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Synthesized nanostructured dendrimer as a solubility enhancer for poorly water-soluble Domperidone

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ABSTRACT

Domperidone (DOM), an antidopaminergic medication, is primarily used as an antiemetic to treat nausea and vomiting caused by a variety of etiologies. It is very insoluble in water and has a poor oral bioavailability of 13-17%. The objective of the current work is to increase domperidone aqueous solubility using nano-structured hydroxy-terminated dendrimers. Dendrimers are distinctive carriers for drug solubilization because of their many special characteristics in terms of size, shape, branching length, and surface functioning. Dendrimers have unique properties that make them potential carriers for many active medicinal compounds due to their structural adaptability. The potential of hydroxy-terminated dendrimers UG1.0, UG2.0, and UG3.0 as solubility enhancers for domperidone was investigated. The effect of concentration and generation of synthesized nano-structured dendritic macromolecules on the solubility of domperidone was studied. The formation of the complexes between domperidone drug molecules and dendrimers was characterized by the FT-IR spectra. The experimental results showed that the solubility of the domperidone was approximately proportional to dendrimer concentration and generation. The water solubility of domperidone has been increased as generation of the hydroxy-terminated dendrimer. Cytotoxicity assay using A-549 lung cancer cell lines and hemolysis results revealed that synthesized dendritic macromolecules are more biocompatible than commercially available polyamidoamine dendrimers (PAMAM).

Keywords: Antiemetic, Cytotoxicity, Dendrimer, Domperidone, Hemolysis, Phase solubility.

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INTRODUCTION

The oral bioavailability of formulations is significantly influenced by solubility, which is a crucial factor in drug liberation and, consequently, drug absorption [1]. Research and development for new medications should be more challenging due to the poor oral bioavailability caused by poor water solubility and low gastrointestinal absorption. The poor solubility of therapeutic candidates in drug discovery and development causes a variety of issues. A drug's rate of dissolution is greatly altered by its water solubility [2]. Oral solid dose forms are among the most often utilized formulation types and they have several merits over other formulations. The difficulty for a pharmaceutical scientist is that medication dissolution from an oral solid formulation (a critical element in drug absorption) is dependent on the drug's water solubility. Therefore, an active ingredient with poor aqueous solubility would display limited dissolution rate absorption and a medication with poor membrane permeability would show limited permeation rate absorption [3].

The oral route of medication absorption comprises the drug's formulation dissolving into the stomach and/or intestinal fluids, permeating through gastrointestinal cell membranes, and then going into systemic circulation [4]. Poorly water-soluble medicines are frequently administered at high doses to accomplish desired therapeutic plasma concentrations. Especially for medications with low therapeutic index, this poses hazards of inferior efficacy and safety due to the variability in exposure that is frequently seen for treatments of this type. In this sense, using smaller doses of medications with higher dissolution rates, improved absorption and enhanced bioavailability is preferable from a therapeutic perspective [5,6]. When formulating a drug to achieve bioavailability and therapeutic action at the target site, the solubility enhancement process for hydrophobic drugs is crucial. Due to their high hydrophobicity, medications that are poorly water-soluble have poor bioavailability and poor absorption of drugs when taken orally [7]. There are multiple tried-and-true methods for improving low aqueous solubility, including salt creation, solid dispersion, particle size reduction, nanosuspension, usage of surfactants, etc [8].

The model drug in this study is domperidone (DOM). Domperidone, an antidopaminergic medication, is used to treating gastroparesis, cytotoxic therapy, radiotherapy, nausea, and vomiting of several etiologies, including those related to cancer therapy and bromocriptine therapy for Parkinson. One potential explanation for its limited bioavailability is its poor water solubility. Due to substantial first-pass hepatic and intestinal metabolism, DMP is insoluble in water and has a limited bioavailability of just 13–17% of the oral dose [9]. The properties of a

drug's solubility have a significant impact on how well it can cross biological membranes. Extremely hydrophobic medicines frequently have issues with bioavailability because of irregular or insufficient absorption through the gastrointestinal system [10].

During the past two decades, numerous scientists have become interested in a novel polymeric nanoarchitecture for solubility enhancement. These substances, known as dendrimers, have been used with success to increase the solubility of hydrophobic drug molecules. It has been demonstrated that dendrimers with a hydrophobic core and a hydrophilic perimeter behave like micelles and have container qualities in solution [11-13]. The characteristics of dendrimers, such as their nano-size, spherical structures, extensive branching, uniformly composed, biocompatibility, increasing water solubility, precise molecular weights, hydrophilic ends groups, and accessible internal cavities, make them superior delivery systems [14,15]. Dendrimers are good prospects for drug delivery systems due to their controlled and adaptable size, interactions with cell membranes and different active drug moieties, and features of their interior structures and voids [16]. Investigations compared the potential of dendrimers to boost solubility, via micelles and cyclodextrins are available, and they lead to the conclusion that dendrimers may end up being more efficient than both of these approaches [17].

Improvements to domperidone solubility and bioavailability have been made in a number of ways, such as inclusion complexation using β-cyclodextrin [18] or methylated β-cyclodextrin [19] and solid dispersion method utilizing PEG 800, urea, and PVP K30 [20]. Ismail et al. examine how inclusion complexation might improve the solubility of domperidone using a combination of LR-CDs and a single LR-CD [9].

Previously, the synthesis and characterization of nanostructured dendritic macromolecules have been reported [21]. The present investigation explored the potential of nano-structured hydroxy-terminated dendrimers as an aqueous solubility enhancer for domperidone API. Domperidone API was subsequently added to the dendrimer generation of UG1, UG2, and UG3 at varied dendrimer concentrations and its solubility was assessed using a UV spectrophotometer. We examined domperidone API-loaded dendrimers by infrared spectroscopy (FT-IR). Dendritic macromolecule has been examined for cytotoxicity and hemolysis in order to determine their toxicity and biocompatibility.

MATERIALS AND METHOD

Materials

Domperidone was generously provided by Aagya Biotech Private Limited, Roorkee. Triazine trichloride, carbamide, sodium hydroxide, acetone, dichloromethane, methanol and distilled

water were used for the experiment. Absorbance was measured on a Shimadzu UV-1800 spectrophotometer.

Synthesis of dendrimer

The approach outlined below was used to construct a dendrimer with a carbamide core. Triazine trichloride (0.02 mmol) and carbamide (0.01 mmol) interacted at 0 to 5˚C to synthesize 1, 3-bis(4,6-dichloro-1,3,5-triazine-2-yl)urea, which was used as a building block in the nanostructured dendrimer synthesis. 1, 3-bis (4, 6-dichloro-1, 3, 5-triazine-2-yl) urea was completely purified by washing with acetone and methanol. Diethanolamine (0.04 mmol) and 1, 3-bis(4,6-dichloro-1,3,5-triazine-2-yl)urea (0.01 mmol) were incorporated to generate hydroxyl terminated generation 1 (UG1.0) dendrimer. The UG1.0 dendrimer was washed by dispersed in dichloromethane (DCM) and then washing it. Similar to the previous stage, the UG1.0 dendrimer (0.01 mmol) and triazine trichloride (0.08 mmol) were combined at 0 to 5˚C to create the chlorine terminated half generation UG1.5 dendrimer (UG1.5). According to the second stage, diethanolamine (0.16 mmol) and chlorine-terminated half-generation dendrimer (UG1.5) (0.01 mmol) were then combined to yield full-generation hydroxyl-ended dendrimer (UG2.0). The two previous procedures were repeated to yield dendrimers of half-generation UG2.5 and full-generation UG3.0. The developed core and all dendrimer generations were characterized using FT-IR, ^{1}H-NMR, ^{13}C-NMR and TEM [21].

Determination λ max of domperidone

The API's maximum absorption wavelength is referred to as the λ max. As part of early studies, λ max of domperidone was determined using a stock solution containing 100 µg/ml of the active ingredient, which was prepared by 10 mg of domperidone diluted up to 100 ml of methanol solvent. From these stock solutions, suitable aliquots were taken and diluted using the appropriate solvent to get dilutions of 3-15µg/ml, and the λ max of the solution concentration (3-15µg/ml) was estimated by scanning from 200 to 400 nm in UV Visible spectrophotometer [22].

Phase Solubility study

A solubility investigation was carried out by implementing the method of Higuchi and Connors. Excess domperidone was inserted into screw-capped vials containing dendrimer generations at a range of concentrations (0.6 mM to 3 mM). Vials were agitated for 48 hours at 37˚C in a shaking water bath. The vials were centrifuged to eliminate any remaining domperidone, and a Shimadzu UV-1800 spectrophotometer was used to estimate the drug's absorbance at a typical 287nm wavelength [23].

Hemolysis study

The hemolytic effects of raising the concentration of nanostructured dendrimer on red blood cell (RBC) suspension have been evaluated. Blood samples were accumulated and centrifuged at 1500 rpm for five minutes. The blood cells were centrifuged, the supernatant plasma was taken out, and the cells were then resuspended in 0.5 ml of phosphate buffer saline (PBS). They were then administered with a number of dosages of nanostructured dendrimer (0.01, 0.1, 1.0 10, 100, and 1000 µg/ml), which were then incubated for an hour. After the samples had been incubated, they were centrifuged. The supernatant was collected and diluted with equal amounts of phosphate buffer saline (PBS), and the absorbance at 540 nm was recorded. As the positive control, distilled water was used to optimize the inhibitory effect. The hemolytic effect of different dendrimer concentrations was calculated using the below equation [24].

% Hemolysis = (Absorbance of test/Absorbance of control) * 100

Cytotoxicity (%Cell Viability)

The Dulbecco's Modified Eagle Medium (DMEM) was used to cultivate human A549 non-small cell lung cancer cells at 37°C in a CO_2 incubator (5% CO_2) together with 10% fetal bovine serum (FBS) and 1% antibiotic-antimycotic solution. Trypsin was utilized for gathering cultured cells, which were then put in a 96-well plate at a density of 10,000 cells per well and incubated for 24 hours to evaluate cell viability. Multiple concentrations of hydroxy-terminated dendrimer (10, 100, and 1000 µg/ml) were administered to the cells after incubation for 24 hours. DMEM was added to the control wells. A medium that contains different dosages of hydroxy-terminated dendrimer was removed from each well after 24 hours of incubation and cells were then incubated with 0.5 mg/ml MTT for 4 hours at 37 °C. After the mixture had been incubated, MTT was removed, and DMSO (100 µl/well) was added to dissolve the formazan crystals. Using an ELISA plate reader to assess each well's absorbance at 550 nm, the equation below was used to calculate the percentage of cell viability [24].

% Cell Viability = (Mean Absorbance of test/Mean Absorbance of Vehicle control) *100.

RESULTS AND DISCUSSION

Preparation mechanism

In a prior study, the synthesis and characterization of the carbamide core-based hydroxy-terminated dendrimers UG1 $(OH)_8$, UG2$(OH)_{32}$, and UG3$(OH)_{128}$ have been reported. Half-generation dendrimers and core molecules were not water soluble; only full-generation dendrimers were. The full-generation dendrimers UG1 $(OH)_8$, UG2$(OH)_{32}$, and UG3$(OH)_{128}$ were employed for solubility enhancement of poorly water-soluble drugs.

UV Spectrum of Domperidone (λ_{max})

The appropriate dilutions were done to develop a 3 to 15µg/ml solution of domperidone from the stock solution. Using a UV spectrophotometer, the solution was checked for its maximum absorption wavelength between 200 nm to 400 nm. Domperidone's absorption maxima were discovered to be at 287 nm and this value was used in this work as the "λ max" value. UV Absorption spectra and overlay spectra of domperidone shown in figure 1 & figure 2.

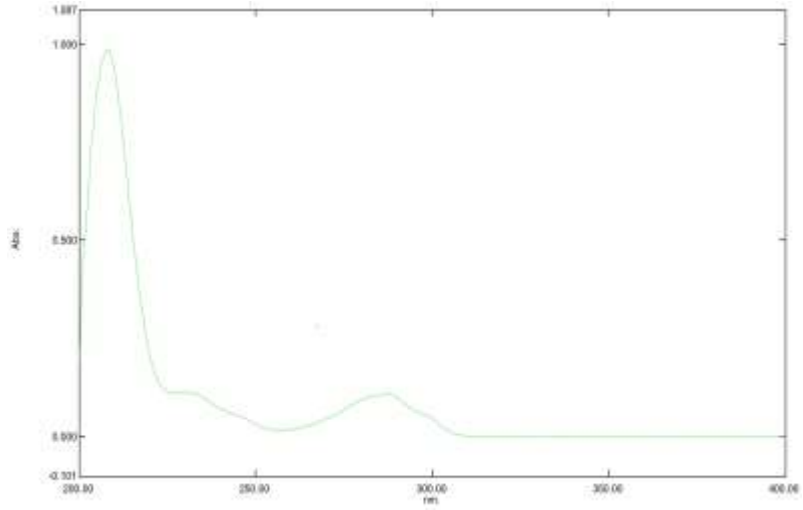

Figure 1: Absorption spectra of domperidone (λ max)

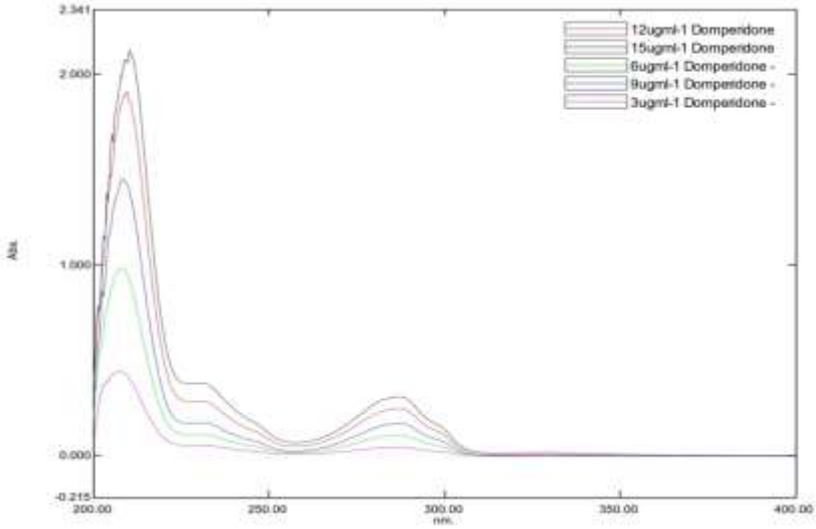

Figure 2: Overlay spectra of domperidone

Drug solubilization

Solubility enhancement of domperidone via hydroxy-terminated dendrimer generation (UG1.0, UG2.0 & UG3.0) was investigated using various concentrations (0.6mM to 3mM) of dendrimer generations. Solubility enhancement results of domperidone are illustrated in figure 3, figure 4 and figure 5. The blank solubility (water) of the domperidone when no dendrimer was present in the water was very low, which is 3.229 µg/ml. It has been observed that nanostructured dendrimer generation helps improve the aqueous solubility of the nearly insoluble medication

domperidone. It was also discovered that the water solubility of domperidone has increased proportionally with the increase in the concentration of all dendritic macromolecules (0.6mM to 3mM). Also, studies showed that domperidone solubility enhanced as the number of dendrimer generations raised (Figure 6). Domperidone was actually more soluble in higher generations of dendrimers than in lower ones (UG1.0 < UG2.0 < UG3.0). According to our research, domperidone's aqueous solubility has been rising up to 48.103µg/ml. Domperidone API's solubility continued to increase along with dendrimer surface area and terminal hydroxyl groups as the generation number increased. The generation three dendrimer (UG3.0) was demonstrated to have improved the solubility of domperidone up to 56.772 µg/ml at pH 1.2. For three weeks, the solubility stability of the domperidone-containing dendrimer was monitored, and results showing that it was stable. As dendritic macromolecules contain hydrophobic triazine rings in their interiors, they may impart hydrophobic interactions, whereas the hydroxyl groups (-OH) on their exteriors may impart hydrogen bonds. As a result, either hydrophilic contacts, hydrogen bonds, or both may be involved in the process. Our research proved that our nanostructured dendrimer performs better than cyclodextrin in improving the solubility of domperidone [9]. Overall it was found that the increase in domperidone solubility by nanostructured dendrimer depended on the concentration of dendrimers, generation of the dendritic macromolecule, pH of the solution, and the number of functional groups present on the dendrimer surface.

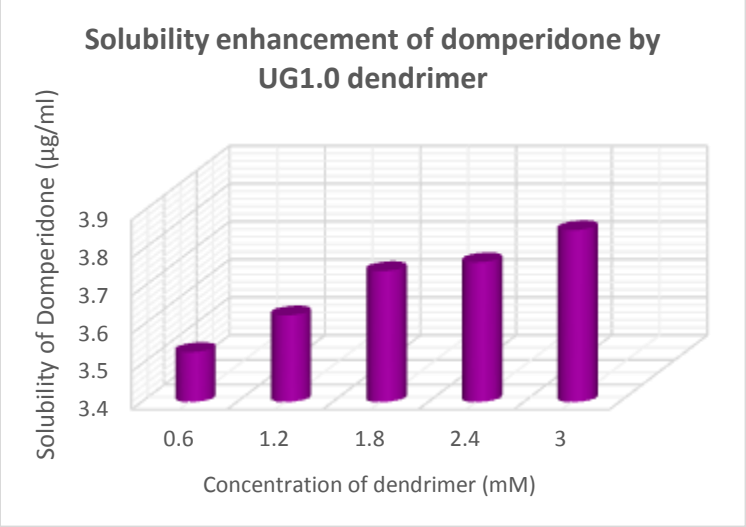

Figure 3: Solubility enhancement of domperidone by UG1.0 dendrimer

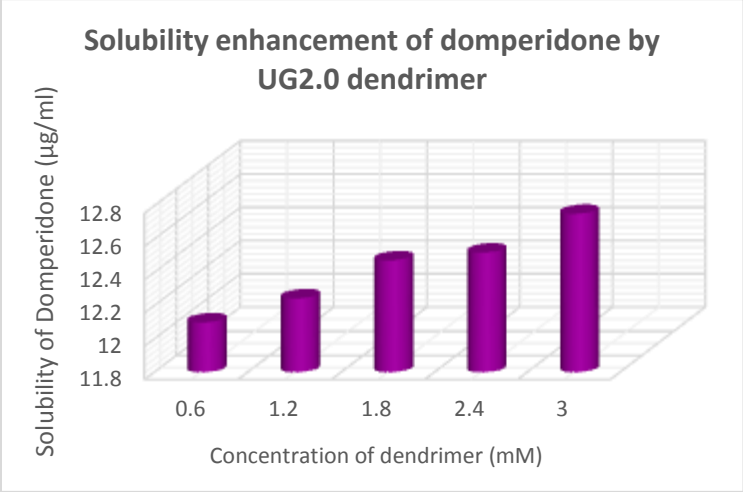

Figure 4: Solubility enhancement of domperidone by UG2.0 dendrimer

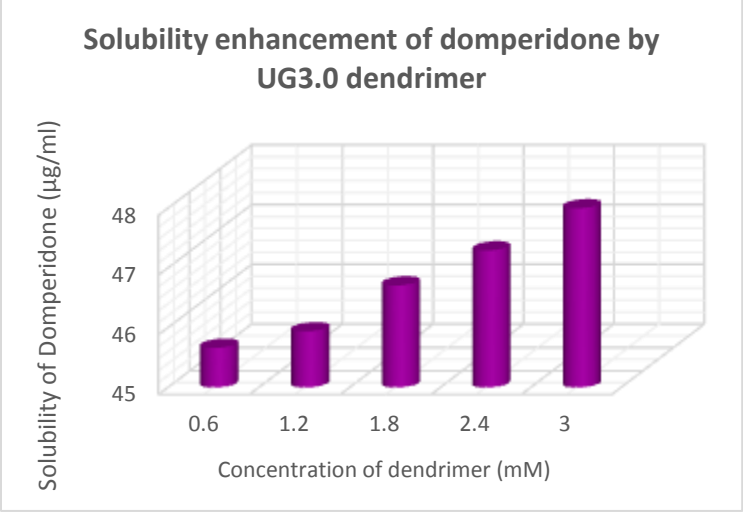

Figure 5: Solubility enhancement of domperidone by UG3.0 dendrimer

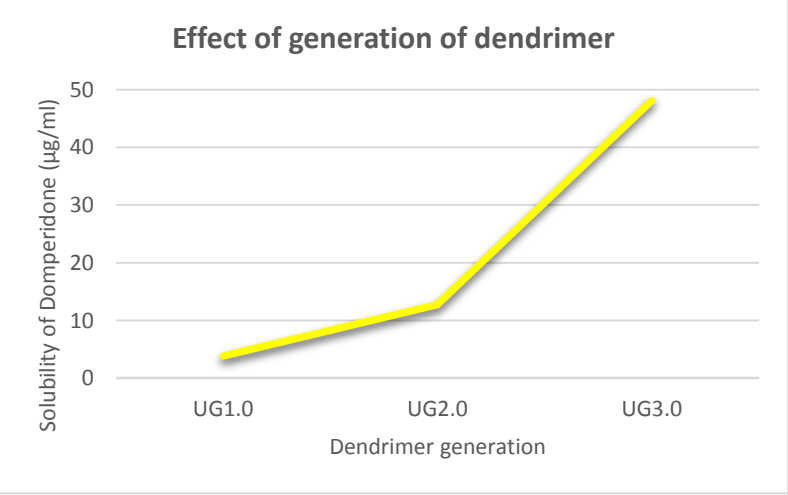

Figure 6: Effect of dendrimer generation

The successful outcome of nano-structured hydroxy-terminated dendrimers as drug delivery vehicle depends on their capacity to bind to the domperidone drug, nature of the terminal groups

(-OH) of the dendritic macromolecule and the electrostatic interaction between the dendrimer and the domperidone drug are also important factors. As a result, the domperidone-containing dendrimers have been analyzed using the FT-IR spectra. FT-IR spectrum of pure UG3 dendrimer showed absorption bands at 3312 cm^{-1} for O-H stretching for hydroxyl groups, at 1750cm^{-1} for C=O stretching of the core molecule and at 1056 $cm^{-1}$for C-O stretching showed in figure 7. FT-IR spectrum of pure domperidone showed absorption bands at 2937.83 cm^{-1} for N-H stretching, at 1693.99 cm^{-1} for C=O stretching, at 1148.47 cm^{-1} for C-N stretching and at 606.44 cm^{-1} for C-Cl stretching showed in figure 8. The presence of almost all characteristics peaks of drug and dendrimer in domperidone containing dendrimer showed absorption bands at 3379.99 cm^{-1} for O-H stretching, at 2939.59 cm^{-1} for N-H stretching, at 1630.67 cm^{-1} for C=O stretching, at 1066.98 cm^{-1} C-O stretching and 619.66 cm^{-1} for C-Cl stretching showed in figure 9. So, overall characteristic bands for both UG3.0 dendrimer and domperidone remained unchanged in FT-IR spectrum of the domperidone-containing dendrimer. As a result, it becomes obvious that nanostructured hydroxy-terminated dendrimers may boost domperidone solubility through hydrogen bonds, or hydrophilic interactions, or a combination of the two.

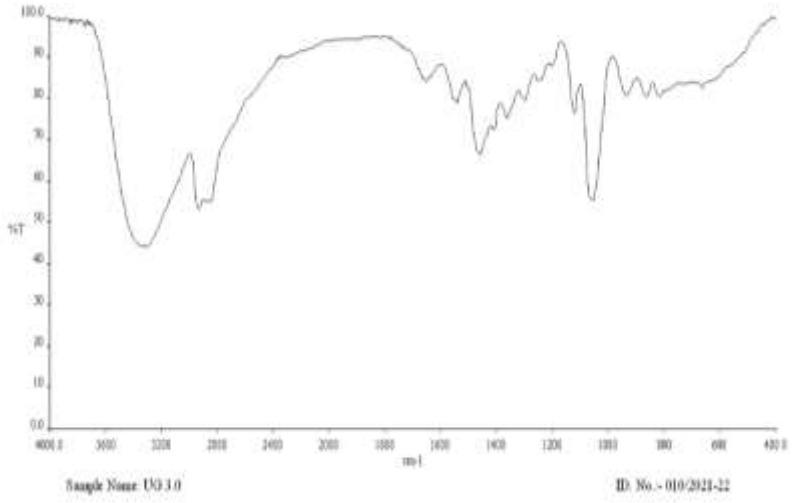

Figure 7: FT-IR spectra of UG3.0 dendrimer

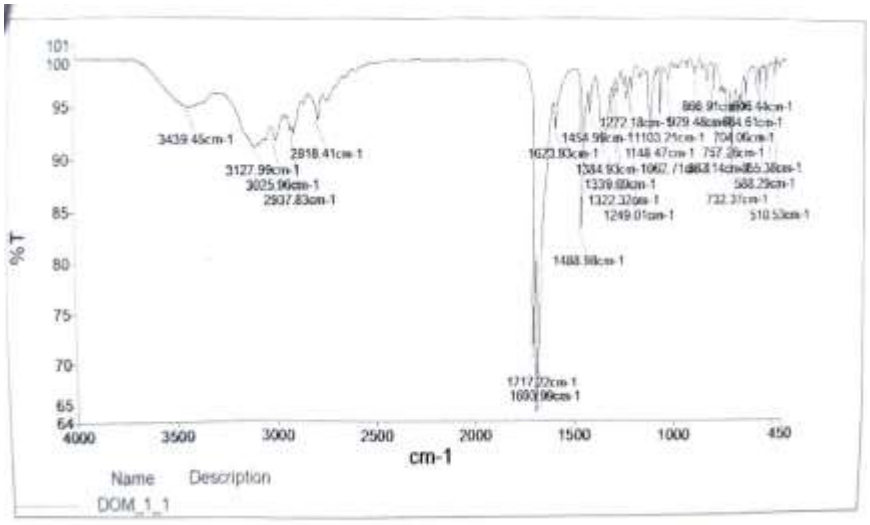

Figure 8: FT-IR Spectra of domperidone (DOM)

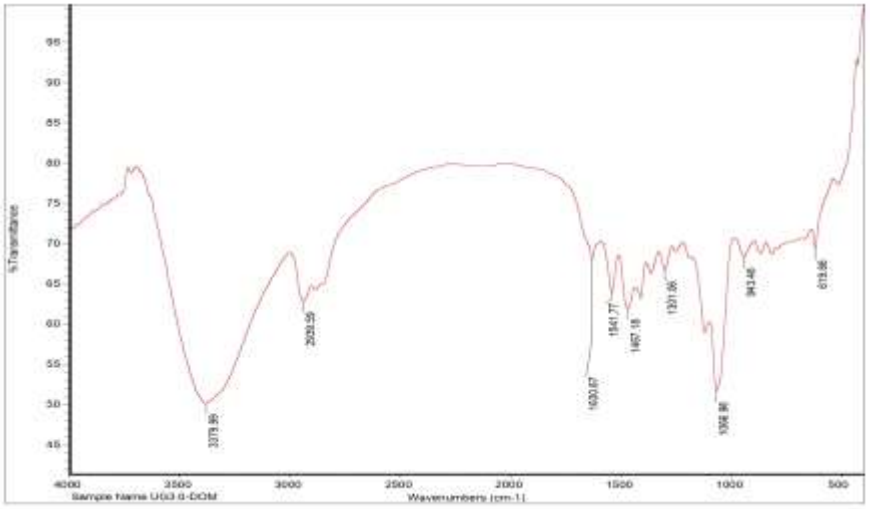

Figure 9: FT-IR Spectra of domperidone containing dendrimer (UG3.0-DOM)

Hemolysis

In pharmacology, "hemolysis" refers to the disintegration of red blood cells. When red blood cells are treated with dendrimers, the hemolysis test gives a quantitative estimate of the amount of hemoglobin released. The outcomes of this assay can serve as a qualitative indicator of potential red blood cell damage after dendrimer treatment. Figure 10 illustrates the percentage of hemolysis at multiple concentrations. The results demonstrated nanostructured generation three dendrimer (UG3.0) exhibited concentration-dependent hemolysis. For generation three dendrimer at concentrations ranging from 0.01µg/ml to 1000µg/ml, the hemolysis impact was less than 9%. However, the nanostructured dendrimer (UG3.0) performed better result in terms of hemolysis than the PAMAM dendrimer [25]. A reaction between the positively charged amine-terminated PAMAM dendrimer and the negatively charged red blood cell surfaces causes

hemolysis [26]. In contrast, hydroxyl end groups on the outer surface of nanoscale dendrimers make them less toxic.

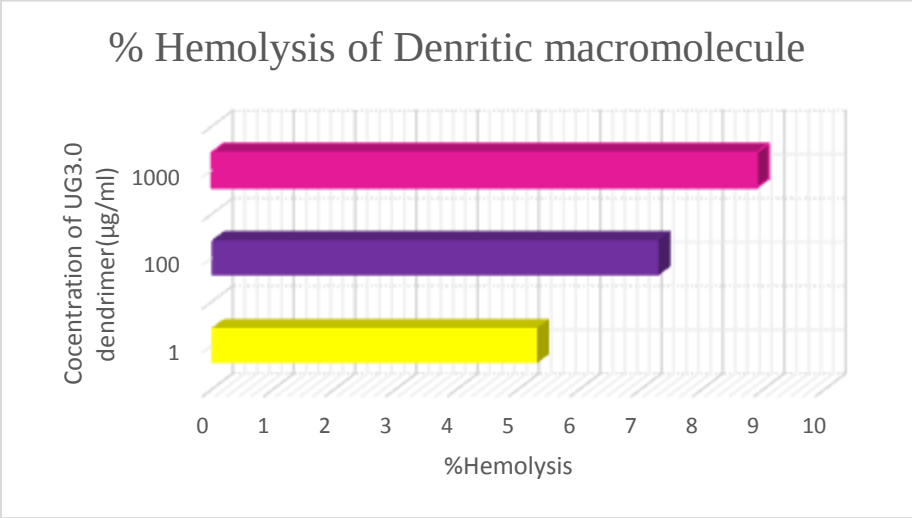

Figure 10: %Hemolysis of dendritic macromolecule (UG3.0)

The percentage of hemolysis for generations (G0.5–G2.5) of various concentrations is shown in Figure 3. The hemolysis effect induced was less than 6% for all generations as the concentrations increased simultaneously. The percentage of hemolysis for generations (G0.5–G2.5) of various concentrations is shown in Figure 3. The hemolysis effect induced was less than 6% for all generations as the concentrations increased simultaneously.

Cytotoxicity

The results were associated with living cells in order to estimate cell viability. It was discovered that dendrimer macromolecule cytotoxicity typically fluctuates with the generation, the number of exterior groups, and a specific type of peripheral moieties. The cytotoxicity test results revealed that the UG3.0 dendritic macromolecule (10µg/ml - 1000µg/ml) had a cell viability of above 90%. Because of this, the UG3.0 dendrimer is significantly less cytotoxic. Using a microscope, it was possible to see how the nanostructured dendrimer affected the morphology of the A-549 cell lines (Figure 11). The anionic end group of our synthesized nanoscale hydroxy-terminated dendrimer makes it less harmful. The most poisonous dendrimers were those from later generations and those with positive surface charges.

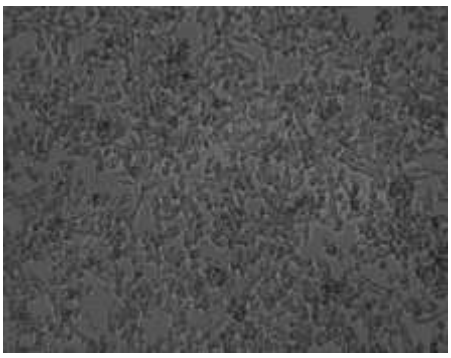

Figure 11(a). Control

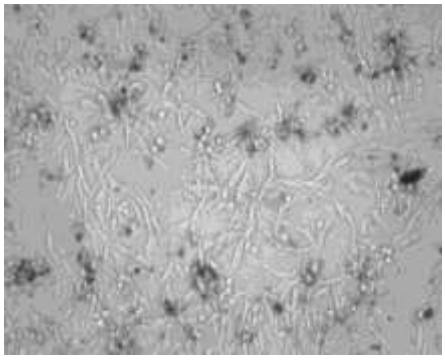

Figure 11(b). 1000 µg/ml (UG3.0)

Figure 11: Microscopic images of A-549 cell lines treated with (a) Control and (b) 1000 µg/ml of UG3.0 Dendrimer

CONCLUSION

The domperidone solubility has been greatly improved by the developed nano-structured dendritic macromolecule. The increase of the domperidone drug solubility in an aqueous solution depends on the concentration (0.6mM to 3mM) and the generation of dendrimer (UG1, UG2 and UG3). The aqueous solubility of domperidone has increased as dendrimer generation and concentration have risen. Hemolysis and cytotoxicity tests disclose that the nanostructured dendritic macromolecule is less cytotoxic and more biocompatible than the PAMAM dendrimer. In comparison to β-cyclodextrin, the dendritic scaffold has been shown to be a more effective carrier for the antiemetic drug domperidone.

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DECLARATION OF COMPETING INTEREST

There is no conflict of interest to disclose.

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REFERENCE

1. Krosuri P, Mothilal M. Recent advances in the development of nanoparticles in enhancement of solubility of poorly soluble drugs. J Pharm Negat 2022; 13(10):3512–3527. https://doi.org/10.47750/pnr.2022.13.S10.422.
2. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. Int J Pharm 2011; 420(1):1–10. https://doi.org/10.1016/j.ijpharm.2011.08.032.
3. Singh G, Kaur I, Gupta GD, Sharma S. Enhancement of the solubility of poorly water soluble drugs through solid dispersion: a comprehensive review. Indian J Pharm Sci 2017; 79(5):674-687. https://doi.org/10.4172/pharmaceutical-sciences.1000279.
4. Patel V, Patel P, Patel JV, Patel PM. Dendrimer as a versatile platform for biomedical application: a review. J. Indian Chem Soc 2022; 99(7):100516. https://doi.org/10.1016/j.jics.2022.100516.
5. Ndlovu ST, Ullah N, Khan S, Ramharack P, Soliman M, Matas M, Shahid M, Sohail M, Imran M, Shah SWA, Hussain Z. Domperidone nanocrystals with boosted oral bioavailability: fabrication, evaluation and molecular insight into the polymer-domperidone nanocrystal interaction. Drug Deliv and Transl Res 2019; 9:284–297. https://doi.org/10.1007/s13346-018-00596-w .
6. Bhalani DV, Nutan B, Kumar A, Chandel AK. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. Biomedicines 2022;10(9): 2055. https://doi.org/10.3390/biomedicines10092055.
7. Jesus AR, Soromenho MR, Raposo LR, Esperança JM, Baptista PV, Fernandes AR, Reis PM. Enhancement of water solubility of poorly water-soluble drugs by new biocompatible N-acetyl amino acid N-alkyl cholinium-based ionic liquids. Eur J Pharm Biopharm 2019; 137:227-232. https://doi.org/10.1016/j.ejpb.2019.03.004.
8. Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int J Pharm Investig. 2012; 2(1):12-17. https://doi.org/10.4103/2230-973X.96921.
9. Ismail A, Kerdpol K, Rungrotmongkol T, Tananuwong K, Ueno T, Ekasit S, Muangsin N, Krusong K. Solubility enhancement of poorly water soluble domperidone by complexation with the large ring cyclodextrin. Int J Pharm 2021; 606:120909. https://doi.org/10.1016/j.ijpharm.2021.120909.

10. Ibrahim EH, El-Faham TH, Mohammed FA, El-Eraky NS. Enhancement of solubility and dissolution rate of domperidone by utilizing different techniques. Bull Pharm Sci Assiut 2011; 34(2):105-120.
11. Fernández L, Sigal E, Otero L, Silber JJ, Santo M. Solubility improvement of an anthelmintic benzimidazole carbamate by association with dendrimers. Braz J Chem Eng 2011; 28(4): 679-689.
12. Patel P, Patel V, Patel PM. Synthetic strategy of dendrimers: a review. J Indian Chem Soc 2022; 99(7): 100514. https://doi.org/10.1016/j.jics.2022.100514.
13. Patel V, Patel P, Patel PM, Patel JV. Highly efficient novel nanostructured dendritic macromolecules for remediation of aquatic heavy metal ions. Inorg Chem Commun 2023; 148:110381. https://doi.org/10.1016/j.inoche.2022.110381.
14. Patel P, Patel V, Patel PM. Novel nanostructured dendrimer based on 1, 3-bis (4, 6-dichloro-1, 3, 5-triazine-2-yl) urea as an excellent adsorbent for Pb2+, Ni2+, Co2+ and Zn2+ metal ions. J Indian Chem Soc 2022; 99(11): 100763. https://doi.org/10.1016/j.jics.2022.100763.
15. Patel V, Patel P, Patel PM, Patel JV. Lead and copper metal ion uptake by novel nanoscale hydroxy-terminated dendritic macromolecules. J Indian Chem Soc 2022; 99(10): 100717. https://doi.org/10.1016/j.jics.2022.100717.
16. Chis AA, Dobrea C, Morgovan C, Arseniu AM, Rus LL, Butuca A, Juncan AM, Totan M, Vonica-Tincu AL, Cormos G, Muntean AC. Applications and limitations of dendrimers in biomedicine. Molecules 2020; 25(17): 3982. https://doi.org/10.3390/molecules25173982.
17. Gupta U, Agashe HB, Asthana A, Jain NK. Dendrimers: novel polymeric nanoarchitectures for solubility enhancement. Biomacromolecules 2006; 7(3): 649–658. https://doi.org/10.1021/bm050802s.
18. Ghorpade VS, Remeth D, Kailas M, Vijay H. Preparation and evaluation of domperidone/β-cyclodextrin/Citric acid/mannitol quaternary inclusion complex: An in vitro study. Asian J Pharm 2016; 10(3): 375-385.
19. Ghodke DS, Nakhat PD, Yeole PG, Naikwade NS, Magdum CS, Shah RR. Preparation and characterization of domperidone inclusion complexes with cyclodextrin: Influence of preparation method. Iran J Pharm Res 2009; 8:145-151.
20. Abd-Alaziz DM, Sammour OA, Elshamy AEAA, Nesseem D. Enhancement of solubility and dissolution rate of poorly water-soluble domperidone by the formulation of

multicomponent solid dispersions using solvent evaporation method. Int J Pharm Sci Rev Res 2013;20: 10-19.

21. Patel P, Patel V, Patel PM. Application of novel nanoscale hydroxy-terminated dendrimer for Cu+2 and Cd+2 ion uptake. Chem Pap 2023; 77:1287-1297. https://doi.org/ 10.1007/s11696-022-02541-1.
22. Sakhare RS. Development And Validation Of Stability Indicating Assay Method For simultaneous Estimation Of Ilaprazole And Domperidone In Bulk And Solid Dosage Form By UV-Spectroscopy. Int Res J Pharm 2016; 7(9):2230-8407. https://doi.org/10.7897/2230-8407.079109
23. Higuchi T, Connors CA, Phase solubility techniques. in: C.N. Reilly (Eds.), Advances in Analytical Chemistry and Instrumentation, Wiley-Interscience, New York, 1965, vol. 4, pp. 117-212.
24. Jain S, Kaur A, Puri R, Utreja P, Jain A, Bhide M, Ratnam R, Singh V, Patil AS, Jayaraman N, Kaushik G. Poly propyl ether imine (PETIM) dendrimer: A novel non-toxic dendrimer for sustained drug delivery. Eur J Med Chem. 2010; 45(11):4997-5005..https://doi.org/10.1016/j.ejmech.2010.08.006.
25. Gothwal A, Nakhate KT, Alexander A, Ajazuddin, Gupta U. Boosted memory and improved brain bioavailability of rivastigmine: targeting effort to the brain using covalently tethered lower generation PAMAM dendrimers with lactoferrin. Mol. Pharmaceutics. 2018; 15(10):4538-49. https://doi.org/10.1021/acs.molpharmaceut.8b00537 .
26. Domański DM, Klajnert B, Bryszewska M. Influence of PAMAM dendrimers on human red blood cells. Bioelectric chemistry. 2004; 63(1-2):189-91. https://doi.org/10.1016/j.bioelechem.2003.09.023 .