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Solubility and Dissolution Enhancement of BCS Class-IV Anti-Diabetic Drug Tolbutamide by Solid Dispersion Technique

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KEYWORDS

Solubility, Dissolution, Solid dispersion, Tolbutamide, Kneading

ABSTRACT:

Even though the oral route of drug administration is typically considered the simplest and easiest technique in clinical applications, the solubility and dissolution of various medications play a major restriction in the process. Solid dispersion by kneading has long been recognised as one of the most promising strategies for improving the solubility of drugs that are poorly soluble. The reason tolbutamide, a new anti-diabetic medication, was selected for this investigation was because of its poor permeability and restricted solubility, which required the creation of a solid dispersion in order to increase its bioavailability. One major obstacle is the drug's limited water solubility, which means that higher doses are needed, which limits its potential for clinical application. To make the solid dispersion, hydrophilic polymers in the ratios of1:1,1:3, and 1:5 were kneaded along with beta cyclodextrin and PEG 4000. In terms of zeta potential, the resulting particles ranged from -58 mV to -17 mV, with a nanometer size dispersion of 240 to 640 nm. Maximum in vitro drug dissolution (determined using the standard USP type II paddle procedure with the sample immersed in a dialysis bag) was seen for a formulation with a drug:beta cyclodextrin ratio of 1:1. When compared to a pure drug suspension (about 10% release), the formulation showed a solubility improvement of roughly 7.5 times. The stability, drug-carrier compatibility, crystalline-to-amorphous transition, and uniform spherical particle production were verified using additional characterisation techniques such as scanning electron microscopy, Fourier transform infrared spectroscopy, and thermogravimetric analysis. The solid dispersion method improved CGF solubility and dissolution in all tested situations.

INTRODUCTION

The therapeutic effectiveness of around 40% of medications with high therapeutic values has been proven to be unsatisfactory in recent years owing to their insoluble nature. In order to improve the pharmacological activity and maintain the therapeutic benefits of these orally delivered medications, it is necessary to revise ways for increasing their bioavailability. Poor solubility in water makes it hard to do even basic toxicity testing on animal models. Increasing a drug's bioavailability is necessary because of the importance of solubility and permeability (Kim et al. 2019).

Tolbutamide, a novel medication used to treat type 2 diabetes, is classified as a poorly soluble BCS class II agent. The amount of glucose absorbed by the kidneys is decreased because the sodium-glucose cotransporter-2 is inhibited. Low bioavailability due to reduced permeability and solubility severely limits the medication's clinical utility and makes the use of greater doses inevitable. As a result, increasing the solubility of this anti-diabetic medication will have a significant influence on the development of novel treatment regimens for diabetic populations (Arafa et al. 2016, Arafa et al. 2017, Mahaffey et al. 2018).

Drug solubility, absorption, and penetration across biological membranes in vivo are all significantly affected by particle size. Nanoparticles, solid dispersion,

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micronization, micelle solubilisation, the supercritical fluid technique, etc., are only some of the methods that have evolved to improve the solubility of active medicinal components. Nanotechnology uses both top-down and bottom-up processes to reduce the particle size of poorly soluble medicines. Enhanced solubility, target specificity, extra viability and stability, easy accessibility to cross in vivo membranes, and enhanced drug delivery systems enabled by nanoparticles are all benefits that the medical field can benefit from, ultimately supporting customised treatments (Hong Su et al. 2018). However, there are several constraints on the widespread use of nanoparticles, such as concerns with medication compatibility, colloidal stability, long-term storage, manufacturing costs, toxicity as a result of dispersion and accumulation in tissues, etc.

The bioavailability of aqueous-insoluble medications has been greatly increased by the use of a solid dispersion approach, which has attracted a lot of attention in recent years for this very reason (Ogienko et al. 2019). Drug delivery applications have been hampered by solubility concerns, however these issues have been solved by the use of solid dispersions of hydrophobic medicines with hydrophilic carriers (Sameer Singh et al., 2011). One or more medicines are dispersed across the solid medium using a water-soluble carrier. To increase the solubility ratio of poorly soluble drugs without changing their chemical features, this method appears to be a workable and viable solution.(Jung et al. 1999, De Oliveira Eloy et al. 2012). According to research, the surface area of many medications formed in a solid dispersion is much higher than that of micronized pharmaceuticals, and is comparable to that of nano-sized particles, offering very active surfaces for their dissolution. The solid dispersion is formed when a little quantity of the medication with an enhanced surface area is disseminated in a carrier matrix. The medication molecules are released from the hydrophilic carriers when they are exposed to water. The dispersion of amorphous solids is often quite diffuse (Lu et al., 2019). Another sign of solid dispersion of poorly soluble medications is an increased rate of dissolution, which leads to increased bioavailability. Dissolution rates of drugs are affected by the kind of polymer employed in their formulation. Different methods, including as fusion, kneading, hot melt extrusion, and supercritical fluid precipitation, are used to disperse solids.

Tolbutamide's solubility and dissolution are being improved by the current effort to knead the medicine into a solid dispersion. In pre-formulation work, possible hydrophilic carriers are screened, the drug:carrier ratio is prepared and experimentally optimised for the solid dispersion process, and in vitro dissolution tests are used to provide proof of concept for solubility improvement.

MATERIALS AND METHODS

Materials

Tolbutamide was received as gift sample from SRL Chem., Mumbai was used to get the beta cyclodextrin and PEG 4000. Double distillation was performed on site to produce the distilled water. They were all high-quality, analytical-grade compounds.

Preparation of Tolbutamide Solid Dispersion Formulations

Using hydrophilic carriers such polyethylene glycol (PEG 4000) and beta-cyclodextrin (β-CD), tolbutamide solid dispersion formulations were created by kneading. (Sapkal *et al*. 2007, Soulairol *et al*. 2015) (Table 1).

Table 1: Formulation of Tolbutamide solid dispersion by kneading process

Formulation code	Carrier	Tolbutamide: Carrier ratio
TC 1	β-CD	1:1
TC 2	β-CD	1:3
TC 3	β-CD	1:5
TP 1	PEG 4000	1:1
TP 2	PEG 4000	1:3
TP 3	PEG 4000	1:5

Micron- or nano-sized carrier encapsulated / matrix particles can be created by kneading, a physical mixing technique in which the drug and hydrophilic carrier are combined in a geometric ratio, with or without the use of water. Spraying 2–3 mL of distilled water was done after properly weighing and triturating the required quantity of carrier material using a mortar and pestle. Tolbutamide was added to the polymer in a measured amount and thoroughly kneaded until a paste formed, following the proportions of the test formulations provided in table 1. After the solvent was entirely evaporated from the paste form, a solid dispersion was formed by drying it in the air. By first forming a paste and then completely removing the solvent, kneading may decrease the particle size of a poorly soluble medication (a top-down technique) so that it can be entrapped or dispersed in a water-soluble carrier. The result is free-flowing

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micro/nanoparticles. The hydrophilic carrier would dissolve first when these particles are put to an appropriate medium (in vitro) or when they are delivered in vivo, allowing the entrapped medicine to be released at the desired spot. The drug's solubility and permeability may be improved if the particle size were reduced. (Modi *et al.* 2006, Ghareeb *et al*, 2018).

Analysis of Drug Content

Using distilled water adjusted to a pH of 7 and lysing 0.1 mL of the formulation with 1 mL of methanol, a final volume of 100 mL containing the desired drug concentration was obtained. The optical density of the diluted samples was measured at the λ_{max} of Tolbutamide using a UV-Visible Spectrophotometer (Evolution 201, Thermo Scientific, USA). The calibration curve was used to compute the drug concentration using the formula (Sundaresan et al., 2012).

"% Drug content = (Absorbance of Test Sample / Absorbance of Standard Pure) × 100"

Analysis of Particle Size and Zeta Potential

An in vitro dissolution study is a crucial examination for determining the drug's stability and release profile over time in specified medium. This research is important because it establishes the in vitro - in vivo connection of the parameters, allowing us to better understand the efficacy and bioavailability of drugs via in vitro procedures. The procedure followed the USP type-II (paddle) dissolving protocol (Sharma et al., 2010) using a DS1000 LabIndia, Mumbai dissolution apparatus. Each 0.5 mL of water and the test sample (solid dispersion/pure medication) were precisely measured and placed into a dialysis membrane bag (Himedia). To facilitate dissolving, 100 mL of distilled water was poured in the cylindrical basket and the dialysis bag was sealed, then linked to the end of the paddle that would be revolved at 100 rpm. Absorbance at a max wavelength of 290 nm was measured using a UV-visible spectrophotometer (Evolution 201, Thermo Scientific, USA). The total quantity of medication released was calculated using the linear equation established for the CGF standard calibration.(Paudel *et al*. 2013)

***In vitro* Dissolution Studies**

An in vitro dissolution research can reveal information about the drug's stability and release profile over time in a specific medium. This research is important because it shows how the parameters measured in vitro and in vivo are related, which advances our knowledge of the efficacy and bioavailability of drugs made in vitro. The DS1000 dissolve equipment from LabIndia, Mumbai was used in accordance with the USP type-II (paddle) dissolving technique (Sharma et al., 2010). Each 0.5 mL of water and the test sample (solid dispersion/pure medicine) were measured and inserted into a dialysis membrane bag (Himedia). The dissolving process was aided by placing 100 mL of distilled water in the cylindrical basket, sealing the dialysis bag, and attaching it to the end of the paddle that would be rotated at 100 rpm. The amount of medication released was determined by measuring the absorbance at 290 nm using a UV-visible spectrophotometer (Evolution 201, Thermo Scientific, USA) that had been calibrated against a standard of CGF concentration obtained from aliquots taken at regular intervals from the basket samples.

Drug Dissolution Kinetics:

Kinetic modelling and DD solver software were used to analyse the solid dispersion formulations' drug release patterns. The Hixon-crowell, Korsmeyer-Peppas, and Higuchi-Hixon models were investigated. Korsemeyer-Peppas kinetics was used to determine the diffusion process, and the model with the greatest correlation factor (R2), the lowest sum of squared residual (SS), and the largest n-value was selected to identify the drug release pattern from the formulation. The release pattern was determined for each model using a unique kinetic analysis technique. (Sharma *et al*. 2011).

Morphological studies

The surface morphology of the optimised solid dispersion formulation was analysed using a JSM 6701F scanner made by Japanese company JEOL. Under low pressure, nano formulations were affixed to blank double-sided stickers taped to a metal stub and coated with platinum. The sample container was loaded with the coated nanoparticles, and scanning was performed at 25kV. (El-Gibaly *et al*. 2002)

Fourier Transform Infrared Spectroscopy (FTIR)

By comparing the spectra of the dry formulation with the pure drug, FTIR (Perkin Elmer System 200, Shelton, Connecticut, USA) was utilised to ascertain the compatibility of the drug and excipient used in the solid

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dispersion formulation. The material was crushed in a hydraulic press after being mixed with IR grade potassium bromide (KBr) and then removed at a dose of about 2 mg. The infrared spectrum, from 4000 to 400 cm^{-1}, was then collected. Identifying and classifying the different functional groups present in the samples may be done using this spectrum. (Duarah *et al*. 2017).

Thermogravimetric analysis and Differential scanning calorimetry (TGA-DSC)

TGA-DTA testing was done on both the unadulterated medication and the kneaded solid dispersion formulation. TGA (TA Instrument, Q100, Michigan, USA) was used to examine the effect of heating a sample from 10 degrees Celsius per minute up to 600 degrees Celsius on its mass, and the results were read off as a function of temperature. "DTA was used to look for thermal changes in the sample's composition rather than in its bulk. In order to see the expected changes in output on the TG and DTA thermograms, the sample was heated to temperatures between 30 and 600 degrees Celsius in the sample holder of the furnace.(Praveen *et al.* 2009).

X-Ray Diffraction (XRD) Studies

Experiments with X-ray diffraction (D8 FOCUS, BRUKER, USA) were performed to look for differences in the crystalline structure between the original medications and the final solid dispersion sample. X-ray images were captured using CuK (Rigaku, Japan), with both the pure drug and the kneaded solid dispersion formulation placed within the sample container and subjected to 30 mA and 40 kV, respectively. Between 20 and 80 °C at 2θ, the samples were scanned. (Duarah *et al*. 2017).

RESULTS AND DISCUSSION

Physico-chemical characterization of Tolbutamide Solid Dispersion Formulations

Table 2: Physico-chemical Characterization studies of Tolbutamide Solid Dispersion Samples

S. No.	Formulation Code	Hydrophilic Carrier (Drug: Carrier Ratio)	Drug Content (%)	Average Particle Size (nm)	Poly Dispersity Index (PDI)	Zeta Potential (mV)
1	**CC 1**	β-CD (1:1)	99.5 ± 1.2	249	0.235	-58.1
2	**CC 2**	β-CD (1:3)	98.2 ± 0.8	316	0.252	-54.3
3	**CC 3**	β-CD (1:5)	96.9 ± 2.1	619	0.259	-34
4	**CP1**	PEG 4000 (1:1)	96.5 ± 0.9	644	0.671	-21.2
5	**CP2**	PEG 4000 (1:3)	95.4 ± 2.2	486	0.625	-17.8
6	**CP3**	PEG 4000 (1:5)	97.2 ± 1.7	293	0.746	-20.2

All solid dispersion formulations were evaluated, and their drug contents were deemed to be suitable (95.0–99.5%). Mean particle sizes of 249-619 nm and 293-644 nm were found in the tolbutamide solid dispersion formulations produced with cyclodextrin and PEG 4000 at 1:1, 1:3, and 1:5 ratios, respectively. The homogeneous size distribution is shown by the single peak with maximum intensity (<95%) in cyclodextrin-based formulations. Instead, the PEG-based formulations displayed two peaks in the distribution curve, indicating the particles generated were poly-disperse. Accordingly, the pdI values for the cyclodextrin and PEG-prepared solid dispersion formulations were found to be in the restricted range of 0.20 to 0.26, while the values for the PEG-prepared formulations were higher, at 0.60 to 0.75. As a result, the nature of the former is monodisperse while that of the later is polydisperse. Tolbutamide-cyclodextrin solid dispersion had zeta potential values between -34 and -58 mV, indicating high colloidal stability. This is in contrast to the PEG solid dispersion formulation, which showed moderate stability (zeta potential values of -17 mV to -21 mV). Higher stability of the formulations was achieved by obtaining a free-flowing dry powder from the solid dispersion using a kneading procedure.

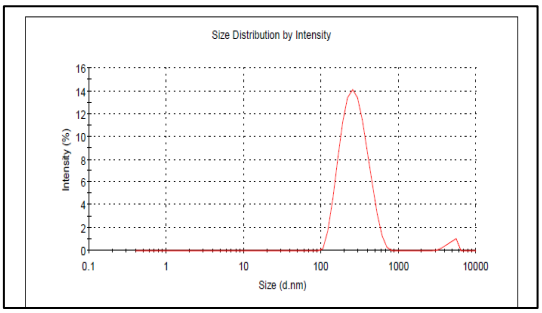

Fig 1: Particle size distribution of CC1 solid dispersion formulation

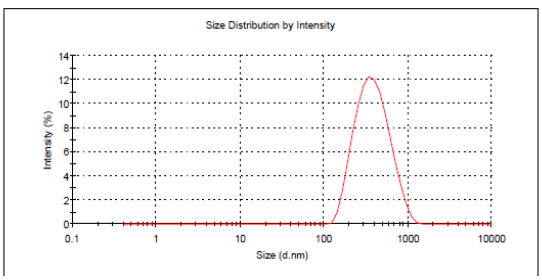

Fig 2: Particle size distribution of CC2 solid dispersion formulation

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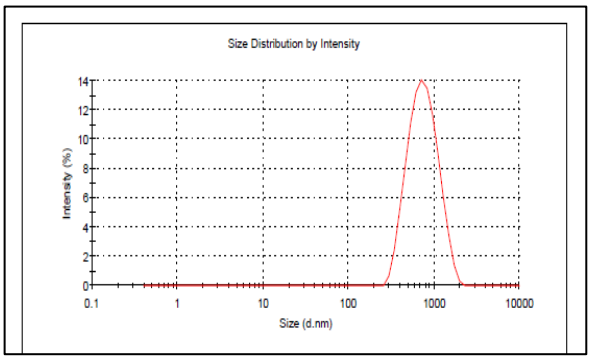

Fig 3: Particle size distribution of CC3 solid dispersion formulation

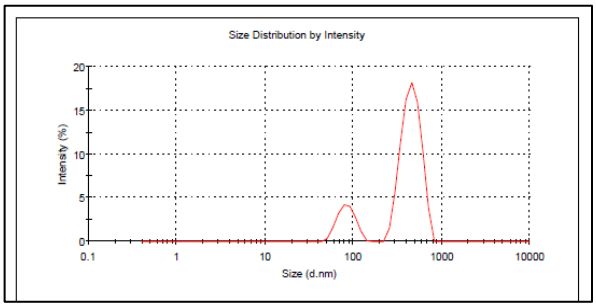

Fig 4: Particle size distribution of CP1 solid dispersion formulation

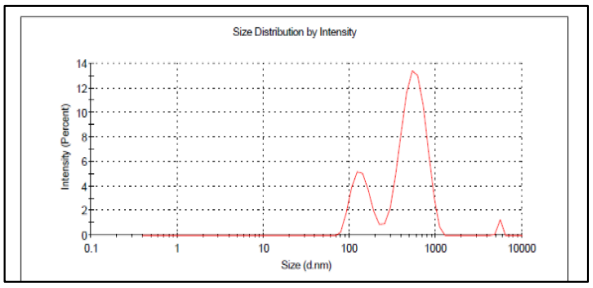

Fig 5: Particle size distribution of CP2 solid dispersion formulation

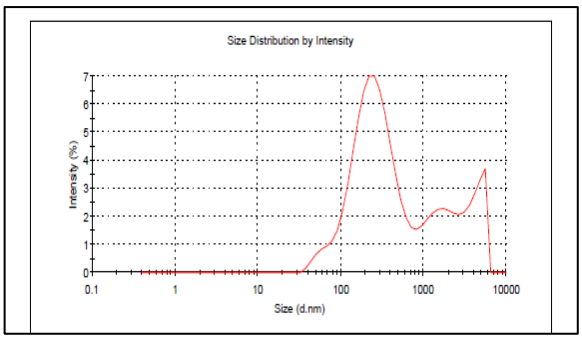

Fig 6: Particle size distribution of CP3 solid dispersion formulation

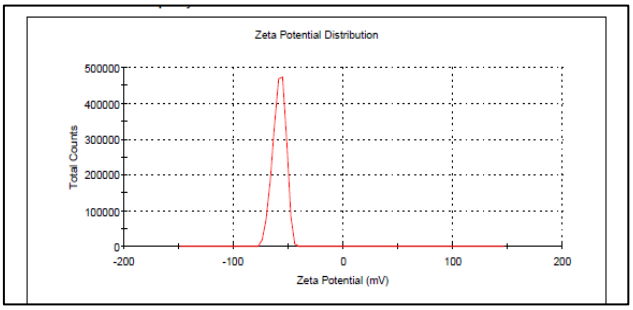

Fig 7: Zeta potential analysis for CC1 solid dispersion formulation

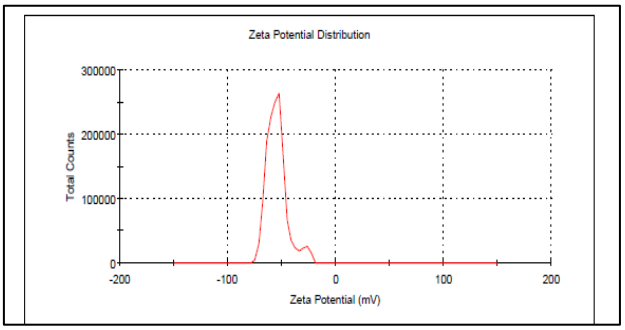

Fig 8: Zeta potential analysis for CC2 solid dispersion formulation

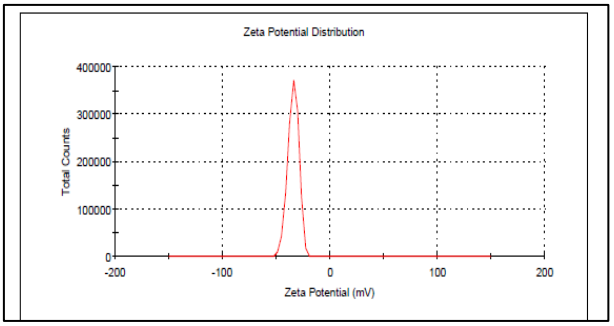

Fig 9: Zeta potential analysis for CC3 solid dispersion formulation

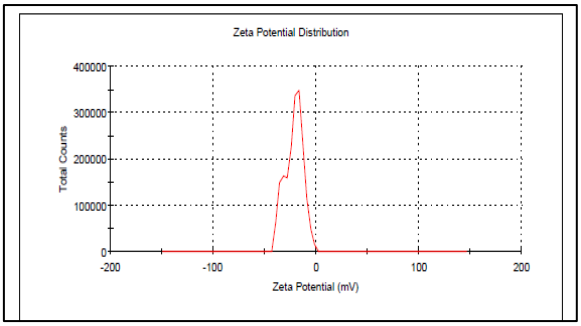

Fig 10: Zeta potential analysis for CP1 solid dispersion formulation

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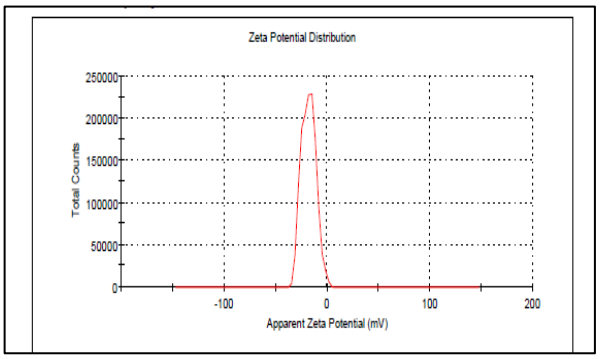

Fig 11: Zeta potential analysis for CP2 solid dispersion formulation

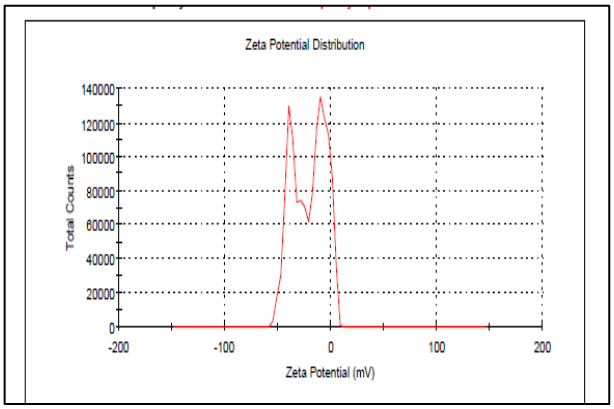

Fig 12: Zeta potential analysis for CP3 solid dispersion formulation

In Vitro Dissolution Studies of Tolbutamide Solid Dispersion Formulations

The cumulative quantity of medication released in vitro from the solid dispersion formulations followed a linear pattern. Dissolution in a distilled water medium of a pure aqueous suspension of the medication was less than 10% after 6 hours. Tolbutamide solubility was dramatically enhanced in six different solid dispersions when hydrophilic carriers such beta cyclodextrin and PEG 400 were included in their preparation. The drug:cyclodextrin ratio of 1:1 in the CC1 formulation resulted in a maximum dissolution of almost 75%. However, the dissolution profile revealed a declining tendency when the content of cyclodextrin was raised to 1:3 and 1:5. Patel et al(2019) .'s study indicates that a 1:1 ratio is the ideal one for mixing cyclodextrin with tolbutamide. At 6 hours, dissolution rates for all three versions of the PEG 4000 based solid dispersion were around 45-50 percent. Tolbutamide's solubility was increased by around 5 fold and 7.5 fold, respectively, when the hydrophilic carriers PEG 4000 and cyclodextrin were included in the solid dispersions. (Herbrink *et al*. 2017)

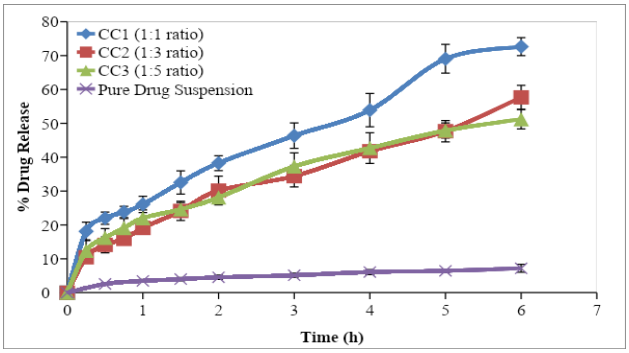

Fig 13: *In vitro* drug release profile of Tolbutamide-Cyclodextrin formulations compared to pure drug

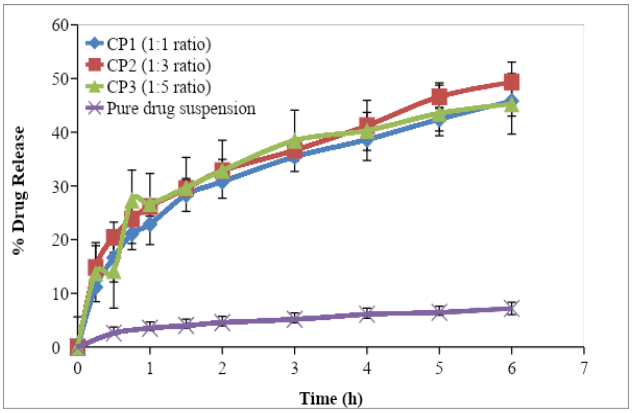

Fig 14: *In vitro* drug release profile of Tolbutamide-PEG 4000 formulations compared to pure drug

Drug Release Kinetics from Tolbutamide solid dispersions

The cumulative amount of drug release values obtained at the specific time points for the formulated solid dispersions was analysed using different release kinetics mathematic modelling to study the drug release pattern and principle behind. Based on the high R2 values (0.99%) and lowest SS values, Korsemeyer-Peppas kinetics was determined to be a good match to the formulations. Thus, molecules from the sample diffused into the dissolving medium, which aided in the drug release. The n numbers reflected the fact that the drug release process was a hybrid of Fickian and non-Fickian diffusion mechanisms. (Afifi 2015, Skolakova *et al.* 2019).

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Table 3: Drug Release Kinetics of Tolbutamide Solid Dispersion Formulations

Kinetics Model	Parameters	Pure Drug	CC1	CC2	CC3	CP1	CP2	CP3
Zero	R^2	0.557	0.766	0.836	0.686	0.422	0.306	0.204
	K_0	1.445	14.028	10.538	10.304	9.580	10.324	9.923
	SS	17.304	1151.928	492.058	792.836	1127.142	1453.917	1595.103
First	R^2	0.583	0.910	0.925	0.836	0.640	0.565	0.483
	K_1	0.015	0.234	0.149	0.147	0.135	0.151	0.144
	SS	16.304	441.816	224.154	412.364	702.640	910.369	1035.507
Higuchi	R^2	0.981	0.981	0.982	0.9952	0.965	0.940	0.895
	K_H	3.035	28.566	21.304	21.188	20.100	21.759	21.069
	SS	0.724	89.630	53.125	12.173	68.408	123.816	209.754
Korsemeyer -Peppas	R^2	0.998	0.983	0.991	0.995	0.995	0.997	0.968
	K_{KP}	3.410	27.553	19.330	21.603	22.781	25.597	25.216
	SS	0.074	82.256	24.515	10.861	9.405	5.536	63.977
	n	0.407	0.530	0.580	0.484	0.393	0.360	0.345
Hixson-Crowell	R^2	0.575	0.879	0.902	0.794	0.574	0.487	0.397
	K_{HC}	0.005	0.067	0.044	0.044	0.040	0.044	0.042
	SS	16.634	596.973	294.200	519.207	831.618	1074.655	1207.765

Morphology of Tolbutamide Solid Dispersion

Pure Tolbutamide sample exhibited heterogeneous morphology, with features of varying form and size. Particles of uniform size and spherical shape were produced by a solid dispersion of the medicine in a hydrophilic carrier, which was made by kneading in the presence of water and then drying entirely. Results from the zeta sizer were found to be somewhat comparable to the average size of the optimised formulation CC1. The particles' homogeneous dissolution and solubility may be improved by their reduced size and spherical shape. (Alshweiat *et al*. 2018).

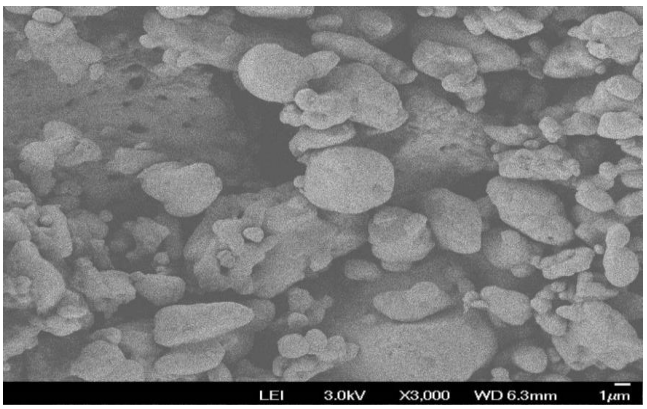

Fig 15: SEM image of pure Tolbutamide

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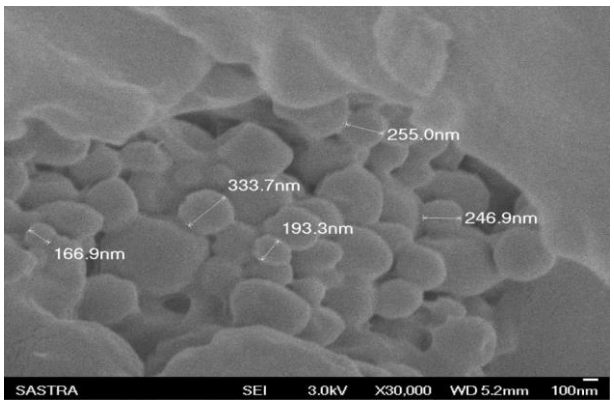

Fig 16: SEM image of Tolbutamide-Cyclodextrin Solid Dispersion

FTIR Analysis of Tolbutamide Solid Dispersion

In order to determine the chemical stability of the medicine and its interactions with the hydrophilic carrier, FTIR analysis was used to compare the spectra of the pure medication, pure cyclodextrin, and the produced solid dispersion. The -OH stretching at 3367 cm^{-1}, aromatic C-H stretching at 2902 cm^{-1}, C-C=C symmetric stretching at 1600 cm^{-1}, C-C=C asymmetric stretching at 1508 cm^{-1}, C-O stretching at 1285 cm^{-1}, C-S stretching at 808 cm^{-1}, C-F stretching at 1438 cm^{-1}, and C-F stretching at 1051 cm^{-1}1 were all clearly visible in the FTIR spectrum of pure tolbutamide. Therefore, the chemical structure verified the efficacy and safety of the medication. The O-H and C-H stretch bands at 3447.15 and 2923.39 cm^{-1}, respectively, showed pure β-cyclodextrin carrier. At 1304.66 cm-1, the -CD's C-O-C stretching bonds could be seen. Dharmasthala et al. (2019) report seeing spectra at 1647.66 cm^{-1} and 1416.33 cm^{-1} for the conventional C=O and conjugated C=C bonds of the βCD, respectively. Using the solid dispersion formula, the peaks that were responsible for the appearance of certain functional groups were found by changing the wavenumber a little. We measured peak frequencies of 3389 cm-1 for OH stretching, 2923 cm^{-1} for aromatic C-H stretching, 1634 cm^{-1} for aromatic C-C=C symmetric stretching, and 1509 cm^{-1} for asymmetric stretching. The C-O, C-S, and C-F axes were stretched at 1232 cm^{-1}, 808 cm^{-1}, and 1029 cm^{-1}, respectively. As a result, the drug's original nature remained unaltered and virtually little chemical interaction was seen between it and the carrier.

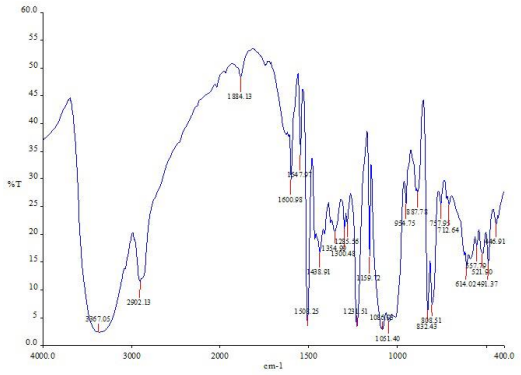

Fig 17: FTIR Spectrum of Pure Tolbutamide

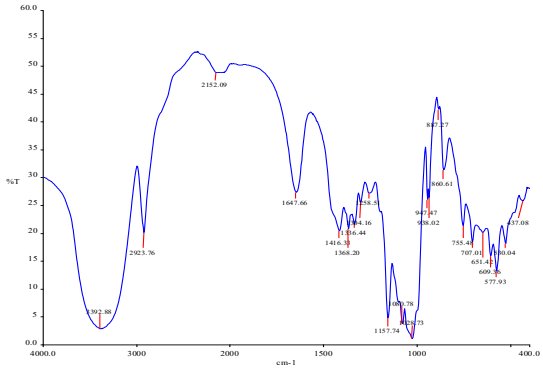

Fig 18: FTIR Spectrum of Pure Cyclodextrin

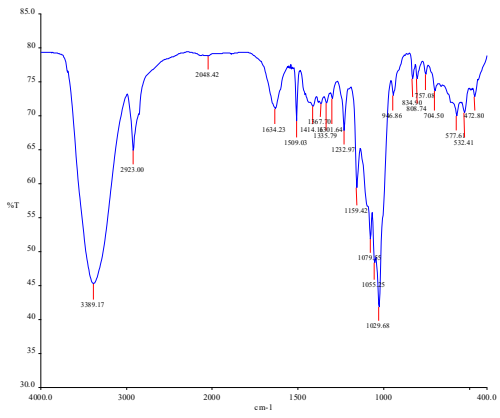

Fig 19: FTIR Spectrum of Tolbutamide-Cyclodextrin Solid Dispersion (1:1 ratio)

TG-DTA Analysis of Tolbutamide Solid Dispersion

The thermal stability and variations in thermal behaviour of the formed solid dispersion were studied using TG-DTA thermogram comparisons with the pure drug and pure carrier. The DTA curve of pure tolbutamide showed a modest exothermic bend up to 400°C, suggesting that the molecule absorbs heat energy, and an

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abrupt endothermic peak at 70°C, which corresponds to its melting point. At 420 degrees Celsius, the drug's decomposition showed a distinct exothermic peak. The TG curve proved the heat breakdown of the medication by showing the rapid decrease in sample weight from 100% at the starting temperature to less than 10% at the corresponding temperature. An endothermic peak occurred close to its melting temperature of around 175 °C in the pure cyclodextrin carrier sample, which was followed by an exothermic curve and a steep decrease at about 379 °C. A similar, rapid decrease in the TG curve of the cyclodextrin pure sample at the same temperature indicated a loss of mass to heat degradation of less than 2.5%. The melting point of the tolbutamide-cyclodextrin solid dispersion sample increased from 70 degrees Celsius to 80 degrees Celsius due to thermal deterioration (low heat compared to pure drug and pure carrier sample). Weak drug-carrier interactions or encapsulation may contribute to the sample's thermal instability. (Grandelli *et al.* 2013).

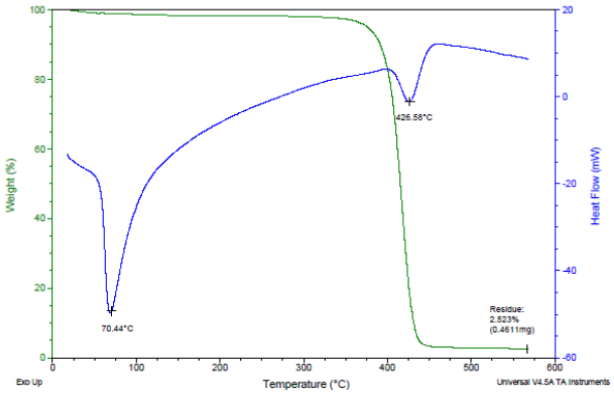

Fig 20: TG-DTA thermogram of Pure Tolbutamide

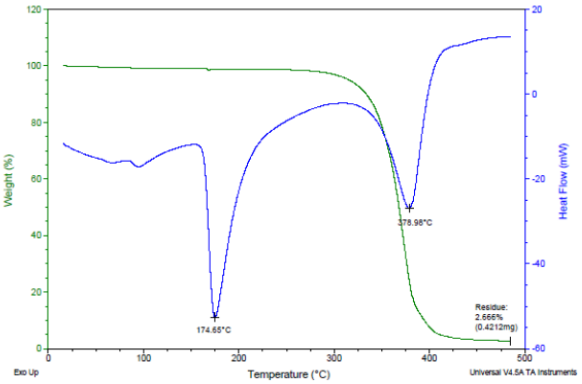

Fig 21: TG-DTA thermogram of Pure Cyclodextrin

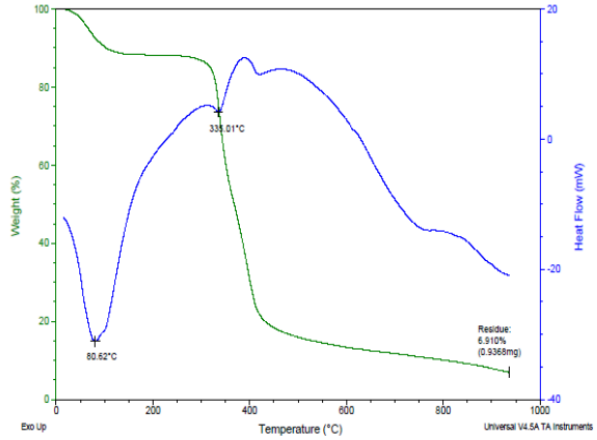

Fig 22: TG-DTA thermogram of Tolbutamide-Cyclodextrin Solid Dispersion (1:1 ratio)

XRD Analysis of Tolbutamide Solid Dispersion

XRD spectrum of pure Tolbutamide showed sharp peaks with high intensity at the 2θ range, due to characteristic crystalline nature of the pure sample, whereas the carrier cyclodextrin was found to be amorphous in nature. Solid dispersion was created by repeatedly kneading along the hydrophilic carrier in the presence of water, which reduced the drug's crystallinity and converted it to an amorphous state". (Lu et al. 2019). Tolbutamide's physical properties may have changed as a result of its encapsulation in the polymer, possibly favouring an increase in solubility and dissolution of the BCS class II prescription by lessening the sudden, powerful peaks of the original drug. (Zhang *et al*. 2004).

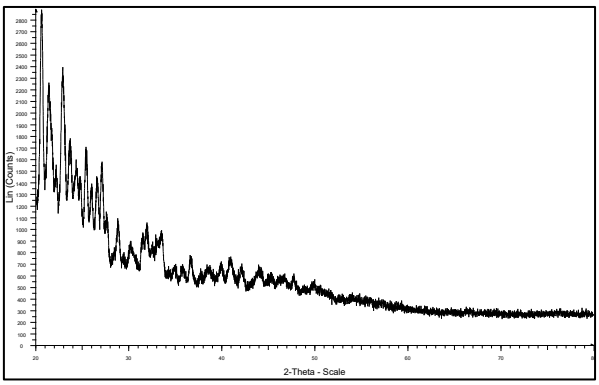

Fig 23: XRD of Pure Tolbutamide

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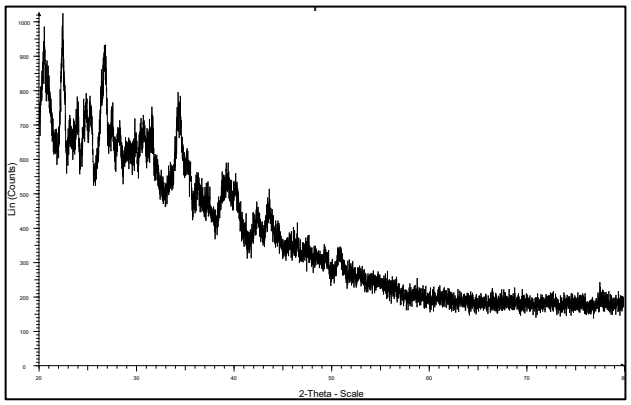

Fig 24: XRD of pure Cyclodextrin

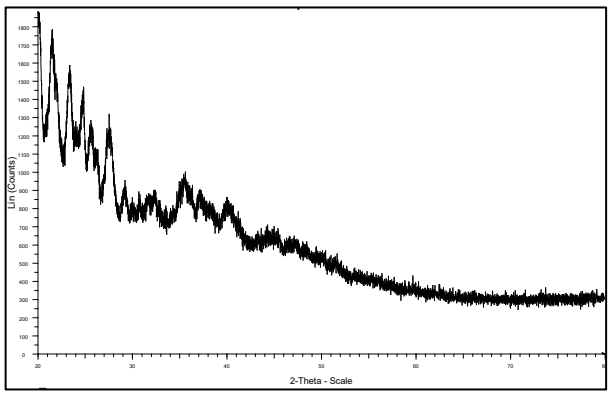

Fig 25: XRD of Tolbutamide-Cyclodextrin Solid Dispersion (1:1 ratio)

CONCLUSION:

By kneading Tolbutamide with water-soluble carriers such beta-cyclodextrin and PEG 4000, solid dispersions were created in three distinct ratios: 1:1, 1:3, and 1:5. All the formulations were found to be in nanoparticle scale range with optimum colloidal stability. The hydrophilic carrier beta cyclodextrin could be considered as more suitable to encapsulate the hydrophobic drug Tolbutamide at 1:1 ratio, as more than 7.5-fold increase in the drug dissolution was favoured in comparison to pure drug aqueous suspension. Also, the analytical methods for size, morphology and drug-carrier interactions proved the suitability and stability of the combination. The enhanced solubility and *in vitro* dissolution of Tolbutamide would improve the *in vivo* absorption of the drug that could achieve higher systemic bioavailability. Therefore, it is expected that low dose administration may be sufficient to attain the required therapeutic concentration and effects in clinical practice, which can reduce the dose-related side effects in patients (Khadka *et al.* 2014, Gupta *et al.* 2013).

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