by Korsemeyer-Peppas kinetics, which displayed the highest R2 value and the lowest SS value. An n-value between 0.4 and 0.5 was indicative of drug release via the Fickian diffusion mechanism in both pure drug and PVA based formulations. However, Pluronic-based nanosuspensions exhibited a drug release behaviour that was in keeping with a non-Fickian Anamolous transport mechanism. This may be due to the formulation's nanoparticles, which promoted higher drug solubility via diffusion.[13]

Table 3: Drug dissolution kinetics of Tolbutamide Nanosuspension

Kinetics Model	Parameters	Pure Drug	1% PVA	3% PVA	5% PVA	1% Pluronic	3% Pluronic	5% Pluronic
Formulation Code		-	CGF1	CGF2	CGF3	CGF4	CGF5	CGF6
Zero	R^2	0.557	0.555	0.553	0.786	0.875	0.879	0.926
	K_0	1.445	2.581	3.886	4.496	3.254	6.502	6.454
	SS	17.304	54.937	125.002	92.735	31.551	123.723	80.003
First	R^2	0.583	0.599	0.618	0.832	0.901	0.925	0.949
	K_1	0.015	0.028	0.044	0.051	0.036	0.079	0.077
	SS	16.304	49.555	106.622	72.810	24.894	76.740	55.488

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Higuchi	**R^2**	0.981	0.966	0.965	0.979	0.977	0.971	0.937
	K_H	3.035	5.412	8.148	9.263	6.645	13.263	13.033
	SS	0.724	4.153	9.910	9.000	5.811	29.812	68.366
Korsemeyer-Peppas	**R^2**	**0.998**	**0.983**	**0.982**	**0.981**	**0.992**	**0.988**	**0.977**
	K_{KP}	3.410	6.102	9.208	8.890	5.744	11.354	9.914
	SS	0.074	2.051	4.975	8.395	2.012	12.744	25.105
	n	**0.407**	**0.404**	**0.403**	**0.532**	**0.613**	**0.620**	**0.709**
Hixson-Crowell	**R^2**	0.575	0.585	0.597	0.818	0.893	0.912	0.943
	K_{HC}	0.005	0.009	0.014	0.016	0.012	0.025	0.024
	SS	16.634	51.307	112.523	79.003	26.984	90.324	61.865

SEM Analysis:

Freeze-dried Tolbutamide nanoparticles looked smooth and round in scanning electron micrographs. When the pure medication was subjected to the nanoprecipitation method, its irregular, flaky structures were converted into smooth nanoparticles. Particle sizes measured by the zeta sizer fell within the region of inquiry. This phase transition could improve medication solubility by reducing crystallinity.[23]

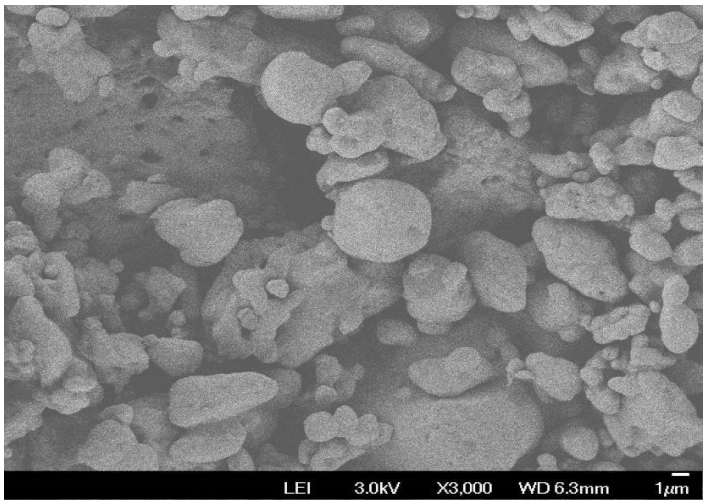

Figure 15: SEM image of pure Tolbutamide

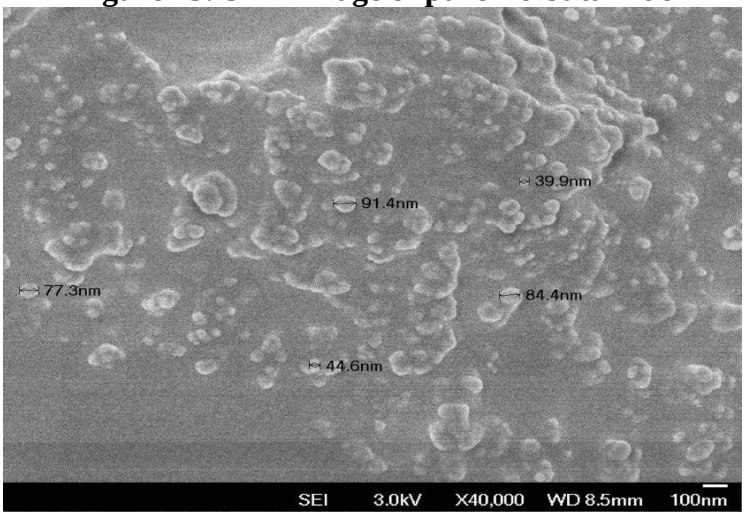

Figure 16: SEM image of Tolbutamide freeze dried nanoparticles

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Fourier Transform Infra – Red (FTIR) Analysis:

The FTIR spectra of the optimally formed nanoparticles were compared to those of the pure drug to establish the nanoparticles' chemical stability and their interactions with any other excipients. At 3367 cm1 for -OH stretching, 2902 cm1 for aromatic C-H stretching, 1600 cm1 for aromatic C-C=C symmetric stretching, 1508 cm1 for C-C=C asymmetric stretching, 1285 cm1 for C-O stretching, 808 cm1 for C-S stretching, 1438 cm1, and 1051 cm1 for C-F stretching were signature peaks in the FTIR spectrum of pure tolbutamide. The molecular structure of the substance confirmed its identity and purity, therefore it may be safely assumed to be genuine. Spectral analysis of the nanoparticles formulation of the drug revealed peaks at 3430 cm1, 2970 cm1, 1633 cm1, 1508 cm1, 1280 cm1, 809 cm1, 1467 cm1, and 1060 cm1 for the medicine's indicated functional groups. Matrix nanoparticle manufacturing involves hydrophobic and hydrogen bonding interactions between surfactant molecules, which slightly shifts the peaks from their original values in the nanoparticles relative to the pure sample. Stable nanoparticles with few chemical interactions could form because of the drug's weak interactions with the excipient.[24]

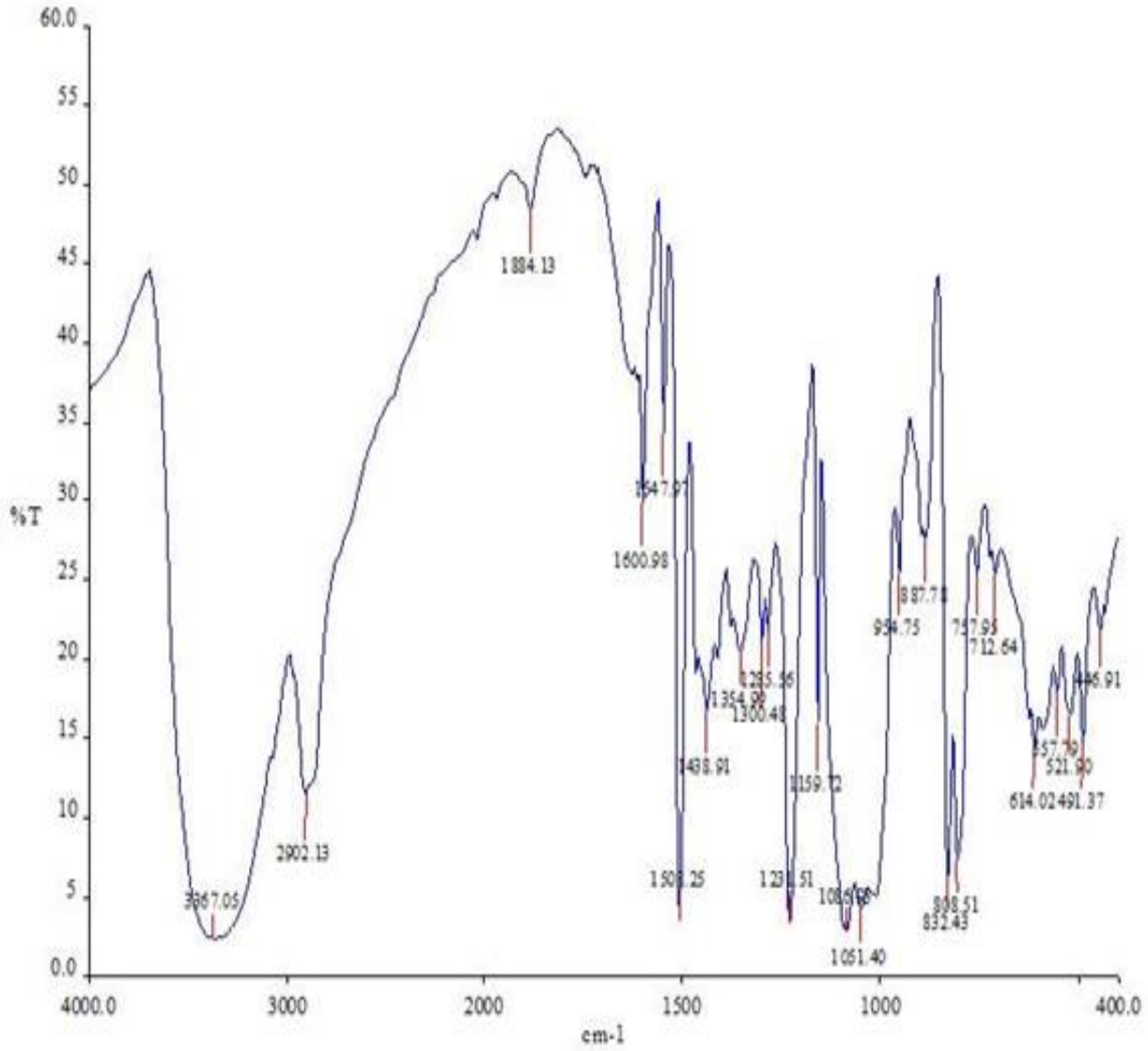

Figure 17: FTIR of Pure Tolbutamide

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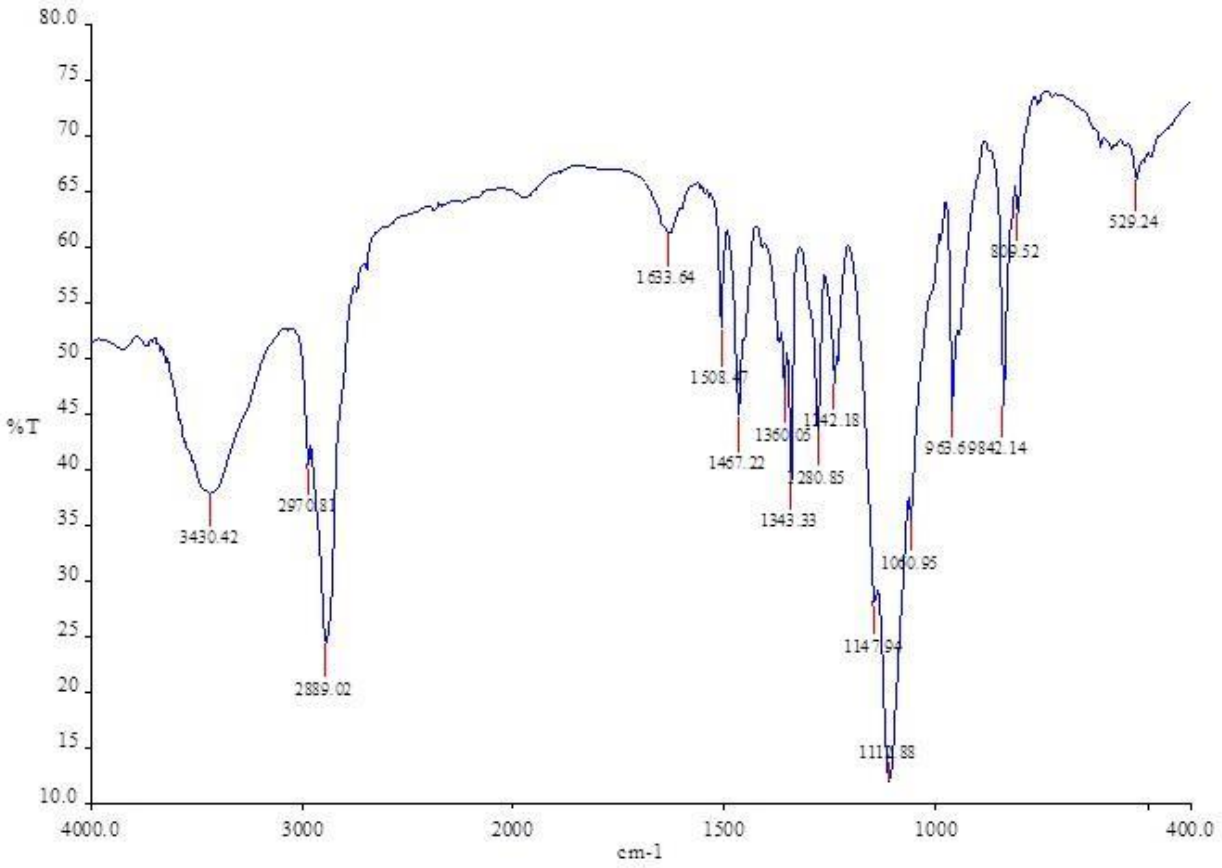

Figure 18: FTIR of Tolbutamide Nanoparticles

Thermogravimetric - Differential Thermal Analysis (TG-DTA):

The TG-DTA thermogram was compared between the pure drug and the produced nanoparticles to look for differences in stability and thermal behaviour. Pure Tolbutamide has a very specific melting point of 70 °C, and the DTA curve for it predictably exhibited an endothermic peak at that temperature. The graph showed a small exothermic shift when the temperature of the material rose above 400 °C". There was a clear exothermic peak in the drug's breakdown around 420 degrees Celsius. At the proper temperature, the TG curve showed a sharp drop in sample weight from 100% to less than 10%, providing confirmation of the drug's thermal breakdown. The endothermic peak at 68 °C (identity melting point) in the DTA curve for the nanoparticles demonstrates that the medicine is present without significant modifications. At 420 degrees Celsius, an endothermic peak was seen, suggesting that the inclusion of surfactant in the freeze-dried nanoparticles sample increased the heat flow (mW) necessary for the degradation of the drug in nanoparticles relative to the pure drug. As an added safety measure, the TG thermogram could guarantee the proportion of drug weight that was not lost owing to thermal deterioration. Surfactant-stabilized nanoparticles may be one solution to the problems of medication degradation and instability.[25]

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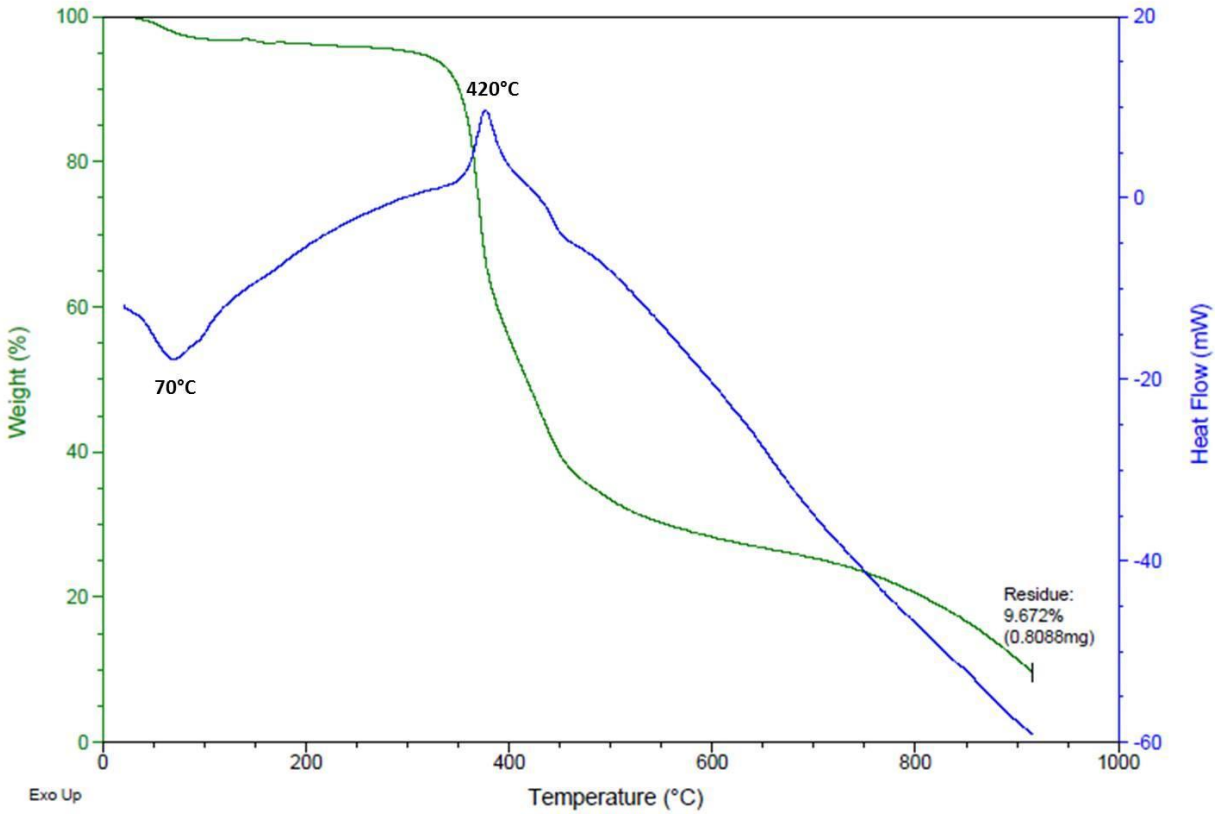

Figure 19: TG-DSC thermogram of Pure Tolbutamide

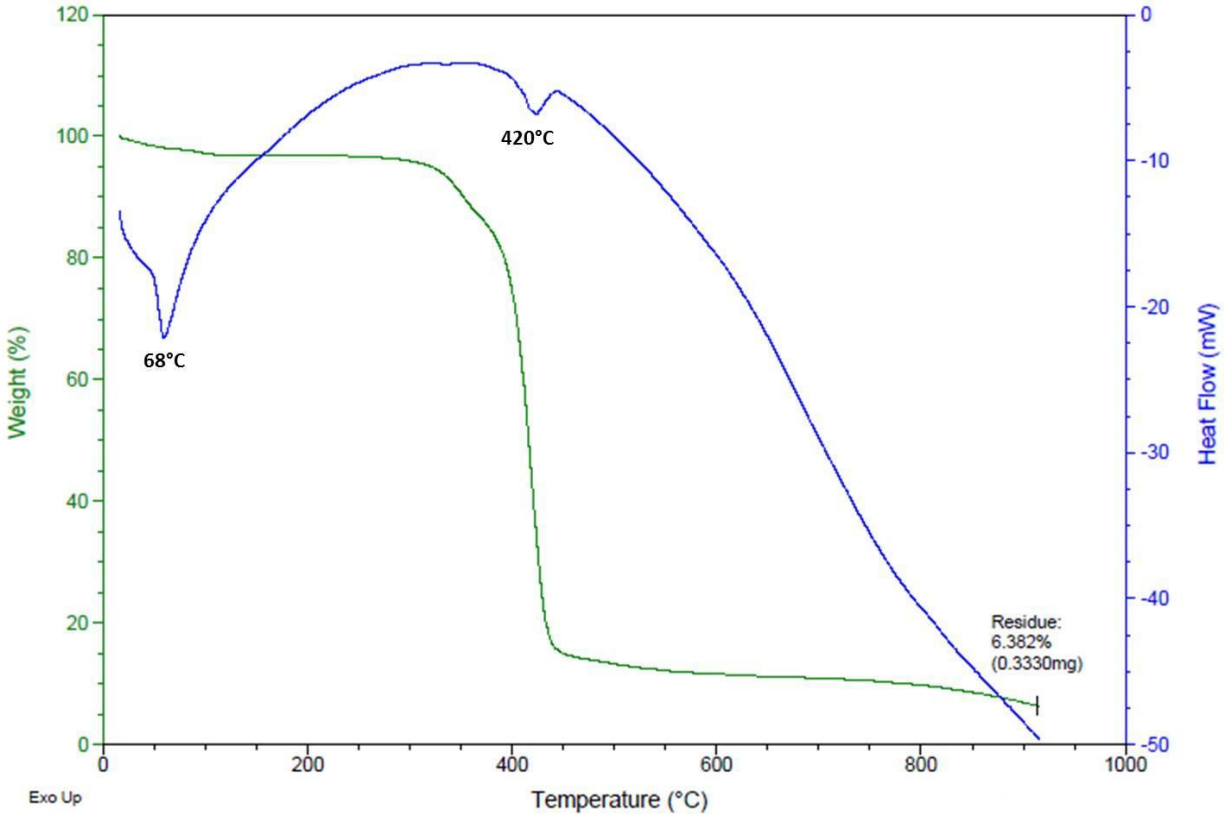

Figure 20: TG-DSC thermogram of Tolbutamide Nanoparticles

CONCLUSION

The Pluronic and PVA nanosuspension formulations showed markedly enhanced medication solubility.

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Nanoparticles were created with homogeneous drug content, low drug-excipient interactions, and optimal thermal stability. They also had a smooth surface and a spherical shape. Nanoparticle generation and diffusion mechanism favoured efficient drug loading and improved drug release from the nanoparticles. Tolbutamide's solubility and efficacy could be enhanced by the use of nanoparticles, which were successfully designed.

Acknowledgement

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