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PERSPECTIVE

Hydroxyl-terminated triazine dendrimers mediated pH-dependent solubility enhancement of glipizide across dendritic generations: A comparative investigation

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Abstract

A huge challenge for the pharmaceutical industry is hydrophobic compounds, which affect aqueous solubility, an important measure of a medicine's efficacy. Several approaches have been used; dendrimers are particularly noteworthy because of their long-term viability, nanoscale size, large payload capacity, and adaptable end functional groups. The unique architecture of dendrimers allows for modified medication delivery and solubility profiles, making them a powerful tool for improving the solubility of hydrophobic drugs. This marks the beginning of a new era in pharmaceutical formulations. A new era in drug formulations has begun with this. As part of this study, we synthesized third-generation hydroxyl-terminated triazine-based dendrimers by meticulously reducing chlorine groups following Michael's addition. We intend to methodically examine the effects of various concentrations of these dendrimers on the solubility behavior of glipizide, a pharmaceutical agent with intrinsic hydrophobicity, across the first, second, and third generations (the full generation). A stimulating tale of solubility improvement emerged from our research. Glipizide's solubility was positively correlated with the concentration and generational progression of the dendrimers. The solubility of hydrophobic drugs in water can be dramatically altered by dendrimers based on hydroxyl-terminated triazine. This field of study benefits from adding new dendrimers with each generation.

Keywords: Triazine dendrimer, Synthesis, Phase solubility, Hydrophobic drug, glipizide.

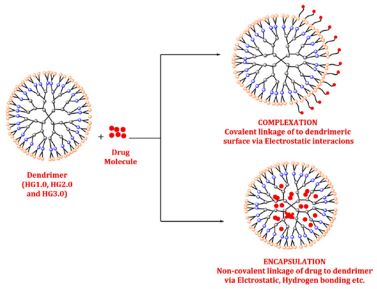

Figure 1: Graphical Abstract

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Introduction

The best method of medication administration is oral because it is feasible, easy, and most commonly used by patients. Considering their significance in clinical practice, it is surprising that most drugs are taken orally. A medicine's efficacy and safety in medical treatments hinge on how well it can traverse the intricate gastrointestinal tract and be absorbed in the intestines. The drug's pharmacological effectiveness depends on its rapid and substantial absorption into the bloodstream from the intestines. Contemporary pharmacological research and development centers on the intricate interplay between medication formulation, intestinal absorption, and release when it comes to oral drug delivery. Bioavailability is an essential physiological metric that measures how quickly and to what degree a medicinal substance enters systemic circulation after administration (Hussain A. S. *et al.*, 2019; Volpe D. A. *et al.* 2010).

The ideal oral bioavailability is achieved when a drug has perfect solubility and maximum permeability at the site of absorption, which is especially important for oral drug delivery [Dahan A. & Miller J. M. *et al.*, 2012, Martinez M. N. & Amidon G. L. *et al.*, 2002]. This viewpoint highlights an important path for further investigation, arguing that by thoroughly studying these vital aspects, we can improve

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medication bioavailability and bring in a new age of predictive pharmacokinetics, which will change the way pharmaceutical research and drug development are done.

Solubility is an essential factor in the process of drug dissolution and absorption in the small intestine, which has a significant impact on the progress of drug development (Shah V. P. & Amidon G. L. *et al.*, 2014, 6 Jagtap S. *et al.*, 2021). Molecular modifications, prodrugs, co-solvent solubilization, particle size reduction, and dendrimeric carriers are some of the areas that are being researched in order to address this complexity and advance advances in pharmaceutical research and development. More than 40% of new pharmaceutical compounds are experiencing difficulties with their solubility (Van der Merwe *et al.,* 2020; Youhanna S. *et al.*, 2021).

Belonging to the sulfonylurea family, glipizide is an oral antidiabetic medicine. It's an empirical-formula of $C_{21}H_{27}N_5O_4S$ (Figure 1) and It has been reported that it is rationally insolvable in aqua and slightly soluble in carbinol (Barzilai, N., *et al.*,1995).

The dendrimers apart from other synthetic polymers. Their unique structure, consisting of a core consisting of radiating branched repeating segments, allows them to easily encapsulate hydrophilic and hydrophobic compounds. Their surface displays an assortment of exposed terminal functionalities, including anionic, neutral, or cationic moieties (Lyu Z. *et al.*, 2019). Dendrimers have a globular shape on the nanometer scale and are remarkably homogeneous and monodisperse (Dubey S. K. *et al.*, 2020). Dendrimers are useful in biology and medicine because of their unusual characteristics, including high branching, water solubility, monodispersity, and internal cavities (Xie F. Li. *et al.*, 2022). Dendrimers have been used in various contexts, one of which is enhancing the water solubility of various pharmaceuticals (Hussain, A. S., *et al.*, 2019).

Materials and Methods

Materials

Following the procedures outlined in of the study, dendrimers containing HG1.0, HG2.0, and HG3.0 were synthesized. Following the rigorous guidelines outlined in the 1996 Indian Pharmacopoeia, the buffers, which comprise buffers with pH values of 4.0, 6.0, and 9.2, were prepared.

Methods

Analytical Techniques

The KBr pellets method for solid specimens and the Nujol oil mull method for liquid specimens were used to obtain FTIR spectra in the 250 to 4000 cm^{-1} region on an FTIR XPM spectrophotometer apparatus. Bruker Avance NEO spectrometers operating at 500 and 125 MHz were used to acquire ^{1}H-NMR and ^{13}C-NMR spectra in DMSO-d_6 and water-$d_2$as solvents, respectively. A UHPLC/Q-TOF-MS

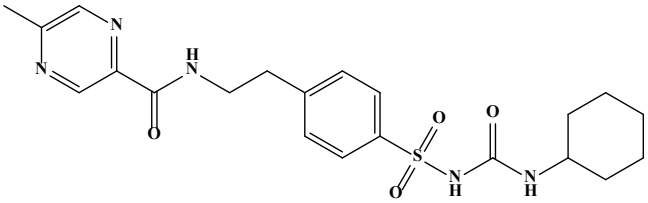


Figure 1: The glipizide chemical structure

apparatus with electrospray ionization was used to record mass spectrum data. UV Visible Spectrophotometer, Screw-capped lids, digital pH meter.

Phase Solubility Study

Drug solubility was examined using the methods described by Higuchi and Connors (Higuchi T. K. A. C. *et al.*, 1965). It entails storing excess medications in containers with screw-top lids and administering dendrimer generation dosages (ranging from 0.6 to 3 mmol) in buffers with pH values of 4.0, 6.0, and 9.2. In a bain-marie at 37°C, the vials were mixed for 48 hours. Dissolved medications were extracted from the vials by spinning them. The optical densities of the drugs were measured on a Shimadzu UV-1800 spectrophotometer, with the characteristic frequencies of(Glipizide at 280 nm), respectively, to determine the concentration (Lo S. T. *et al.*, 2010). This allowed for precise solubility determination across different pH levels and dendrimer generations.

- *Solubility Study of Glipizide in Different solubilizers*

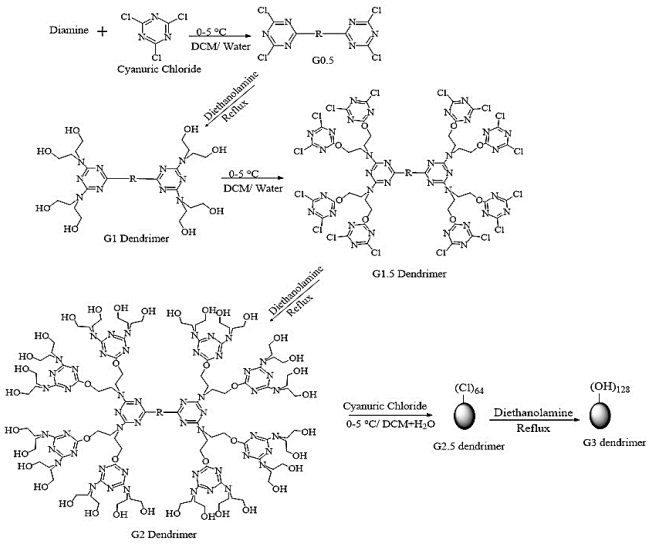
The solubility of glipizide rose dramatically from 0.010 to 0.022 mg/mL with the addition of polyethylene glycol 400 (PEG400). A distinct growing solubility trend was observed for PEG8000, beginning at 0.010 mg/mL and culminating at 0.156 mg/mL. From 0.0102 mg/mL to a little dip to 0.021 mg/mL, propylene glycol (PG) values displayed a dynamic solubility pattern with changes. These results provide insight on the distinct impacts of PEG400, PEG8000, and propylene Glycol, which vary the solubility characteristics of glipizide (Seedher N. *et al.*, 2009).

Reaction Scheme

Reaction Scheme is shown in Scheme 1.

Synthesis Of Hydroxyl-Terminated Triazine Dendrimers

After being immersed in dichloromethane (DCM) and agitated on a hot plate stirrer for two hours, cyanuric chloride (0.02 mmol) was poured. During stirring, the temperature was kept by 0 to 5°C followed by a mixture of homopiperazine (0.02 mmol) and sodium hydrate (0.04 mmol) was added to the assortment in a dropwise manner to produce 1,4-bis(4,6-dichloro-1,3,5-triazine-2-yl)-1,4-diazepine (HG0.5) as the core. To confiscate the processed dichloromethane and cyanuric chloride, HG0.5 was rinsed with MeOH and acetone. HG0.5 was mixed with diethanolamine and refluxed for two hours using a condenser equipped with a water-cooled jacket. After



Scheme 1: Synthesis of hydroxy-terminated dendrimers building block

completion of the reaction, the reaction mass was allowed to cool down to room temperature, and finally, the desirable product HG1.0 was filtered and washed with acetone and DCM. HG1.0 dendrimer was again utilized and reacted with triazine trichloride, giving dendrimer generation HG1.5. Then, all the steps were repeated until dendrimer generation three was synthesized (Gajjar D. G. *et al.*, 2015), (Elwahy A. H. *et al.*, 2023), (Washio I. *et al.*, 2007), (Crampton H. *et al.*, 2007).

Results

Hydroxyl-Terminated Triazine-Based

Dendrimers' Physical Characteristics

The physicochemical characteristics of hydroxyl-terminated triazine-based dendrimers are laid forth in Table 1 **(M A Malek *et al.*, 2023).** Dendrimers that were concluded with hydroxyl (HG1.0, HG2.0, and HG3.0) appeared as lightly brown liquids that could be dissolved in water, but dendrimers that concluded with chlorine (Core, HG1.5, and HG2.5) were solids of sparkling white color and totally impenetrable to water. Differentiating between solubility and material state reveals important details about how termination groups affect the characteristics of the produced dendrimers. One possible explanation for half-generation dendrimers' poor water solubility is the presence of hydrophobic triazine rings at their terminals. Conversely, hydroxyl groups tied to the ends of full-generation dendrimers could provide exquisite water-dissolvability **(Dilly S. J. *et al.*, 2006)**. DMSO-d_6 was the sole solvent for half-generation chlorine-terminated dendrimers.

Infrared Spectrometry

Dendrimers of the synthesized half-generations H0.5 (core), HG1.5, and HG2.5 terminated their tertiary structures with chlorine functional groups. In contrast, dendrimers of all three generations (HG-1.0, HG-2.0, and HG-3.0) that were designed for synthesis have hydroxyl functional groups included in their tertiary structures to accomplish termination. More precisely, the abundance of hydroxyl groups on the periphery of the full-generation was apparent in the stretch frequencies of HG1.0, HG2.0, and HG3.0 for hydroxyl groups (-OH) at 3457, 3448, and 3457 cm^{-1}, correspondingly. Since these compounds lack the C-Cl stretch, a hydroxyl group on the tertiary indicates that they represent full-generation dendrimers. The aliphatic functional group C-H and their stretch frequencies were detected in HG0.5, HG1.0, HG1.5, HG2.0, HG2.5, and HG3.0 dendrimers, and they are as follows: 2971, 2985, 2842, 2949, 2837, 2984 cm^{-1}, correspondingly (M A Malek. *et al.*, 2023).

While, the functional group C=N and their stretch frequencies were detected in HG0.5, HG1.0, HG1.5, HG2.0, HG2.5, and HG3.0 dendrimers, and they are as follows: 1717, 1670, 1659, 1567, 1663, 1654 cm^{-1}, correspondingly. The functional group C-O and their stretch frequencies were detected in HG1.0, HG1.5, HG2.0, HG2.5, and HG-3.0 dendrimers, and they are as follows: 1063, 1055, 1062, 1073, 1053 cm^{-1}, correspondingly. Accordingly, since either hydroxyl or ether links were present, it was noticed that the C-O frequency was not detected in the HG0.5 dendrimer (core). While the hydroxyl groups are covered by the chlorine tertiary of these half-generation dendritic molecules, their stretching frequencies observed for the C-Cl are 771 cm^{-1}, 780 cm^{-1}, and 827 cm^{-1}, respectively (M A Malek., *et al.*, 2023). Figure 2 showed HG2.0's infrared spectrum.

^{1}H-NMR Spectrometry

The HG-0.5 dendrimer's ^{1}H-NMR spectra revealed maximum signals in the multiplets at δ/ppm ranging from 2.3550

Table 1: Description of the hydroxyl-terminated triazine-based dendrimers' physical characteristics (M A Malek., et. al, 2023).

Dendrimer Generations	*Chemical Formula*	*Physicality*	*Solvency in water*	*Speculative Surface Functional Groups (Numbers)*
HG0.5 (Core)	$C_{11}H_{10}Cl_4N_8$	Solid-white	Insolvable	$Cl_{(4)}$
HG1.0	$C_{27}H_{50}N_{12}O_8$	Brown-liquid	Solvable	$OH_{(8)}$
HG1.5	$C_{51}H_{42}N_{36}Cl_{16}O_8$	Solid-white	Insolvable	$Cl_{(16)}$
HG2.0	$C_{115}H_{202}N_{52}O_{40}$	Brown-liquid	Solvable	$OH_{(32)}$
HG2.5	$C_{211}H_{170}Cl_{64}N_{148}O_{40}$	Solid-white	Insolvable	$Cl_{(64)}$
HG3.0	$C_{467}H_{810}N_{212O16}8$	Brown-liquid	Solvable	$OH_{(128)}$

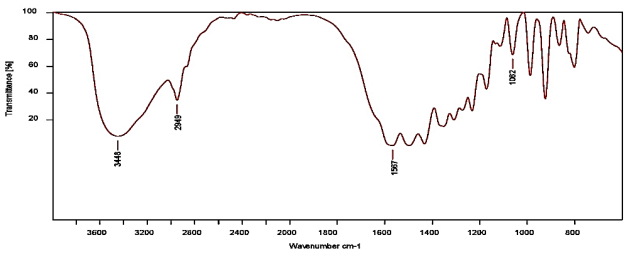


Figure 2: FTIR of dendrimer-HG2.0

to 2.4127 and in the multiplets at δ /ppm ranging from 2.7028 to 2.8115 band that matched the methylene groups of homopiperazine (core). The ^{1}H-NMR spectra for the HG-1.0 display the multiplets at δ/ppm 2.1108-2.1588 and 2.8558-2.8953 show homopiperazine core in it and δ/ppm 3.5942-3.7007 fields, triplets at δ/ppm 3.9818-4.0529 and 4.4938-4.5566 fields these values as of the two methyl protons attach with the hydroxyl groups of diethanolamine and both of these protons have diverse atmospheres. The HG-1.5 dendrimer's ^{1}H-NMR spectra signify multiplets at δ/ppm 2.1106-2.2170 and a triplet at δ/ppm 2.7104-2.8117, suggesting the presence of a proton-containing homopiperazine core. Downfield diethanolamine bonds are two triplets at δ/ppm, 3.9706-4.0154, and 4.4708-4.5644 (M A Malek., *et al*., 2023).

As for the HG2.0 dendrimer as shown in (Figure 3), the spectrum of ^{1}H-NMR displays the multiplets at 2.1524-2.2008 δ/ppm, 2.8570-2.9012 **δ**/ppm, as of methylene protons of homopiperazine. As triplets at δ/ppm 3.9647-4.0678 and 4.4453 to 4.5680 δ/ppm fields for methyl groups of diethanolamine bonds as four methyl groups of inner and outer linkages of diamines diamines which were detected as a diversified environment. As for the HG2.5 dendrimer, the spectrum of ^{1}H-NMR displays the multiplets at 2.2071 to 2.2325 δ/ppm, 2.8244 to 2.9012 δ/ppm, as of methylene protons of homopiperazine. As triplets at δ/ppm 3.9806 to 4.0207 and 4.5323 to 4.5809 δ/ppm fields for methyl groups of diethanolamine bonds as four methyl groups of inner and outer linkages of diamines which were detected as a diversified environment. As for the HG3.0 dendrimer, ^{1}H-NMR displays as the triplets at δ/ppm 2.7780-2.9754 show homopiperazine core and 3.5815-3.660 fields. As triplets at δ/ppm 3.9884 to 4.0257 and 4.5249 to 4.6028 fields for methyl groups of diethanolamine bonds as four methyl groups of inner and outer linkages of diamines observed as diverse atmosphere (M A Malek. *et al*., 2023).

ESI-Mass Spectroscopy

All of the synthesized dendrimer generations were All of the synthesized dendrimer generations were additionally characterized through ESI-Mass spectrometry. There is substantial concordance when comparing the estimated molecular weights with the resulting molecular ion spectra peaks. In the case of HG3.0 dendrimer, the molecular ion

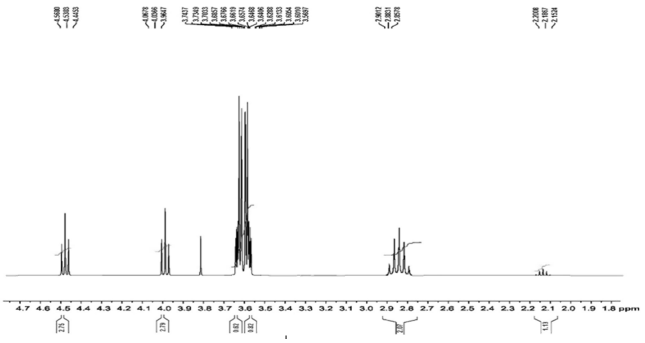


Figure 3: ^{1}H-NMR of dendrimer-HG2.0

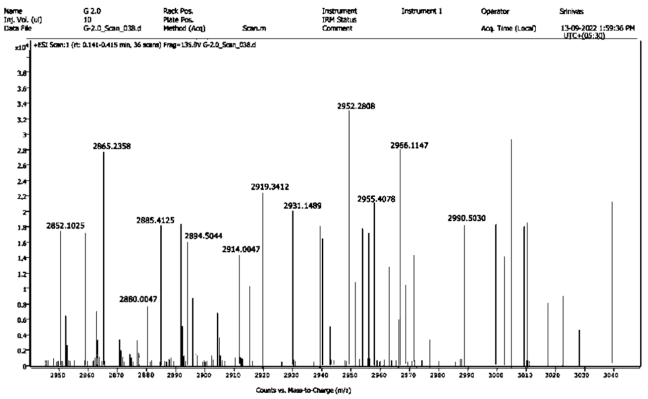


Figure 4: ESI-Mass Spectrum of dendrimer-HG2.0

peak was found to be 12071 daltons (M A Malek *et al*., 2023), while the estimated molecular weight was 12070 dalton; in the case of HG2.0 dendrimer the molecular ion peak was found to be 2952 dalton, while the calculated molecular weight was 2950 dalton as seen in (Figure 4). The molecular ion peaks were measured at 672 daltons, slightly heavier than the expected molecular weight of 670 daltons for the HG1.0 dendrimer.

Drug-solubilization in Full-generation

Dendrimers

The research conducted by (Seedher N. et al., 2009) showed that the purposeful inclusion of several solubility enhancers considerably enhanced the water solubility of glipizide. The solubility was much enhanced, rising from 0.010 to 0.022 mg/mL, when polyethylene glycol 400 (PEG400) was used. Also, the solubility level reached 0.156 mg/mL, which is much better when the concentration of PEG8000 is increased. It should be noted that the solubility was favorably impacted over the examined range by the addition of propylene glycol.

The following are the outcomes of the solubilization experiments applied to glipizide, a poorly water-soluble compound, using hydroxyl-terminated triazine-based dendrimers designated as HG1.0, HG2.0, and HG3.0. Glipizide was found to be soluble in HG1.0, HG2.0, and HG3.0 dendrimers at concentrations of 0.93, 1.81, and 2.20 mg/mL, respectively, when tested at a pH of 4.0. Particularly,

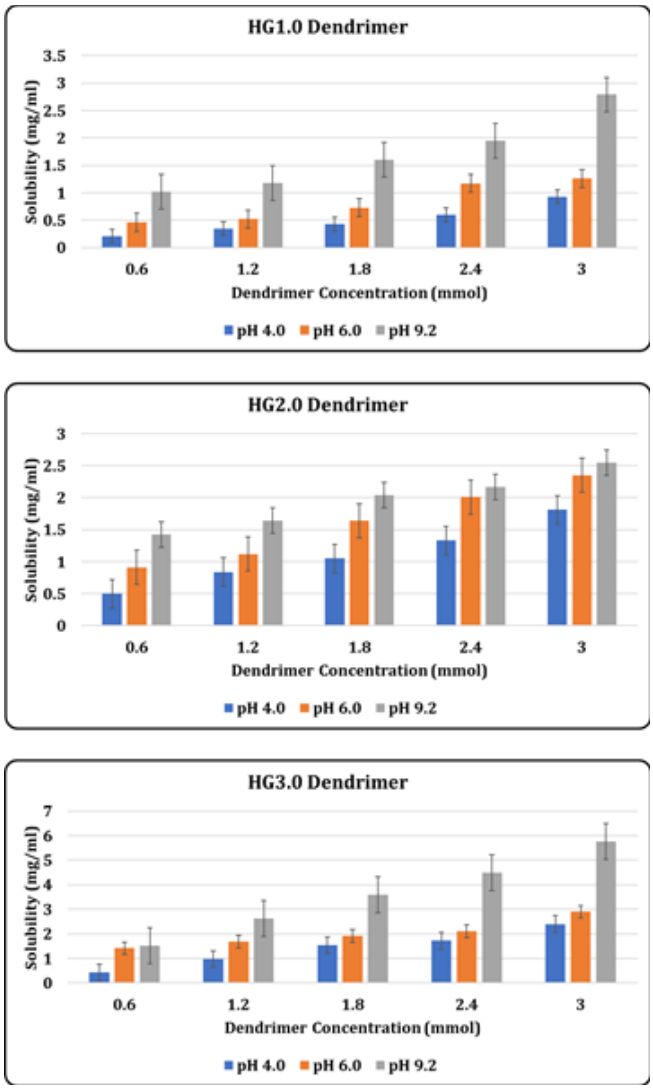


Figure 5: Effect of the pH on (HG1.0, HG2.0 and HG3.0) of triazine-based hydroxyl-terminated dendrimers and pH on aqueous solubilization of glipizide

at pH 6.0, dendrimers of HG1.0, HG2.0, and HG3.0 showed an increase in solubility, with values reaching 1.26, 2.35, and 2.90 mg/mL, respectively. Further, dendrimers from HG1.0, HG2.0, and HG3.0 showed increased solubility at pH 9.2, with values of 2.79, 2.55, and 5.76 mg/mL, respectively. The effectiveness of these dendritic carriers in improving glipizide's solubility profile is demonstrated by the pH-dependent solubility enhancements that they achieve. Findings are shown in Figure 5.

Characterisation of Drug-containing Dendrimer

Characterisation of Drug-containing Dendrimer is depicted in Figures 4 and 5.

Discussion

Figure 6, which presents the glipizide FTIR spectral analysis results, shows the drug's vibrational spectrum and the bands corresponding to its intrinsic molecular vibrations. Glipizide

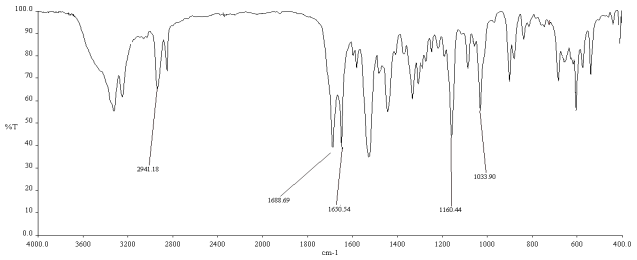


Figure 6: Pure glipizide infrared spectrum

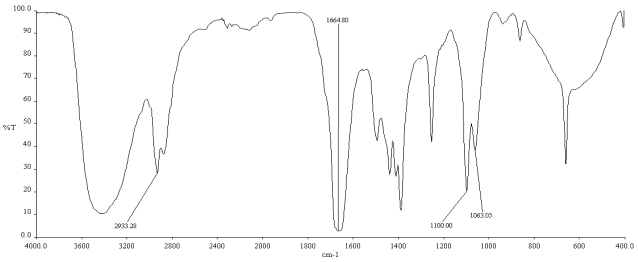


Figure 7: Encased glipizide infrared spectrum within HG3.0 dendrimer

contains aliphatic hydrocarbon components, as shown by C-H stretching vibrations, which may be detected via a resonance at 2941 cm^{-1}. The spectrum signature confirms the existence of amide functional groups vital to glipizide's structure at 1688 cm^{-1}, which is indicative of C=O stretching vibrations. In addition, the presence of a band at 1160 cm^{-1} suggests the presence of C-N stretching vibrations, a unique vibrational mode caused by the amine functionalities of the molecule. According to the research, glipizide may have sulfonyl functions, namely S=O stretching vibrations, as shown by vibrational modes at 1650 and 1033 cm^{-1}.

Findings from an FTIR spectroscopic study of glipizide encapsulated in generation 3.0 (HG3.0) are shown in Figure 7. Glipizide is suggested to interact with the dendrimeric matrix via changes in vibrational band patterns. Peaking at 2933 cm^{-1}, which is caused by C-H stretching vibrations, indicates changes in the hydrocarbon structure after encapsulation. At the same time, changes in the C=O stretching vibrations of amide groups provide evidence of a possible complexation interpretationation, as shown by a band at 1100 and 1063 cm^{-1}, further indicating vibrations of strained C-N bonds and sulfonyl (S=O) bonds, respectively. The alterations in the spectrum point to substantial interactions among glipizide and the HG3.0 dendrimer, offering spectral evidence that lends credence to the notion of a strong binding relationship. Our fundamental knowledge for creating dendrimer-based drug delivery systems is enhanced by gaining insight into these spectral fluctuations, which in turn help us comprehend the molecular dynamics of the Glipizide-dendrimer complexation process.

A novel method for increasing the hydrophobic drug solubility of glipizide, has been designed utilizing

the HG1.0-HG3.0 family of full-generation dendrimers. The remarkable solubilization capabilities and intricate structure of dendrimers make them an attractive candidate. Dendrimers are able to dissolve due to their intricate structure, which includes an array of hydroxyl groups surrounding the molecule and hydrophobic triazine rings positioned in its center. A key tenet of this innovative approach is the possibility that lipophilic drug molecules can disperse more easily when water is hydrogen-bonded to the peripheral hydroxyl groups. The addition of hydrophobic cores makes dendrimers considerably more water-soluble through interactions that accelerate solubilization, even though dendrimers dissolve in water naturally adaptability (Rangel-Yagui C. O. *et al.*, 2005), (Patel R. M. *et al.*, 2014), (Bansal, K. K. *et al.*, 2010).

Conclusion

This study shows that glipizide, a hydrophobic pharmaceutical agent, can be made much more soluble by employing dendrimers based on hydroxyl-terminated triazine across three generations (HG1.0, HG2.0, and HG3.0). Specifically at a pH of 9.2, the study found that the third-generation dendrimer (HG3.0) had the greatest solubility of glipizide, demonstrating a clear positive correlation between dendrimer generation and glipizide's solubility. An innovative mechanism for increasing drug solubility through enhanced dispersion and hydrogen bonding with water molecules is made possible by the unique structural composition of these dendrimers, which feature a hydrophobic triazine core surrounded by hydrophilic hydroxyl terminations. This research lays the groundwork for future pharmaceutical formulations that aim to improve the bioavailability of hydrophobic drugs through dendrimeric carriers. It also highlights the critical role of dendrimer architecture and functional group modification in drug solubility enhancement.

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Access To Data

Any and all data utilized or analyzed in this work can be requested directly from the author.

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