TRIAZINE DENDRIMERS: AN EXCELLENT DRUG CARRIER FOR IMPROVING THE SOLUBILITY OF GLYBURIDE AN ANTIDIABETIC AGENT

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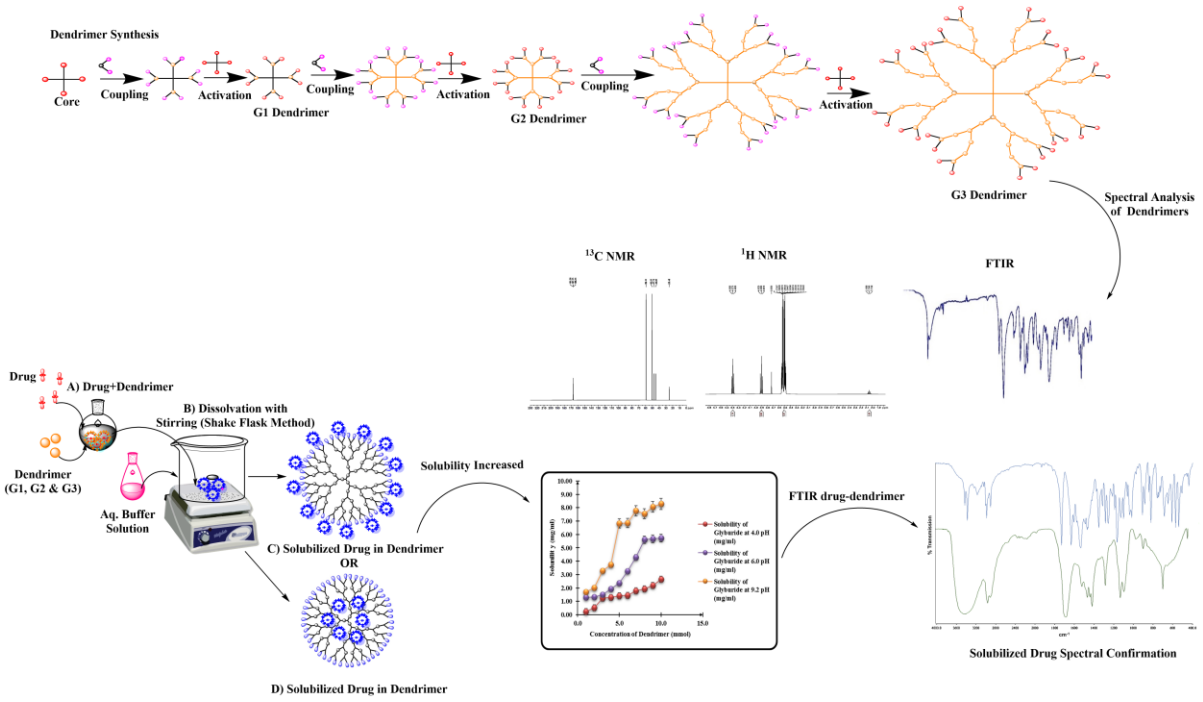
Abstract

The intent of this work was to synthesized, develop and characterize a novel dendrimer and drug-dendrimer solutions to resolve poorly aqueous solubility of glyburide which is an antidiabetic BSC class-II drug's problem. Drug- dendrimer complex formation is one of the widely reported method for solubility enhancement of the drug which can increase the efficiency of the drug. A number of glyburide drug solutions were formulated with different quantities of G1, G2 and G3 dendrimers via Higuchi and Connors method. The effects of pH, dendrimer concentration and generation of dendrimers (G1-G3) on the aqueous solubility of drug was investigated and characterized by FT-IR, NMR (^{1}H and ^{13}C). The experimental outcomes recommended that solubility of glyburide was significantly enhanced with the increasing concentration of dendrimers as well as the generations of dendrimers.

Keywords: Phase Solubility, Glyburide, Triazine Dendrimer, Dendrimer as Solubility Enhancer, Drug solubility

Graphical Abstract



Introduction

As the extensively of the medications have poor solvency in water, low bioavailability is one of the significant detriments of the oral defeat of medication organization. On account of inadequately water-solvent medications, disintegration is the rate-constraining advance during the time spent medication retention. At the point when a functioning specialist is managed orally, it should initially break down in gastric as well as intestinal liquids before it can pervade the films of the GIT to arrive at foundational dissemination and thus two territories of pharmaceutical research that attention on improving the oral bioavailability of dynamic operators incorporate; upgrading of dissolvability and disintegration pace of ineffectively water solvent drugs [1-3]**.** It is notable that low watery solvency of the new pharmaceutical dynamic operator is an issue for the pharmaceutical advancement process which ought to be tended to at an opportune time during compound improvement [4-6]**.**

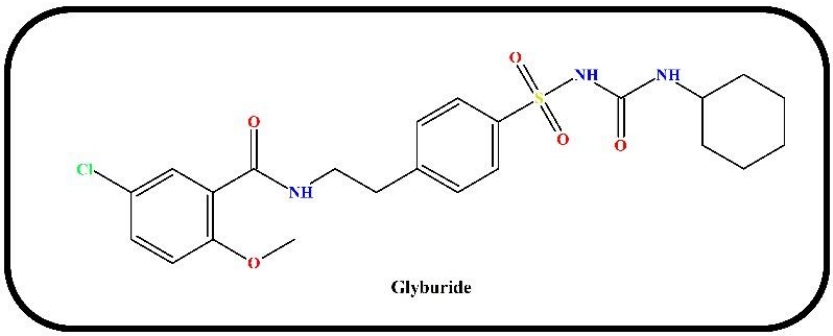


Fig. 1 Glyburide (GLB)

Dendrimers are three dimensional, nano sized macromolecules having monodisperse sub-atomic weight dissemination acquired by the redundant arrangement of responses [16,17]. Dendrimer have possessed the extraordinary properties which differ it from any other polymer the properties are nano scale monodispersity, amplifiable and functional surface groups and measurements that impersonates the biomolecules [18,19]. Subsequently these dendrimers are regularly utilized in various biomedical applications like drug solubilization, as drug delivery, as MRI differentiate operators and so many more [20]. Utilization of dendrimer as a vehicle

for tranquilize conveyance has been of incredible intrigue [21-23].

In this present study we have synthesized dendritic architecture using divergent method with 1,4-bis(4,6-dichloro-1,3,5-triazin-2-yl)-1,4-diazepane as the core which ended by linkages of triazine trichloride and hydroxyl groups. Dendrimers were synthesized from core to G3 generations, and characterized by Infrared Spectroscopy (FTIR), ^{1}H NMR and ^{13}C NMR [24, 31, 32]. The solubility enhancement study of glyburide (GLB) was investigated in dendrimer generation (G1 – G3). The factors like generation of dendrimers, pH, and concentration of dendrimers on glyburide's solubility were also investigated. The solubility formulations were further examined by FTIR spectroscopy.

Result and Discussion

Spectral studies

FTIR study for synthesized dendrimers

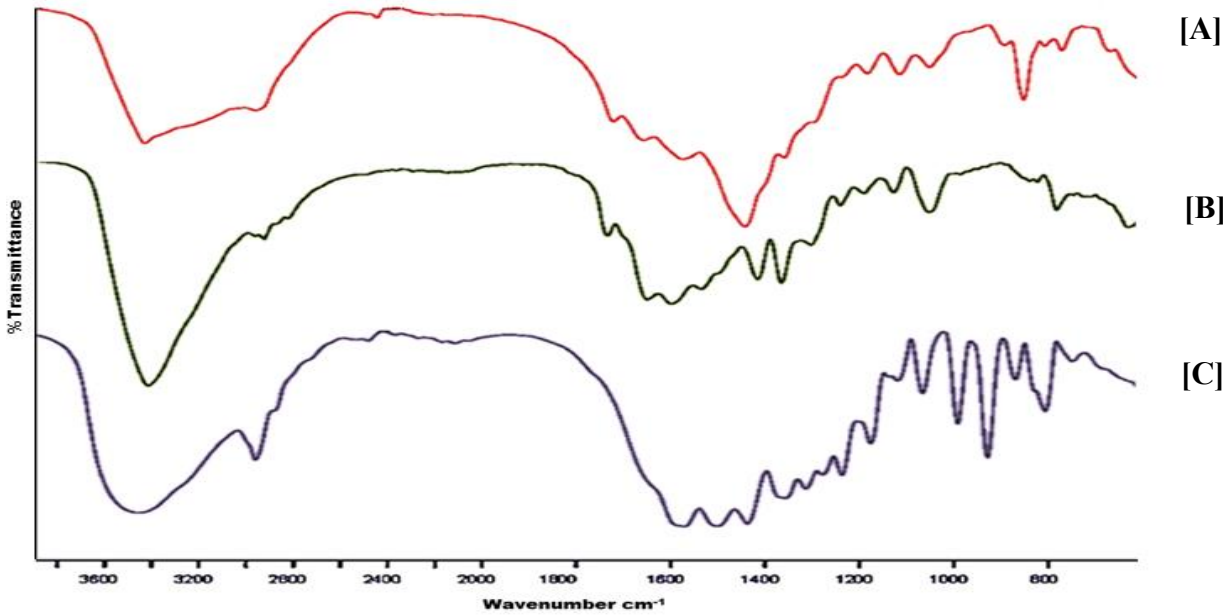


Fig. 2.1 FTIR A) G1 dendrimer, B) G2 dendrimer, C) G3 dendrimer.

FTIR spectroscopy was also performed for dendrimers G1, G2 and G3 and their result are discussed below:

FTIR study for G1 dendrimer

FTIR (Nujol, cm^{-1}): 3457 (O-H stretching of terminal OH groups), 2985 (C-H stretching of aliphatic C-H groups), 1670 (C = N stretching of triazine ring), 1063 (C-O stretching of hydroxyl groups).

FTIR study for G2 dendrimer

FTIR (Nujol, cm^{-1}): 3448 (O-H stretching of terminal OH groups), 2949.72 (C-H stretching of aliphatic C-H groups), 1567 (C = N stretching of triazine ring), 1062 (C-O stretching of ether linkages or hydroxyl group).

FTIR study for G3 dendrimer

FTIR (Nujol, cm^{-1}): 3441 (OH stretching of terminal OH groups), 2984, 2947, 2844 (C-H stretching of aliphatic C-H groups), 1654 (C = N stretching of triazine ring), 1053 (C-O stretching of ether or alcohol linkages).

FTIR study of glyburide-dendrimer solutions

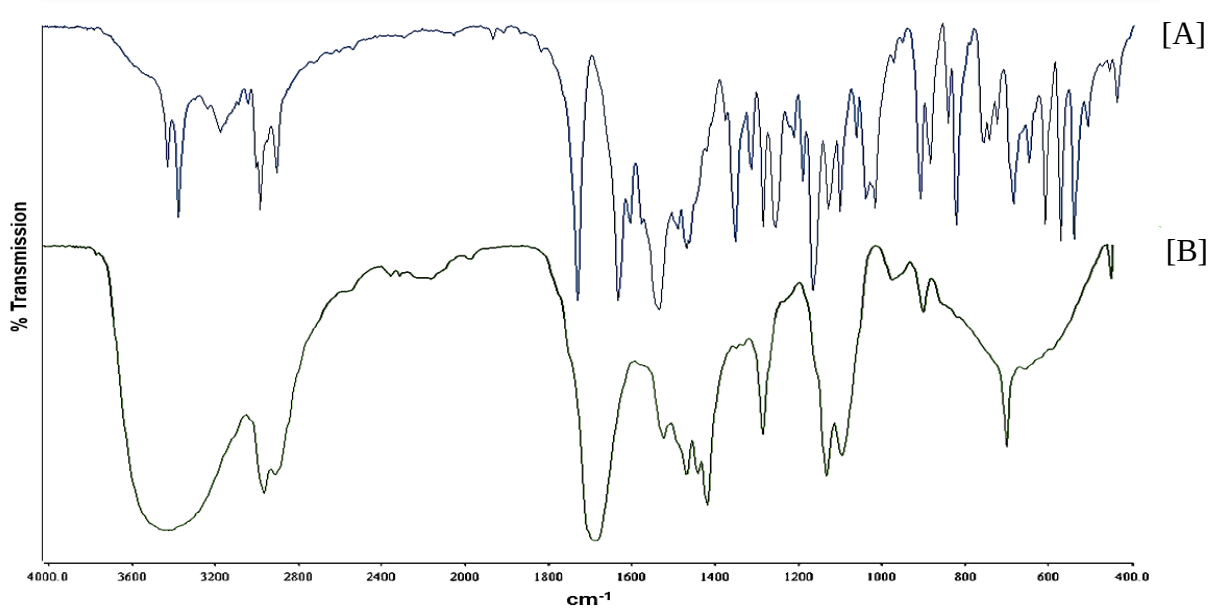


Fig. 2.2 FTIR A) Glyburide, B) G3 dendrimer and glyburide complex.

FTIR study for glyburide

FTIR (KBr, cm^{-1}): 3315 (N-H stretching of N-H group), 2930 (C-H stretching of aliphatic C-H groups), 1715 (C-O stretching of aliphatic C-O groups), 1365 (C-N stretching of C-N), 685 (C-Cl stretching of C-Cl groups) [43].

FTIR study for G3 and glyburide dendrimer complex

FTIR (KBr, cm^{-1}): 3393 (N-H stretching of N-H group), 2933 (C-H stretching of aliphatic C-H groups), 1663 (C-O stretching of aliphatic C-O groups), 1390 (C-N stretching of C-N), 662 (C-Cl stretching of C-Cl groups) [37].

^{1}H NMR study

NMR spectroscopy technique can reveal important information regarding change in number of protons as well as carbon molecules which helps in elucidating structural properties of synthesized dendrimer [38]. The proton NMR spectroscopic patterns of G1, G2 and G3 dendrimers are depicted in Fig.2.3 -2.5 (A-C).

[A]

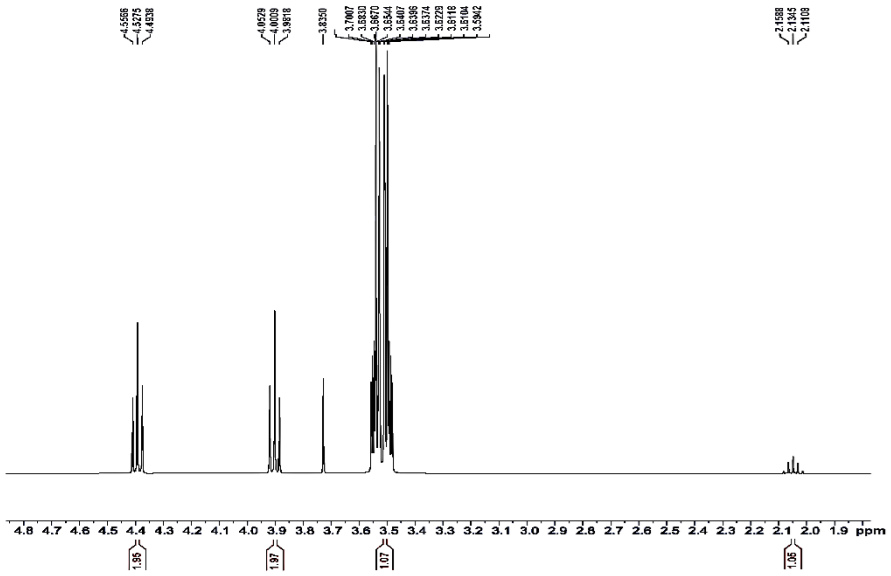


Fig. 2.3 (A) ^{1}H NMR of G1 dendrimer.

[B]

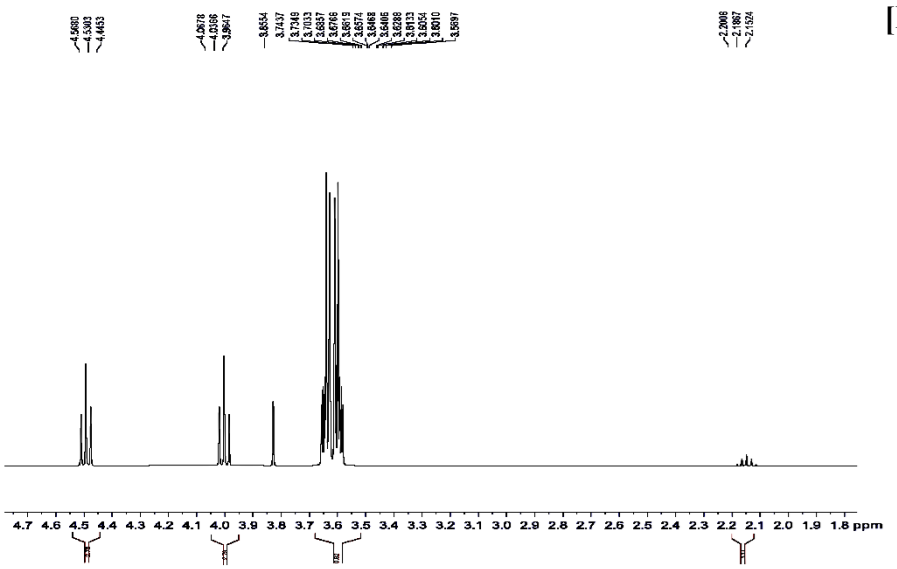


Fig. 2.4 ^{1}H NMR of G2 dendrimer.

[C]

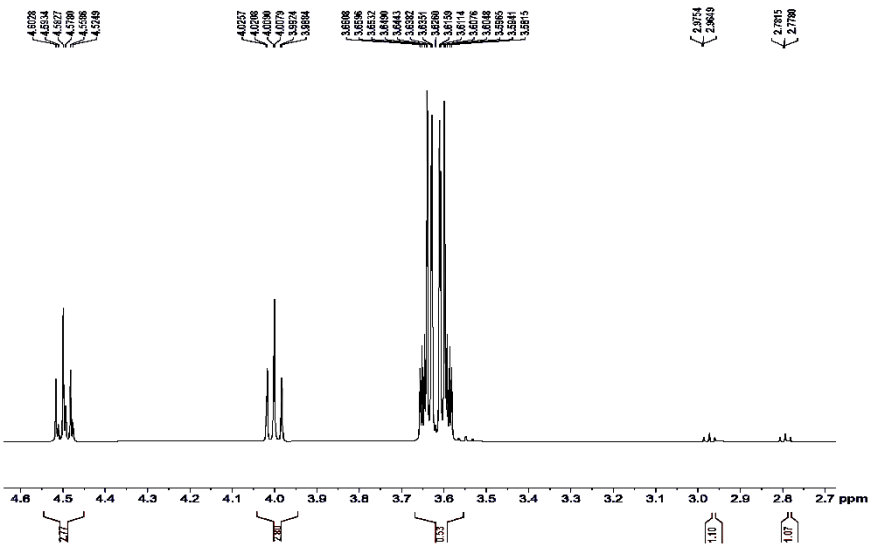


Fig. 2.5 (C) ^{1}H NMR of G3 dendrimer.

So the peak description for the ^{1}H NMR for synthesized dendrimers are as follow [25].

^{1}H NMR study for G1 dendrimer

^{1}H-NMR (500 MHz, D_2O, δ/ppm): 2.1108-2.1588 (m, 8H, -CH_2), 3.5942-3.7007 (m, 2H -CH_2) as Homopiperazine Core, 3.9818-4.0529 (t, 16H, N-$\underline{CH_2}$-CH_2-OH), 4.4938-4.5566 (t, 16H, N-CH_2-$\underline{CH_2}$-OH).

^{1}H NMR study for G2 dendrimer

^{1}H-NMR (500 MHz, D_2O, δ/ppm): 2.1524-2.2008 (m, 8H, -CH_2), 3.5697-3.7437 (m, 2H -CH_2) as Homopiperazine Core, 3.9647-4.0678 (t, 64H, N-$\underline{CH_2}$-CH_2-OH), 4.4453-4.5680 (t, 64 H, N-CH_2-$\underline{CH_2}$-OH).

^{1}H NMR study for G3 dendrimer

^{1}H-NMR (500 MHz, D_2O, δ/ppm): 2.7780-2.7815, 2.9649-2.9754 (t, 8H, -CH_2), 3.5815-3.6608 (m, 2H -CH_2) as Homopiperazine core, 3.9884-4.0257 (t, 264H, N-$\underline{CH_2}$-CH_2-OH, inner), 4.5249-4.6028 (m, 264H, N-CH_2-$\underline{CH_2}$-OH, outer).

^{13}C NMR study

^{13}C NMR is one of the most preferred technique for complete structural elucidation of organic molecules [40]. The carbon NMR spectroscopic patterns of G1, G2 and G3 dendrimers are depicted in Fig. 2.6 - 2.8.

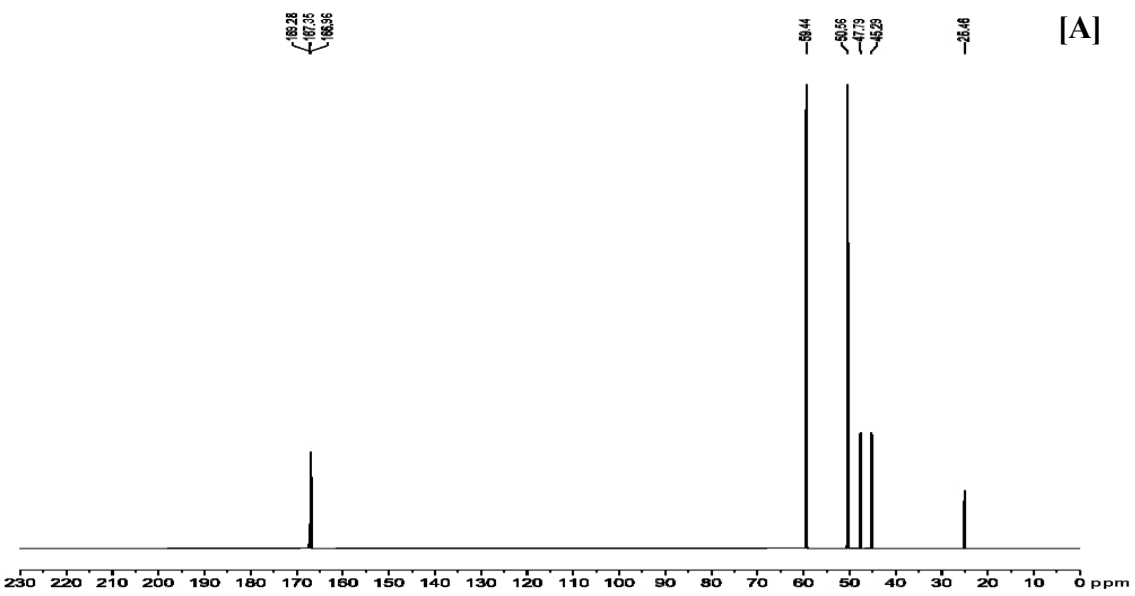


Fig. 2.6 (A) ^{13}C NMR of G1 dendrimer.

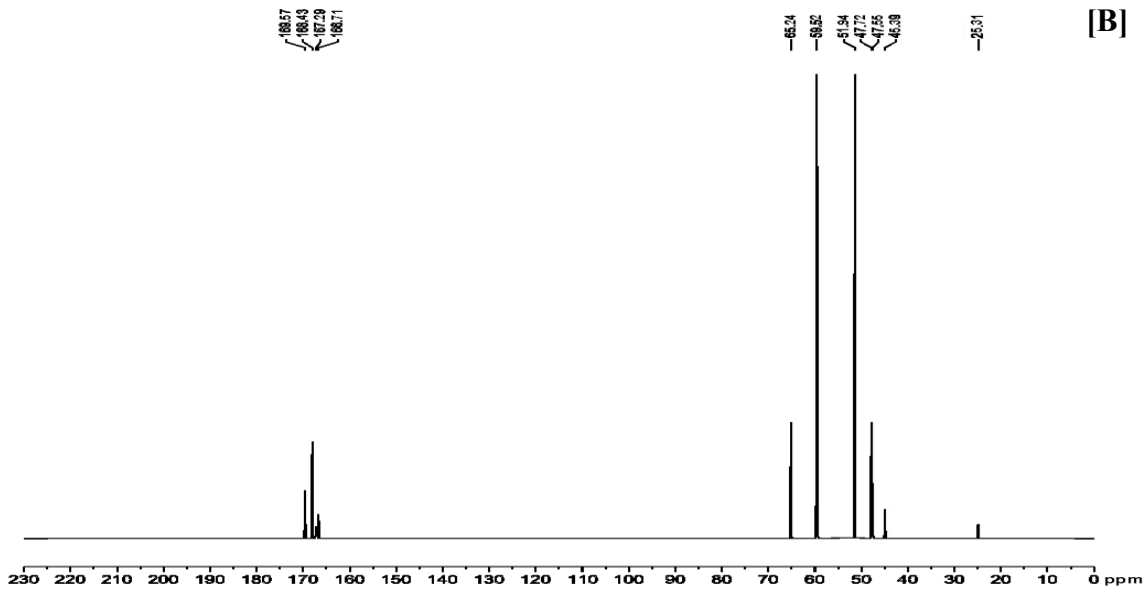


Fig. 2.7 (B) ^{13}C NMR of G2 dendrimer.

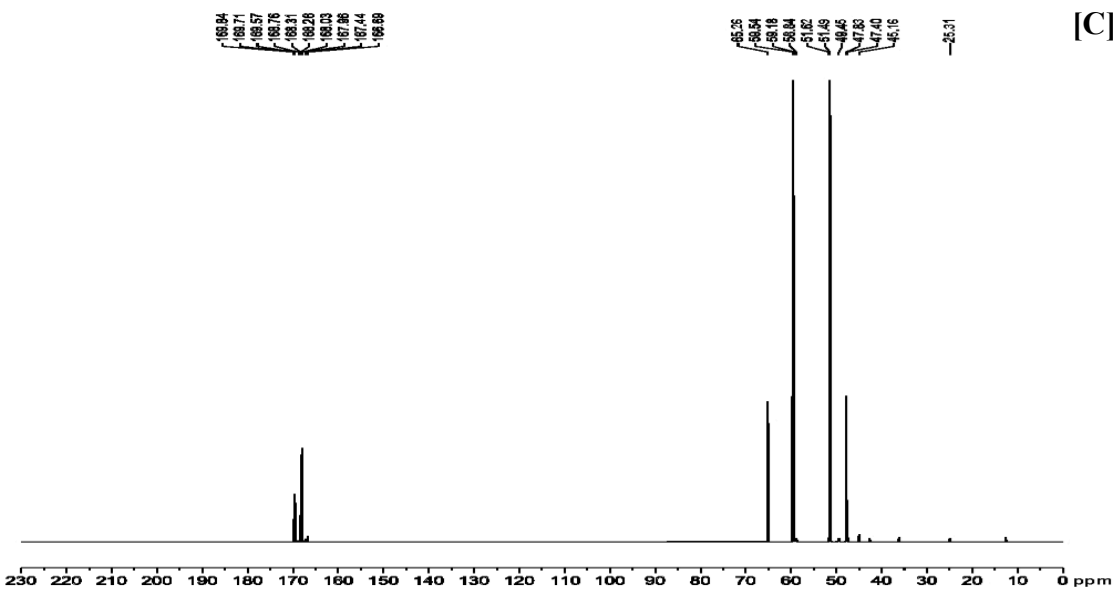


Fig. 2.8 (C) ^{13}C NMR of G3 dendrimer.

So the peak description for the ^{13}C NMR for synthesized dendrimers are as follow;

^{13}C NMR study for G1 dendrimer

^{13}C-NMR (125 MHz, D_2O, δ/ppm): 25.46, 45.29, 47.79 (Homopiperazine carbon), 50.56 (N-CH_2-CH_2-OH), 59.44 (N-CH_2-CH_2-OH), 166.96, 167.35, 169.28 [(triazine C-N-(CH_2-CH_2-OH)$_2$].

^{13}C NMR study for G2 dendrimer

^{13}C-NMR (125 MHz, D_2O, δ/ppm): 25.31, 45.39, 47.55 - 47.72 (Homopiperazine carbon), 51.94 (N-CH_2-CH_2-OH), 59.52 (N-CH_2-CH_2-O-tri), 65.24 (N-CH_2-CH_2-OH), 166.71 (triazine C-N), 167.29 triazine [(C-N-(CH_2-CH_2-O-)$_2$], 168.43 (triazine C-O), 169.57 (triazine C-N(CH_2-CH_2-OH).

^{13}C NMR study for G3 dendrimer

^{13}C-NMR (125 MHz, D_2O, δ/ppm): 25.31, 45.16, 47.40 - 47.83 (Homopiperazine carbon), 51.49 - 51.62 (N-CH_2-CH_2-OH), 58.84, 59.18, 59.54, 65.26 (N-CH_2-CH_2-O-tri), 166.69 (triazine C-N), 167.44 - 167.96 [(C-N-(CH_2-CH_2-O-)]$_2$, 168.03-168.76 [(C-N-(CH_2-CH_2-O-)2], 169.71, 169.84 (triazine C-O).

Physical properties of synthesized dendrimers

Full generation dendrimers having hydroxyl terminated functional groups possess dark- honey like consistency. The full generations G1, G2 and G3 dendrimers were soluble in water and their physical properties are tabulated in Table 1[26].

Generation of dendrimer	**Molecular Formula**	**Physical appearance**	**Solvency in water**	**Number of surface active groups present**
G1	$C_{26}H_{48}N_{12}O_8$	Brown liquid	Soluble	$OH_{(8)}$
G2	$C_{114}H_{200}N_{52}O_{40}$	Brown liquid	Soluble	$OH_{(32)}$
G3	$C_{466}H_{808}N_{212}O_{168}$	Brown liquid	Soluble	$OH_{(128)}$

Table 1 Physical properties of dendrimers.

Drug solubilization

For the drug solubility series of investigational experiments for glyburide by the full generation dendrimers were carried out by using the concentration of dendrimer (0.6 to 6 mmol) at pH 4.0, 6.0, and 9.2. The results of solubility study are displayed in fig. 2.9 (A, B & C).

Effects of dendrimers concentration on solubility of glyburide

A sequences for experiments of solubility of glyburide were carried out utilizing G1, G2 and G3 dendrimers which have terminal hydroxyl groups found OH_8, OH_{32} and OH_{128} respectively. In the presence of the full generation dendrimer the solubility of glyburide linearly increased with the increase in the concentrations of the dendrimer which may be due to the terminal hydroxyl groups which may attach with glyburide drug molecules [41,42].

Effect of pH on solubility of glyburide

The samples of glyburide with triazine full generation dendrimer were prepared at 4.0, 6.0 and 9.2 pH values with fixed concentrations of dendrimers for the determination of the solubilization of glyburide. The results for the pH dependent solubility is displayed in fig. 2.9 (A, B & C). The maximum solubility of glyburide in triazine full generation dendrimers was observed at pH 9.2, followed by pH 6 and pH 4.

Thus, it is anticipated that the enhancement of the solubility is because of the attachments found in between of the surface hydroxyl groups of the dendritic molecule and the sulfonyl groups of glyburide. The reason behind the low solubility at low pH was that in weakly acidic

phase the molecule of glyburide was not completely ionized and thus it cannot liberally attach as electrostatically form with dendritic molecules.

Effect of dendrimer generations on solubility of glyburide

The effect of dendritic generations on glyburide solubility was investigated. The results of the study are displayed in fig. 2.9 (A, B & C). It was observed that the solubility of glyburide was maximum in higher generation G3 dendrimer than the lower generations G2 and G1 dendrimers. The solubility depends on the surface area of dendritic molecules and hydroxyl groups of triazine dendrimers which is clearly observed in fig.3 and table 1. G3 has possess more surface area as well as more number of hydroxyl active functional groups at its terminal end so that the molecule of glyburide can easily interact and absorb with G3 dendrimer then the G2 and G1.

Solubility profiling of glyburide drug

The results of the solubilization of poorly water soluble glyburide in G1, G2 and G3 dendrimers are as follow. At pH 4, the solubility of glyburide was 0.67 mg/ml, 1.26 mg/ml, and 2.65 mg/ml in 6 mmol of G1, G2 and G3 dendrimers respectively. However, the solubility at pH 6 was increased up to 1.28 mg/ml., 3.38 mg/ml and 5.74 mg/ml in 6 mmol of G1, G2 and G3 dendrimers respectively. Moreover, the solubility at pH 9.2 was increased up to 5.62 mg/ml., 6.66 mg/ml and 8.29 mg/ml 6 mmol of G1, G2 and G3 dendrimers respectively. It was also observed that the solubility of the glyburide was found maximum in G3 dendrimer at pH 9.2.

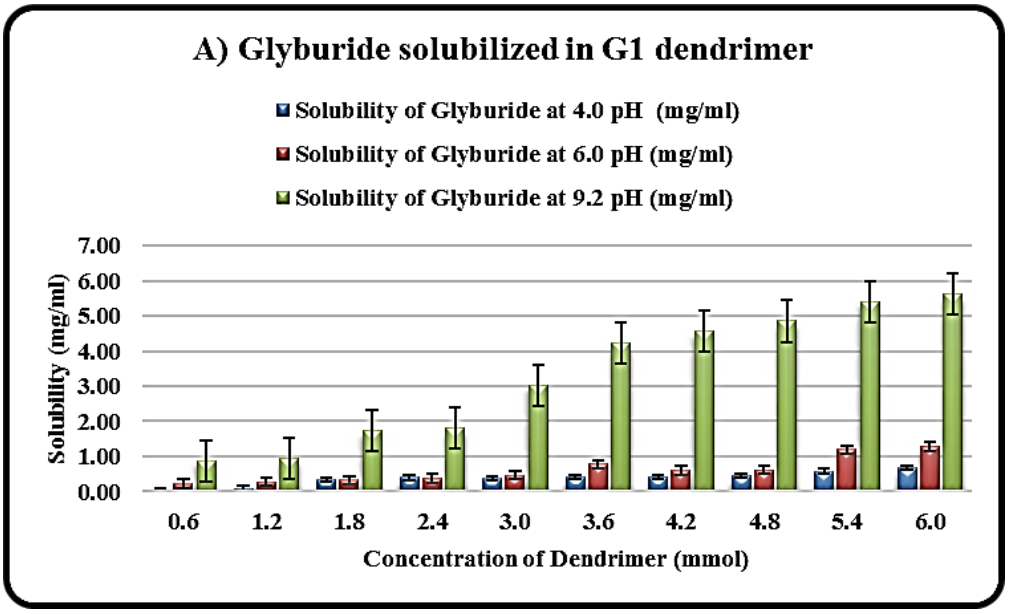


Fig. 2.9 (A): Effect of pH and generation of dendrimer on solubility of glyburide in G1 dendrimer.

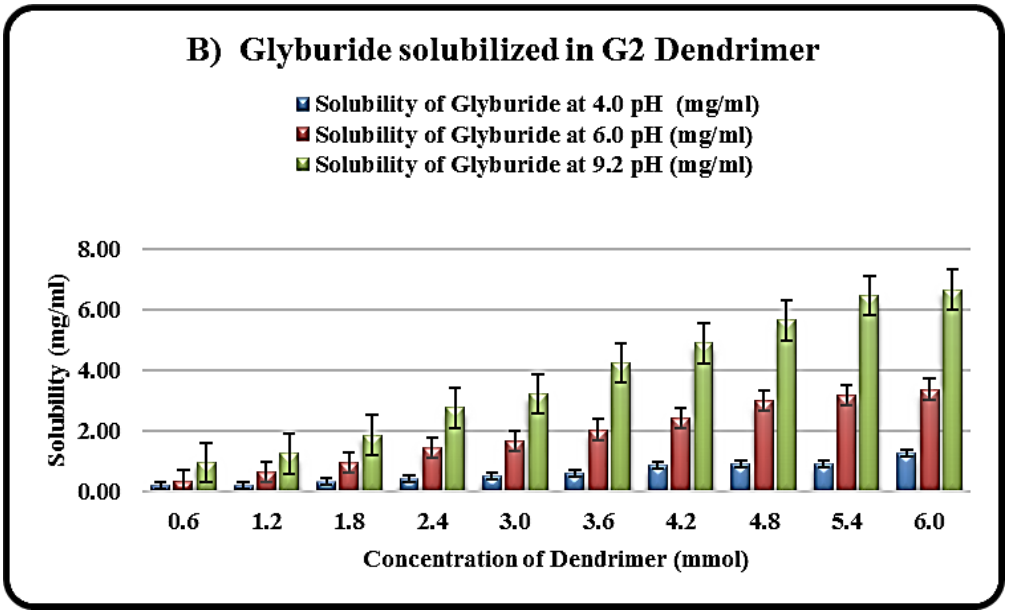


Fig. 2.9 (B): Effect of pH and generation of dendrimer on solubility of glyburide in G2 dendrimer.

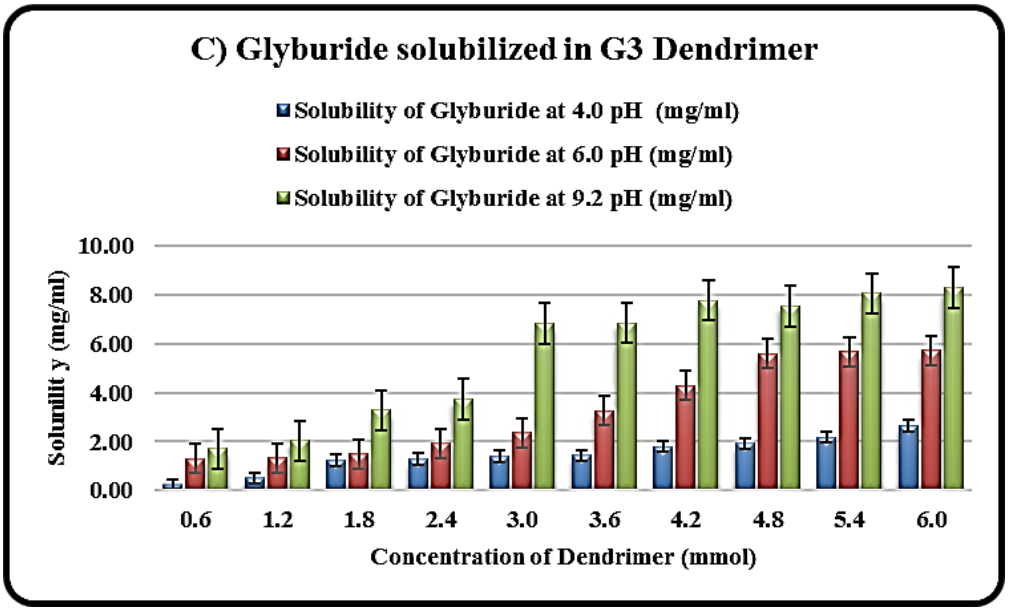


Fig. 2.9 (C): Effect of pH and generation of dendrimer on solubility of glyburide in G3 dendrimer.

Conclusion

Many drugs that are important to human health are hydrophobic in nature. Their hydrophobicity limits bioavailability and reduced their overall potential in terms of drug solubility. Glyburide is one such important drug (antidiabetic) which is hydrophobic in nature and there have been many attempts to enhance its solubility. One of the effective method for enhancement the solubility of hydrophobic drugs is the complex formation with different class of dendrimers. In the present study we synthesized and used triazine class of dendrimers as solubility enhancer for glyburide. They were characterized by FTIR and NMR spectroscopy. The solubility enhancement of poorly water soluble glyburide was carried out in G1 to G3 full generation dendrimers, it was observed that the solubility of glyburide was enhanced with G3 dendrimer showed maximum solubility at pH 9.2 The above observations are the evidence of interactions between the hydroxyl groups and carbonyl group of glyburide as shown in FTIR

spectra. Furthermore, NMR spectral analysis proves the increase in number of hydroxyl groups in outer territory of dendrimer which could explain the solubility enhancement of the drug.

Materials and methods

Materials

Dichloromethane (DCM), diethanolamine (DEA) and triazine trichloride (cyanuric chloride) were purchased from Avra synthesis Pvt. Ltd., (Hyderabad, India). Homopiperazine and glyburide were purchased from benzchem enterprise (Vadodara, Gujarat, India). Acetone, Methanol, Sodium hydroxide were purchased from HiMedia (Mumbai, India). Phosphate buffer solution of different pH viz. 4.0, 6.0 and 9.2 were prepared as per the method established by Indian Pharmacopeia (1996). All the reagents and buffers were freshly prepared before onset of the experiment. Fourier Transform Infrared (FTIR) spectroscopy was performed using an FT-IR Spectrometer XPM instrument through Nujol oil scheme for liquid models. The NMR spectra of ^{1}H and ^{13}C were analyzed and verified at NMR 500 MHz with Avance NEO in which D_2O used as solvents for the characterization [38].

Methods

Synthesis of dendrimers

The proposed scheme for the synthesis of G3 dendrimer from 1,4-bis(4,6-dichloro-1,3,5-triazin-2-yl)-1,4-diazepane core is as under. The scheme follows the temperature controlled nucleophilic replacement of triazine trichloride and fussiness of triazine trichloride to aromatic amine to hydramine was used. For dendrimer synthesis homopiperazine was reacted with cyanuric chloride at low temperature 0-5 °C which gives 1,4-bis(4,6-dichloro-1,3,5-triazin-2-

yl)-1,4-diazepane as core. Furthermore, the reaction between core compound and diethanolamine was carried out, where diethanolamine was used as mutual reactant and solvent for preparing dendrimer generation 1 (G1). G1 dendrimer was again utilized and reacted with cyanuric chloride which gives dendrimer generation 1.5 (G1.5). Then all the steps were carried out repeatedly till dendrimer generation 3 (G3) was synthesized [25-27, 31].

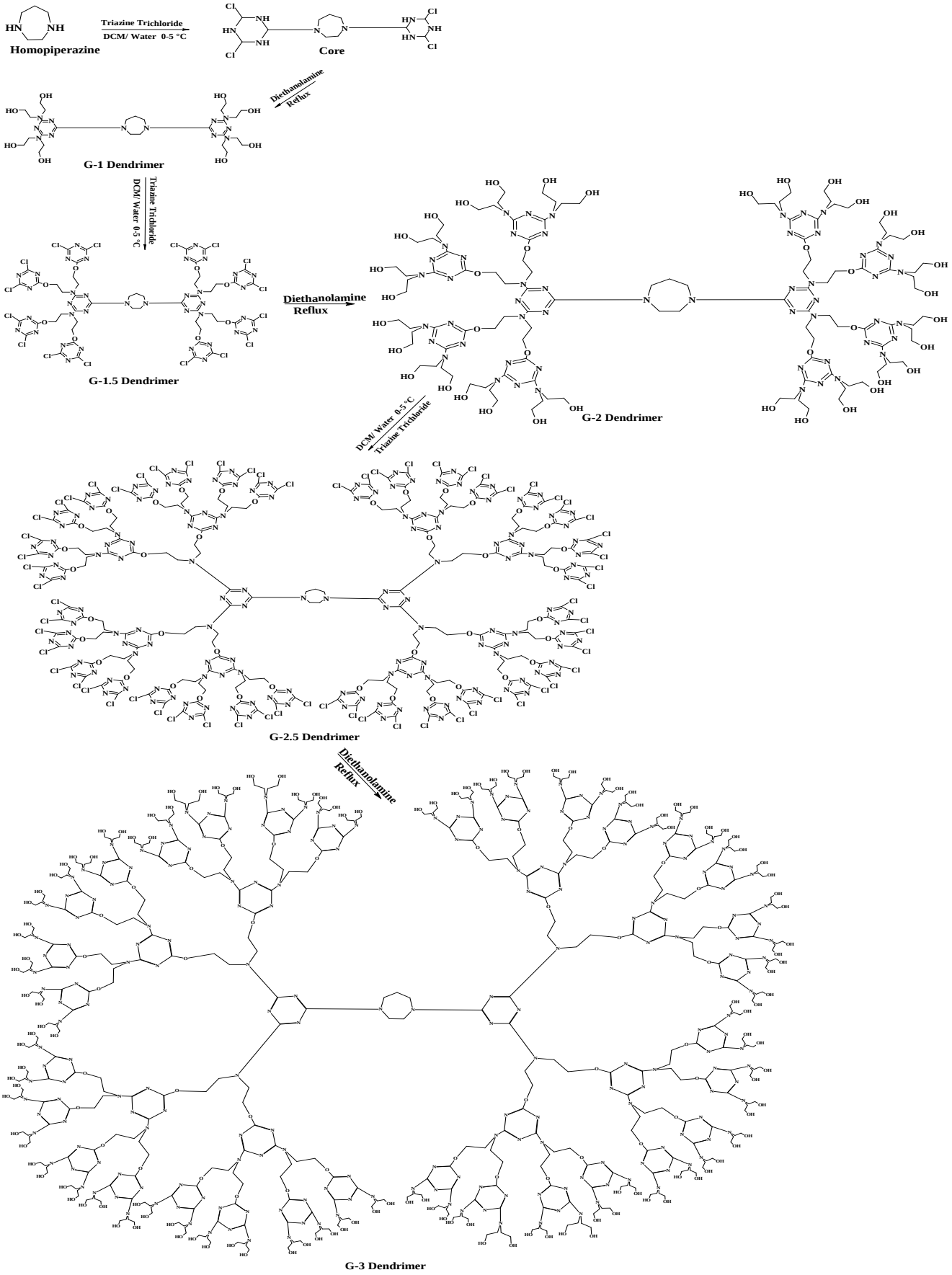


Fig. 3. Proposed synthesis scheme of triazine dendrimers

Phase solubility study

The solvency studies of glyburide in the presence of full generations dendrimers were performed using the method proposed by T. Higuchi and A. Connors (1965) [33,44]. In the process, excess amount of glyburide was added to glass canister and dissolve in dendrimer and drug-dendrimer complexes were prepared in phosphate buffer pH at 4.0, 6.0 and 9.2. The concentration taken of the solution ranging in between 0.6 to 6.0 mmol of solution of glyburide with full generation dendrimers. The above drug dendrimer solutions were shaken for 48 hours at 37 ºC and 120 rpm in an orbital shaking incubator. After incubation period, the solutions were centrifuged at 10000 rpm for 15 minutes to remove undissolved glyburide. The resulting supernatant solution was filtered using Whattman Filter Paper #41 and 10 ml filtrate of the drug-dendrimer solutions was further diluted in phosphate buffer. Then the solutions were vigorously stirred and absorbance were estimated at 228 nm in Shimadzu UV-1800 spectrophotometer [28,29].

Characterizations study

FTIR study

Fourier Transform Infrared (FTIR) analysis was performed in the range of 250-4000 cm^{-1} using a FT-IR Spectrometer XPM instrument using Nujol oil scheme for liquid full generation dendrimers. The samples were prepared in mull by taking 1 mg of sample with addition of Nujol oil and grind it to make paste. For the solid glyburide drug sample, KBr pressed pellets technique was used for sample preparation. The samples were prepared by using small amount of glyburide drug mixed with 200 to 250 mg of KBr and were crushed into a transparent thin pellet which were ready to analyze in FTIR [39].

NMR study

For NMR studies, 5 mg of dendrimers were pipetted out using pasture pipette in NMR tube and mixed with 1ml of D_2O solvent. The ^{1}H NMR studies was performed at 500 MHz, whereas ^{13}C NMR at 125 MHz using Bruker Avence NEO [40].

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Declaration of interest

The authors declare that they have no conflict of interest.

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