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

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Abstract

This work aims to enhance the solubility of poorly water-soluble drug glyburide by using the synthesised dendrimer. The potential of dendritic macromolecules generation one, generation two and generation three (HG1.0, HG2.0 and HG3.0) as solubility enhancers of drugs were investigated by applying the Higuchi and Connors method. The effect of pH, concentration and generation of synthesised dendrimers on the solubility of Glyburide was studied. FT-IR, ^{1}H NMR & Mass spectroscopy to explore and evaluate the structure of synthesised dendrimers. The results of the experiment suggested that Glyburide's solubility was improved with increasing dendrimer concentration and dendrimer generation.

Keywords: Triazine dendrimer, Synthesis, Phase Solubility, Glyburide, Drug

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1.0 Introduction

Since most medications are not water soluble, pharmaceutical firms face a significant obstacle in the form of low bioavailability when it comes to oral administration. Disintegration is the rate limiting advancement throughout pharmaceutical retention due to insufficient water-solvent medicines. When a drug is taken orally, it first dissolve in the fluids of the stomach and intestines before it can make its way through the films of the gastrointestinal tract and reach its fundamental dispersion. As a result, there are segments of pharmaceutical research focused on increasing ineffective water-solvent drugs' solubility to boost their oral bioavailability [1, 2]. It is critical to note that the new pharmaceutical moiety's poor aqueous solubility presents a barrier to progress in drug research. [3,4].

Dendrimers are nano-scale, three-dimensional, monodisperse macromolecules with distinct properties that distinguish them from conventional polymers [5-7] and these specific properties include nano-scale monodispersity, amplifiable and functional groups and measurements that mimic biomolecules. Thus, synthesised dendrimers. are often practised in assort biological usances, such as drug transmittal, medicine solubilisation, MRI differentiation operant, and plenty others [8-11]. Dendrimers have been the focus of a lot of research in drug administration because of their suitability as a vehicle for the delivery of medicines. [12, 13]. For this study, we used the divergent approach to synthesise these triazine-based dendrimers starting from Hexahydro-1,4-diazepine as the core component of a dendritic architecture. FT-IR, ^{1}H NMR, and mass spectroscopy were implemented to characterise these synthesised dendrimers, which originated from core and went up to generation three [14-19].

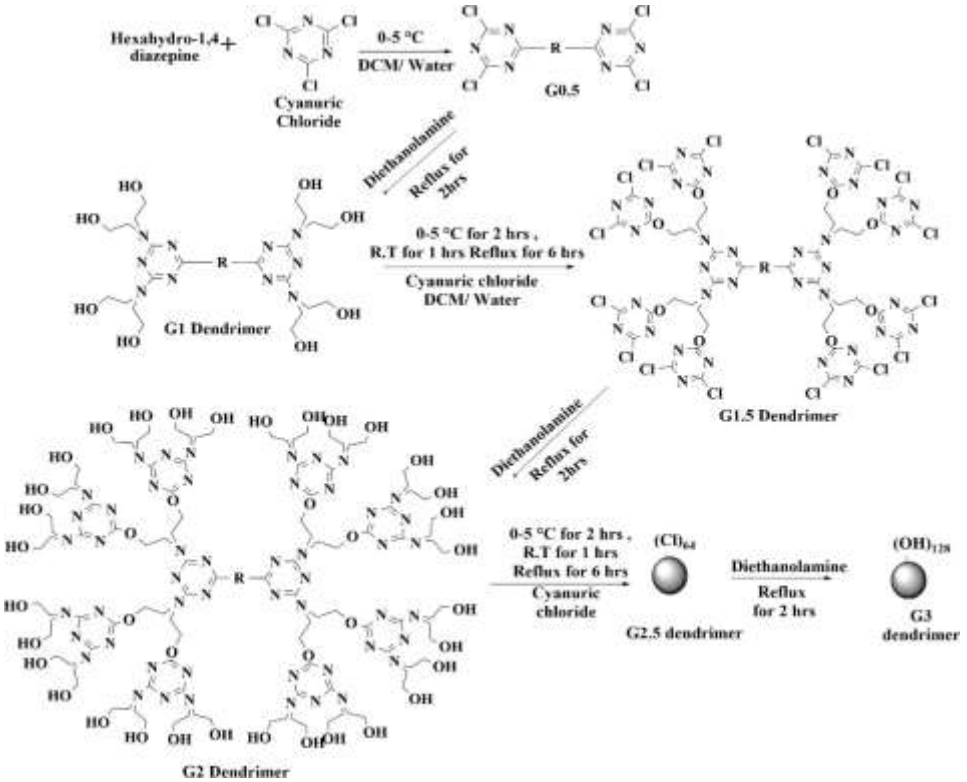
An investigation into ways to study the solubility of Glyburide (GLB) [20-22] was carried out using dendrimer generations ranging from HG1.0 to HG3.0. This study included the pH, generations and concentration of dendrimers [23, 24]. In addition, FT-IR spectroscopy was used to probe solubility formulations further.

2.0 Material and Methods

2.1 Materials

Diethanolamine (DEA), Triaizne trichloride (Cyanuric chloride), Methylene dichloride/Dichloro-methane (DCM), Homo-piperazine (Hexahydro-1,4 diazepine), Acetone, and Sodium Hydroxide.

2.2 Reaction Scheme



Reaction Scheme l. Synthesis of hydroxy-terminated dendrimers building block

2.3 Synthesis of Dendrimer

The proposed scheme for synthesising HG3.0 dendrimer from Hexahydro-1,4 diazepine is as under. As shown in Reaction Scheme 1, the nucleophilic substitution of triazine trichloride occurs beneath a temperature-controlled surround.

1,4-bis(4,6-dichloro-1,3,5-triazine-2-yl)-1,4-diazepine represented as a core was synthesised by reacting homo-piperazine and cyanuric chloride at low temperatures (0-5°C) considered as the initiated step of dendrimer synthesis. Furthermore, the reaction betwixt diethanolamine and the core compound was carried out, in which diethanolamine was adopted as both solvent & reactant in the syntheses of generation one dendrimer (HG1.0). The generation 1.0 (HG 1.0) dendrimer that had been earlier synthesised underwent a reaction in the presence of cyanuric chloride, forming the generation 1.5 (HG 1.5) dendrimer. The process was then continued until dendrimers of generation three (HG3.0) were synthesised [25-31]. Yield: 83.52%

2.4 Phase Solubility

Excess Glyburide was added to screw-capped vessels holding varying quantities (0.6 mmol to 3 mmol) of dendrimer generations in buffers of 4.0, 6.0, and 9.2 pH to conduct a solubility investigation following the methodology established by Higuchi and Connors [32]. The vials were shaken in a brain-marie/water bath for 48 hours at 37 ˚C. Undissolved Glyburide was spun out of the vials. Then the concentration was perceived by quantifying the optical density of the Glyburide at its characteristic frequency of 254 nm on the Shimadzu UV-1800 spectrophotometer [32-37].

3.0 Result & Discussion

3.1. Characterisation of Dendrimer

Full-generation dendrimers with functional groups ended with hydroxyl have a consistency identical to that of dark honey. The full-generations of dendrimers (HG1.0, HG2.0, and HG3.0) were water-soluble, and the result is presented in Table 1.

Table 1 Physical properties of dendrimers.

Dendrimer Generations	Chemical Formulary	Physicality	Solvency in water	Speculative Surface Functional Groups (Numbers)
Core	$C_{11}H_{10}Cl_4N_8$	Solid white	Insoluble	Cl (4)
HG1.0	$C_{27}H_{50}N_{12}O_8$	Brown liquid	Soluble	OH (8)
HG1.5	$C_{51}H_{42}Cl_{16}N_{36}O_8$	Solid white	Insoluble	Cl (16)
HG2.0	$C_{115}H_{202}N_{52}O_{40}$	Brown liquid	Soluble	OH (32)
HG2.5	$C_{211}H_{170}Cl_{64}N_{148}O_{40}$	Solid white	Insoluble	Cl (64)
HG3.0	$C_{467}H_{810}N_{212}O_{168}$	Brown liquid	Soluble	OH (128)

The infrared spectrum flaunted the stretching frequency of O-H at 3457 cm^{-1}, 3448 cm^{-1}, and 3441cm^{-1} for HG1.0, HG2.0 and HG3.0 dendrimers, as depicted in (figure.1). Infrared spectrum showed stretching frequency of C-Cl at 771 $cm^{-1.}$,780 $cm^{-1.}$, and 827 $cm^{-1.}$ in half-generation dendrimers core, HG1.5 and HG2.5. O-H stretching was unexposed, which indicated that chlorine groups were present on the perimeter of these (core, Hg1.5 and Hg2.5) molecules and that the hydroxyl group was not extant. 1H NMR probes the progression of a chemical reaction. ^{1}H NMR spectrum indicates the presence of proton in the core demonstrated at 2.7780-2.9754 δ ppm. Two multiplets for methylene proton at 3.6114-3.6608 δ ppm and 3.9884-4.6028 δ ppm attached to nitrogen and oxygen, respectively, as shown in (figure.2) for HG3.0 dendrimer. The molecular weight of HG3.0 dendrimer was observed 12071 Dalton.

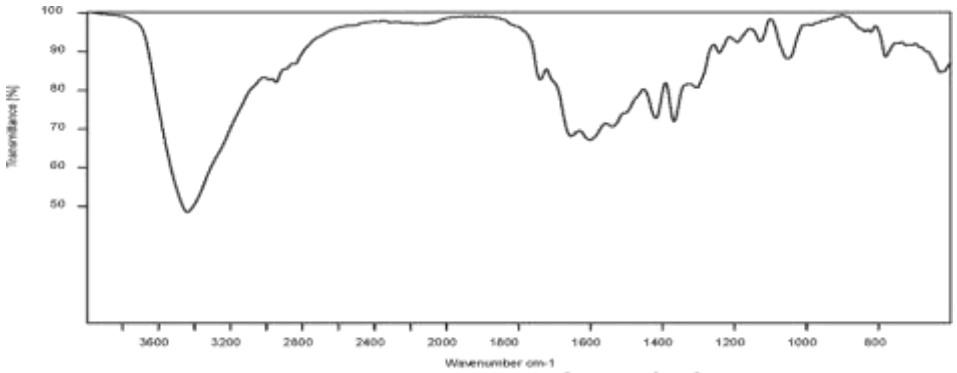


Figure 1. FT-IR spectrum of HG3.0 dendrimer

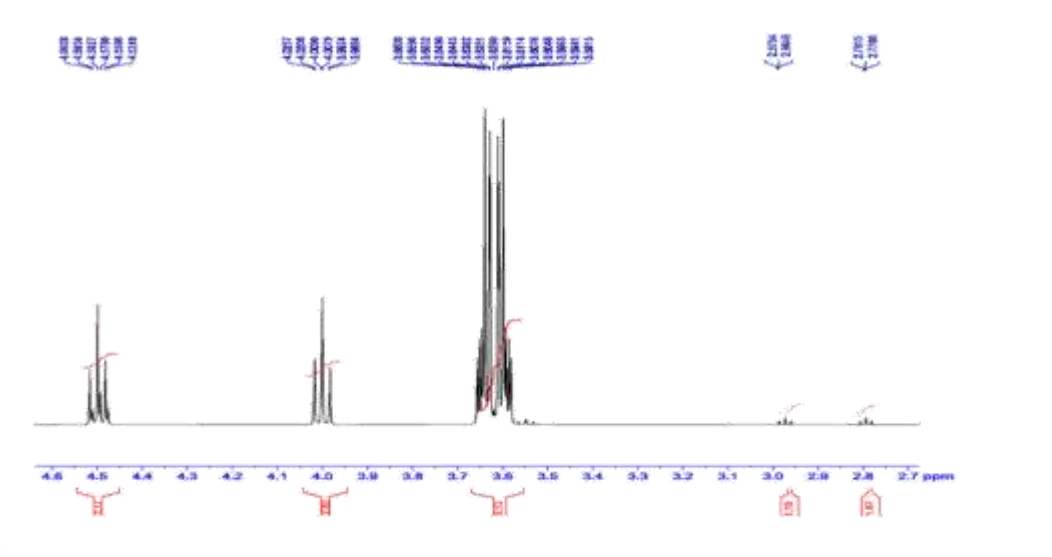


Figure 2. ^{1}H NMR spectrum of HG3.0 dendrimer

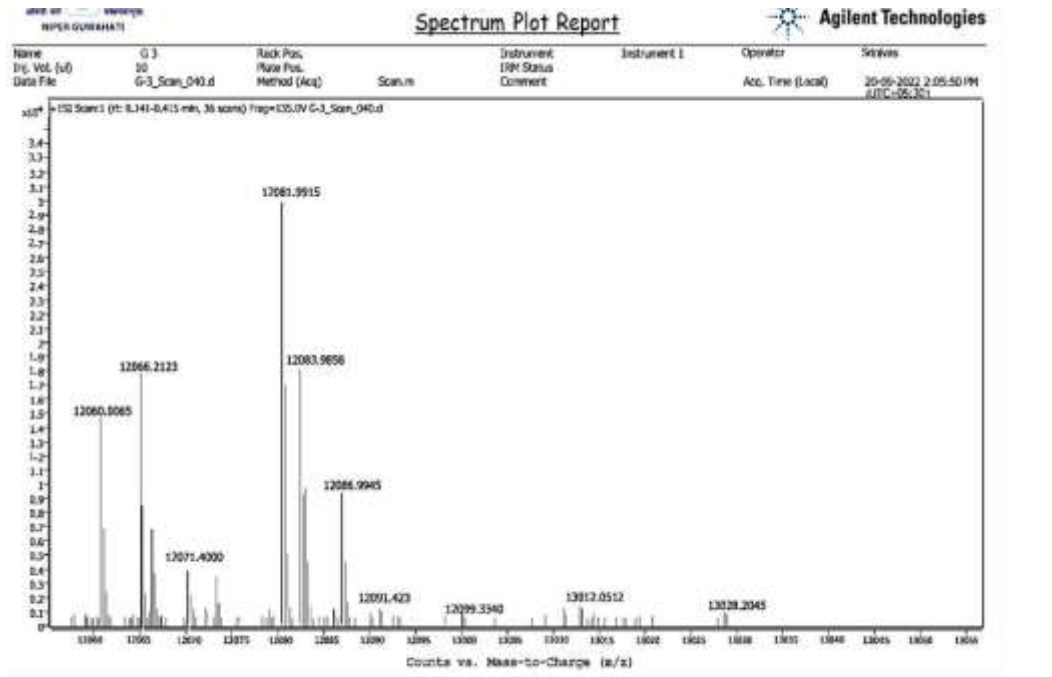


Figure 3. Mass spectra of HG3.0 dendrimer

3.2 Drug Solubilisation

The solubility of Glyburide by the full-generation dendrimers was determined using the dendrimer concentration (0.6 to 3 mmol) at pH 4.0, 6.0, and 9.2 using HG1.0, HG2.0, and HG3.0 [31, 32, 39,40]. The solubility results are displayed in (Tables 2, 3, and 4).

The results of the solubilisation of poorly water-soluble Glyburide in HG1.0, HG2.0, and HG3.0 are as follow. At pH 4.0, the solubility of glyburide was 0.36 mg/ml, 0.53 mg/ml and 1.03 mg/ml of HG1.0, HG2.0 and HG3.0 dendrimers, respectively. On the other hand, the solubility at pH 6.0 was improved to 0.47 mg/ml, 1.69 mg/ml, and 2.36 mg/ml of HG1.0, HG2.0 and HG3.0 dendrimers, respectively. Furthermore, the solubility at pH 9.2 was enhanced up to 3.03 mg/ml, 3.28 mg/ml, and 6.82 mg/ml of HG1.0, HG2.0 and HG3.0 dendrimers, respectively.

The solubility of API is in the range of 3.03 mg/ml to 6.82 mg/ml for generation 1 to 3 at pH 9.2. The results are displayed in (Table 4). The present solubility results suggest that the solubility of glyburide rose linearly with the rise in the concentrations of dendrimers, too [41-44].

Table 2 Effect of pH on aqueous solubilisation of Glyburide at pH 4.0

Solubility of Glyburide (mg/ml.) at 4.0 pH			
Dendrimer Concentration (mmol)	HG1.0 (mg/ml.)	HG2.0 (mg/ml.)	HG3.0 (mg/ml.)
0.6	0.03	0.21	0.02
1.2	0.09	0.22	0.36
1.8	0.03	0.32	0.63
2.4	0.39	0.41	0.73
3.0	0.36	0.53	1.03

Table 3 Effect of pH on aqueous solubilisation of Glyburide at pH 6.0

Solubility of Glyburide (mg/ml.) at 6.0 pH			
Dendrimer Concentration (mmol)	HG1.0 (mg/ml.)	HG2.0 (mg/ml.)	HG3.0 (mg/ml.)
0.6	0.22	0.35	1.30
1.2	0.28	0.65	1.33
1.8	0.32	0.95	1.49
2.4	0.37	1.45	1.93
3.0	0.47	1.69	2.36

Table 4 Effect of pH on aqueous solubilisation of Glyburide at pH 9.2

Solubility of Glyburide (mg/ml.) at 9.2 pH			
Dendrimer Concentration (mmol)	HG1.0 (mg/ml.)	HG2.0 (mg/ml.)	HG3.0 (mg/ml.)
0.6	0.87	0.96	1.71
1.2	0.95	1.26	2.03
1.8	1.72	1.87	3.29
2.4	1.80	2.78	3.73
3.0	3.03	3.28	6.82

3.3 Characterisation of Drug-containing Dendrimer

Glyburide-loaded dendrimer was additionally explored by infrared spectroscopy. The FT-IR spectrum of pure HG3.0 dendrimer (Figure 1) showed absorption bands for O-H stretching at 3441 cm^{-1} for hydroxyl groups; 1053 cm^{-1} for C-O stretching of ether linkages. FT-IR spectrum of Glyburide showed absorption bands showed in (Figure 4). FT-IR spectrum of Glyburide loaded with HG3.0 dendrimer showed an adsorption band at 3393 cm^{-1} for O-H stretching, at 2933 cm^{-1} for C-H stretching, at 1663 cm^{-1} for carbonyl stretching and at 1063 cm^{-1} for C-O stretching displayed (Figure 5). Thus, the overall characteristic bands for HG3.0 dendrimer and Glyburide were unchanged in the IR spectra of Glyburide loaded dendrimer. Since of this, it has been clearly understood that the dendrimer may have improved the solubility of Glyburide since it has a hydrophobic triazine ring in the inner portion that may convey hydrophobic interlinkage and the hydroxyl groups in the outer region that can induce hydrogen bonding.

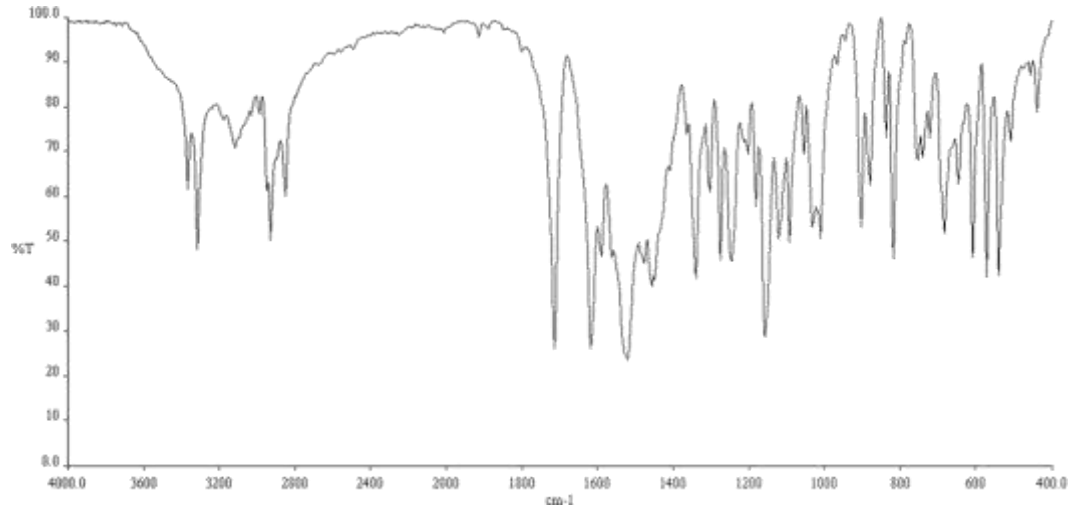


Figure. 4 FT-IR spectrum of Glyburide drug

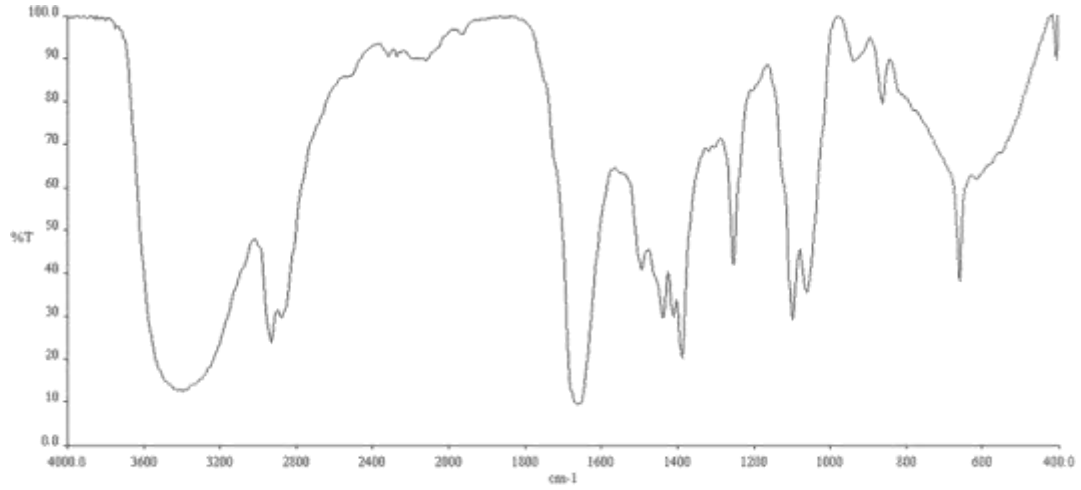


Figure 5 FT-IR spectrum of Glyburide loaded with HG3.0 dendrimer

4.0 Conclusion

Many drugs that are important to human health are hydrophobic in nature. Their hydrophobicity limits bioavailability and reduces their overall potential in drug solubility. Glyburide is one such important drug (antidiabetic) that is also hydrophobic and there have been many attempts to enhance its solubility. In the present study, we synthesised and used the triazine class of dendrimers as a solubility enhancer for Glyburide. They were characterised by FT-IR and NMR spectroscopy. The solubility enhancement of poorly water-soluble and was carried out in HG1.0 to HG3.0 full-generation dendrimers, it was observed that the solubility of Glyburide was enhanced with HG3.0 dendrimer showed maximum solubility at pH 9.2.

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Conflict of Interest.

There are no discrepancies to be disclosed.

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Ethics Statement

Nil

Data Availability

All relevant data used and/or analysed throughout this work may be obtained from the author.

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