

Solubilization of Poorly Water-Soluble Drug, Glibenclamide by Micellization with Different Surfactants

Nirmal Singh

PG Department of Chemistry, R.S.D. College Ferozepur City - Punjab

Email: drnirmalsingh@rsdcollege.ac.in

Abstract:

Gemini surfactants are a class of self-assembling molecules that consist of two conventional surfactants connected via a spacer; they have lower CMC values compared to conventional surfactants, i.e., having one nonpolar tail and one polar head. In this paper, two series of Gemini surfactants were explored for solubilization and thus, improving the bioavailability of a poorly water-soluble drug, i.e., Glibenclamide by micellization. The first series of Gemini surfactants comprises carbohydrate derived conventional surfactants, carrying a sugar moiety and the second series comprises nonionic Gemini surfactants without sugar moiety, both with varying tail lengths, i.e., C₁₂, C₁₄, C₁₆. It was found that sugar moiety plays a vital role in encapsulating the drug molecule in an aqueous medium. By comparison, it was found that the sugar moiety potentially enhances the aqueous solubility of Glibenclamide. It was also found that with an increase in tail length, the solubility of the drug increased over many folds.

Keywords — Bioavailability, Poorly water-soluble drug, Carbohydrate derived surfactants, Solubilization, Glibenclamide, micellization

I. INTRODUCTION

Gemini surfactants are the self-assembling molecules which comprise two hydrophobic and two hydrophilic moieties connected by aliphatic or aromatic spacer group of varying carbon chain lengths. Depending upon the charge on the head group, surfactants are classified as anionic Gemini surfactants, Cationic Gemini surfactants, non-ionic Gemini surfactants. If the head group carry sugar moiety, then such Gemini surfactants form a new class of surfactants, known as carbohydrate, derived non-ionic Gemini surfactants.

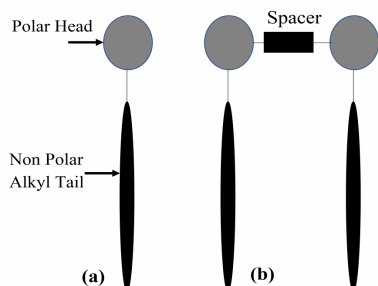


Fig. (1). Schematic diagram of (a) Conventional surfactant and (b) Gemini surfactant

Carbohydrate derived Surfactants

Generally, surfactants, also known as surface active agents, are added to a liquid to increase its wetting or spreading properties due to their ability to lower the surface tension of a liquid and the interfacial tension between two liquids, or between a liquid and a solid. On dissolving surfactants in water above its CMC (moles per liter), they form aggregates (micelles). In these micelles, the polar head group (hydrophilic part of the surfactant) is in contact with water while the nonpolar hydrocarbon tail (hydrophobic part) remains inside the micelle. Carbohydrate surfactants are amphiphile molecules possessing a sugar moiety as a hydrophilic structural part and a long alkyl chain derived from the epoxy compound as a usual hydrophobic part. These surfactants are nontoxic and biodegradable in nature. The CMC of the surfactants is much less than normal conventional surfactants, so they required in very small amount for micelle formation. Different types of sugar-based surfactants were reported(1–10). From their increased use, it is found that alkyl

polyglycoside becomes an excellent alternative to other nonionic surfactants. The reason for their popularity is that they can be synthesized on a large scale from renewable raw materials. Due to the advantages regarding performance, health of consumers, and environmental compatibility, sugar-based surfactants are gaining increased attention. Alkylpolyglycoside (APG) is a nonionic surfactant synthesized(11) from renewable raw materials, namely, glucose and fatty alcohol. These surfactants were found to show surface-active properties due to the presence of the hydrophilic sugar moiety and hydrophobic fatty alcohol residues. Sugar-based surfactants derived from glucose and (R)-12-hydroxystearic acid were already reported.

Non-ionic Gemini surfactants

Gemini surfactants (12) (Fig. 1a) are a class of amphiphile molecules comprising two hydrophobic tails and two hydrophilic heads connected via a rigid(13) or flexible(14) spacer. On the other side, conventional surfactants are simple types of surface-active agents having one polar head and one non-polar tail just like in soap and detergents. When two such conventional surfactants are connected by a spacer group at their head level, it forms Gemini or dimeric surfactants. Depending upon the nature of the spacer and overall charge on head group of the Gemini surfactants, varieties of Gemini surfactants were reported in last 37 years (15).

Depending upon the nature of the head group, whether it is anionic, cationic or neutral, the Gemini surfactants comprise: Anionic Gemini surfactants, Cationic Gemini surfactants and non-ionic Gemini surfactants respectively. Gemini surfactants may be classified according to the nature and structure of spacer groups, some are with rigid aromatic spacer, and others have flexible aliphatic spacer. The surfactants with rigid spacers may behave as inclusion molecules, which encapsulate any molecule without forming any bond with that. From the viewpoint of industrial application, after the anionic surfactants, non-ionic Gemini surfactants get the most significance. The non-ionic Gemini surfactants comprising polyether hydrophilic head were found to have very low CMC and showed

highly solubilization tendencies. The non-ionic surfactants have more tendency to aggregate as there is no repulsive forces as compared to ionic (cation or anionic). The numerous kinds of non-ionic Gemini surfactants were synthesized in literature and their critical micellization concentration (CMC) and self-assembling behavior were studied(9,11,16–20). The solubilization and aggregation behavior of mixed micellar systems formed by Gemini lipoamino acid and a non-ionic surfactant was studied recently(21). It was found that the mixed surfactants enhanced the solubility of polycyclic aromatic hydrocarbons i.e. naphthalene, phenanthrene and pyrene. Some Gemini surfactants were used as antiviral against Influenza A virus (IAV)(22) Four new nonionic Gemini surfactants, 1-alkylaminoglycerol with varying tail lengths C8 and C12, were synthesized and characterized by ¹H NMR, ¹³C NMR, and HRMS.(23)The cationic Gemini Surfactants were used as modifiers to boost CO₂ electroreduction to formate. The Gemini surfactants found to enhance the selectivity, activity and stability of the catalysts.(24)

These Gemini surfactants were used to encapsulate many poorly water-soluble drugs, amino acids etc. by micellization or reverse micellization. The micelle formation was detected by measuring the concentration of encapsulated molecules (drug, amino acids etc.) by monitoring UV spectrophotometer.

MICELLIZATION

There is a category of compounds, which when dissolved in aqueous medium at concentration, aggregates to form a group, termed as micelle. The concentration above which micellization takes place is known as CMC (Critical Micellization Concentration). Soaps and detergents are surface active agents having CMC values in the range of 10⁻³ – 10⁻² M.

The micellar system is an aggregate of surfactant molecules, with the hydrophobic head groups, which is polar, and remains in contact with the surrounding solvent, and the hydrophilic tail group, which is non-polar, and remains in the micellar center referred to

as core (Fig. 2). The core can effectively be used for the solubilization of water-insoluble substances in a mixture of ethanol and water or in pure water. Solubilization plays an important role in industrial and biological processes (25). Non-ionic surfactants aggregate easily as there is no repulsion among the head group but occurs in the case of anionic and cationic surfactants, yet there is just a weak interaction because of the hydration shell of solvent. So, they form micelle rapidly.

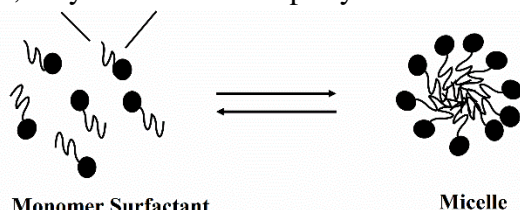


Fig.(2). Micelle and Reverse Micelle formation

Oral administration is the most common method of drug delivery because of its simplicity and convenience, especially where repeated doses are required(26–28). It is estimated that about 70% of new chemical entities are poorly water-soluble, and about 40% of currently marketed oral drugs are practically insoluble in water(29). Low solubility limits the drug dissolution rate, lower bioavailability of drug in body plasma and low biodegradability(30).

Nanotechnology has many advantages in drug delivery, especially for oral drugs. By increasing the water solubility, the bioavailability of drugs can be enhanced, and that helps to reduce the side effects and thus increase the pharmacological effect. The purpose of this paper is to show the effect of sugar moiety over the non-sugar surfactant in encapsulation of poorly water-soluble drug i.e., Glibenclamide. Sugar moiety facilitates micelle formation. The self-aggregation behavior of different drugs and their interaction with anionic, cationic, and Gemini surfactants were studied recently.(31)

SOLUBILITY

Solubility is expressed in terms of the solubilization capacity (SC) or micellar ratio that is defined as the ratio of the concentration of micelle-solubilized additive at saturation over the concentration of micellized surfactant (i.e., C_t / C_s) where C_t and C_s are the concentration of trapped or micelle

solubilized molecule and concentration of surfactant, respectively). So

$$\text{Micellar ratio} = \frac{\text{Conc.of trapped molecules i.e.PAH } (C_t)}{\text{Conc.of surfactant } (C_s)}$$

and

$$C_t = ((A - A_0) **) / (\epsilon \cdot l)$$

where A = Absorbance of PAHs in surfactant solution, A_0 = Absorbance of PAHs in ethanol / water (1:5 by vol) without surfactant,

ϵ = molar extinction coefficient of PAH,

l = path length

**For correction of solubility, $A - A_0$ is taken in the formula instead of A .

MATERIALS AND METHOD

Materials

Glibenclamide was taken from Sigma Aldrich, USA, double distilled water, ethanol from nice chemicals pvt. Ltd, Kerala, carbohydrate derived non-ionic surfactants and non-ionic Gemini surfactants were synthesized in lab, Shaheed Bhagat Singh State Technical Campus, Ferozepur, Punjab. Other chemicals were of AR grade and used without further purification.

Chemicals were of LR / AR grade and were used without further purification. Doubly distilled water and doubly distilled alcohol were used for spectroscopy. PAHs were purchased from Sigma Aldrich.

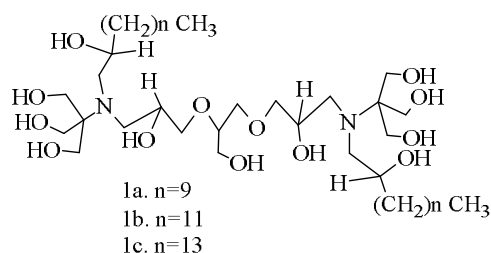
Methods

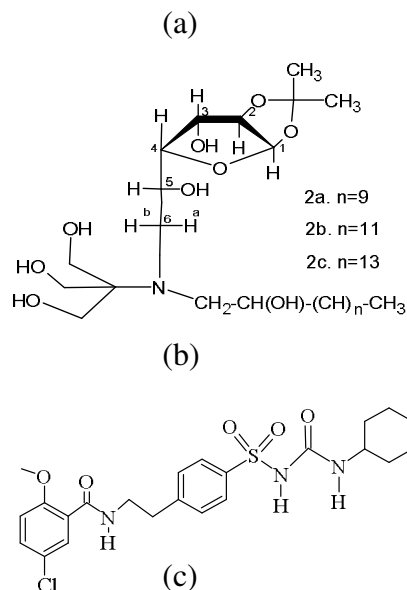
Synthesis of Gemini surfactants

The synthesis and characterization i.e. ^1H NMR, ^{13}C NMR, m/z etc. of Series I surfactants(32) (1a, 1b, 1c) and that of Series II surfactants(33) (2a, 2b, 2c) were reported by us. This paper mainly emphasized the role of sugar moiety which is linked with sugar surfactants (Series II).

Preparation of 5, 6-anhydro-1, 2-O-isopropylidene- α -D-glucofuranose– (sugar moiety)

The compound was synthesized as described in literature(34) . M.pt. 133°C . ESI – mass m/z 224.7 ($M - H + Na$) $^+$.





Scheme 1. Structure of (a) Non-ionic Gemini surfactant(32)(b) Carbohydrate derived surfactants(33) and (c) Drug (Glibenclamide) used for study.

Determination of the CMC of surfactants

Critical micelle concentration was determined by adding specified volumes of a sugar-based surfactant solution to a volume of double distilled water containing methylene blue dye. By taking the UV-spectra, it was found that the λ_{max} for dye is 665 nm, so at this wavelength the absorbance were noted and plot of absorbance against concentration of surfactant were constructed, and a clear discontinuity gave their CMC values. The CMC values of the sugar-based surfactants (2a-2c; Series 2) are given in table 1.

The CMC of non-ionic Gemini surfactants (1a -1c; Series 1) was determined by adding a known volume of concentrated surfactant solution (1 mM), to a volume of 15% aqueous-ethanol system. After each addition the contents were mixed thoroughly and absorbance determined by double beam spectrophotometer 299 nm. The plots of absorbance

vs. concentration of surfactants were drawn and a distinct discontinuity gave the value of cmc.

Solubilization of poorly water-soluble drugs using non-ionic surfactants

Sugar based non-ionic surfactants were explored as micellization probes for the solubilization of poorly water-soluble drugs like glibenclamide drug under double beam UV monitoring. The surfactants (5millimol) were shaken in water ethanol mixture (20ml) at room temperature with poorly water-soluble drugs (20mg) for 25 min and filtered. The filtrate was extracted with double distilled n-hexane (2 x 10ml) solution, and the concentration of poorly water-soluble drugs in n-hexane were determined by double beam spectrophotometer at 299nm. Micellar ratio is determined as the ratio of concentration of encapsulated drugs molecules to concentration of surfactants in mole per liter used for encapsulation. (Scheme 2)

Micellar ratio

$$= \frac{\text{concentration of encapsulated drug molecule}}{\text{concentration of surfactant}}$$

The surfactants carrying sugar moiety (series I) have more HLB value (Fig. 3) which directly means that they are more water soluble and can solubilize the drugs molecules up to more extent. Novel glucose-based non-ionic Gemini surfactants comprise two sugar head groups, two hydrophobic tails having varying chain length were synthesized and investigated for their micellar encapsulation properties.(34)

Similarly, more CMC value also indicates that they have the more tendencies to form micelle or aggregate which in turn help to encapsulate the drug molecule. The surfactants with sugar moiety series 1) have much more CMC values (Fig 4) as compared to the surfactants without sugar moiety(33) (series 2). Both the above factors favor the solubilization of drug in aqueous medium. The Fig 5 b clearly shows that the surfactants which have sugar moiety are more effective for solubilization of drug in aqueous medium.

10 ml mix. of ethanol & water (15:85) + 20 mg Drug

Shaken for 25 minutes

Filtered the mixture

Extracted with 2x5 ml n-hexane

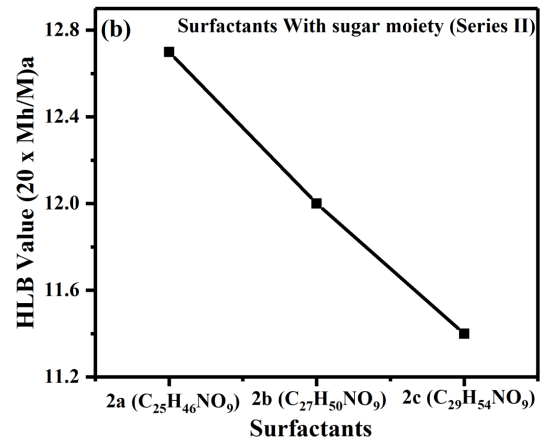
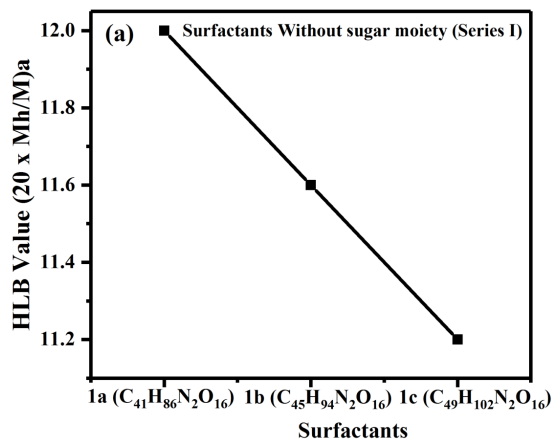
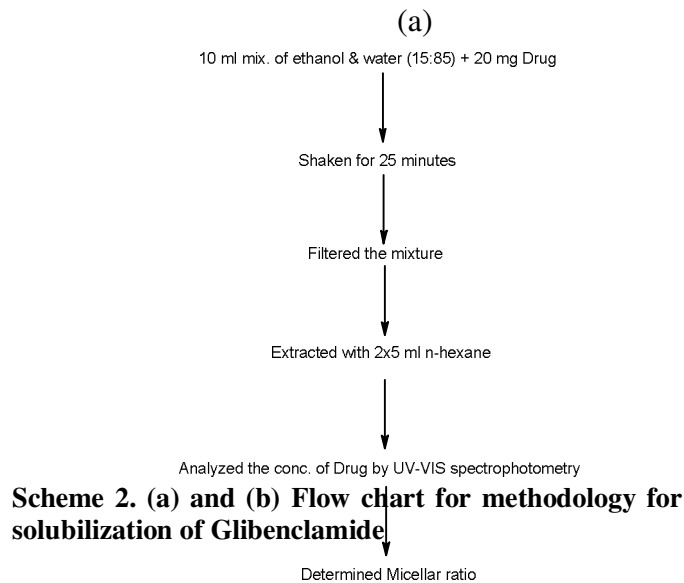


Fig. (3). HLB (Hydrophilic- Lipophilic Balance) vs. Tail length (a) for Surfactants without sugar moiety (b) for surfactants with sugar moiety.

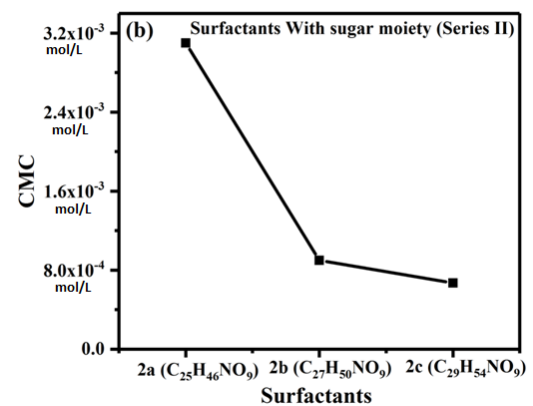
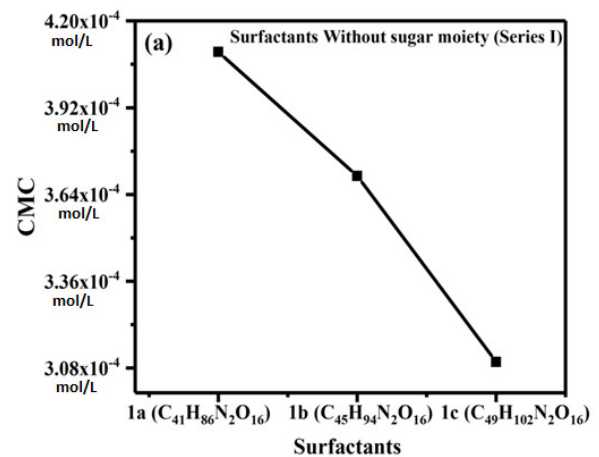


Fig. (4). CMC (Critical Micellization Concentration in mol/L) vs. tail length (a) for surfactants without sugar moiety (b) for surfactants with sugar moiety

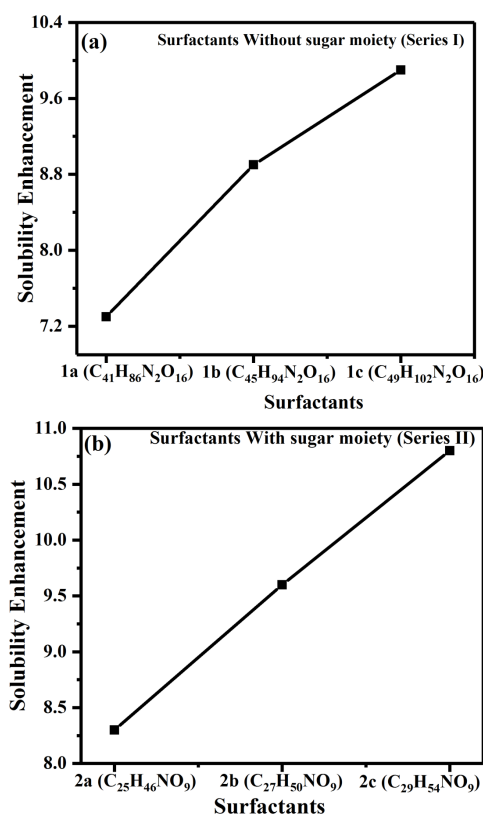


Fig. (5). Solubility enhancement vs. tail length (a) for surfactants without sugar moiety (b) for surfactants with sugar moiety

RESULT AND DISCUSSION

The main driving force for the encapsulation of drugs by non-ionic surfactants is the presence of sugar moiety. As per the study, the simple conventional surfactants without sugar moiety did not show any remarkable results. Hydroxyl groups of sugar moiety interact with the drug molecules in two ways. As a donor, it is responsible for free rotation of C-OH angle. This helps in the formation of a linear bond with drug molecules. Hydrophobic portions on sugar surfaces and long alkyl tails contact the hydrophobic portions on drugs. It is also found that the carbohydrate derived surfactants showed more efficiency to encapsulate poorly water-soluble drugs as compared to non-sugar surfactants.

Table 1. HLB (Hydrophilic-Lipophilic Balance) of surfactants(32,33) used for encapsulation of Glibenclamide-comparison

Surfactants Without sugar moiety(32) (Series I)	HLB Value (20 x Mh/ M) ^a	CMC (mol/ L)	Surfactants With sugar moiety(33) (Series 2)	HLB Value (20 x Mh/ M) ^a	CMC (mol/ L)
1a ($C_{41}H_{86}N_2O_{16}$)	12.0	4.1×10^{-4}	2a ($C_{25}H_{46}NO_9$)	12.7	3.1×10^{-3}
1b ($C_{45}H_{94}N_2O_{16}$)	11.6	3.7×10^{-4}	2b ($C_{27}H_{50}NO_9$)	12.0	9.0×10^{-4}
1c ($C_{49}H_{102}N_2O_{16}$)	11.2	3.1×10^{-4}	2c ($C_{29}H_{54}NO_9$)	11.4	6.7×10^{-4}

*Mh: molecular mass of hydrophobic portion of carbohydrate surfactant M: molecular mass of the whole carbohydrate surfactant

Hydrophilic-lipophilic balance (HLB) values (Griffin, (1954) of the surfactants are documented in table 1. HLB values are calculated using the formula

Table 2. Solubility enhancement of Glibenclamide by various surfactants(32,33) used in the study

Surfactants Without sugar moiety (Series 1)	Solubility Enhancement (times as compared to without surfactant)	Surfactants With Sugar moiety (Series 2)	Solubility Enhancement (x times as compared to without surfactant)	Net %age Enhancement (effect of Sugar moiety)
1a	7.3	2a	8.3	13.69%
1b	8.9	2b	9.6	7.87%
1c	9.9	2c	10.8	9.09 %

Table 2 clearly shows that, the solubility of poorly water-soluble drugs viz. Glibenclamide increased 7.3 times in an aqueous medium by surfactants of Series 1 (1a-1c; Structure given in Scheme 1). This surfactant series contains three surfactants having a varying tail length (C12, C14, C16) and solubility increases as the tail length increases. Similarly, the solubility of Glibenclamide is enhanced 8.3 times by surfactants of Series II, the surfactants molecules of

this series carrying sugar moiety (2a – 2c; Structure is given in Scheme1) in an aqueous medium. Surfactants in Series 2 were found to show more encapsulation power than surfactants of Series 1. Overall, it is found that the surfactants containing sugar moiety show more efficient results for encapsulation i.e. approximately 14 % more tendencies to encapsulate the drug under study. In the case of non-ionic Gemini surfactants, the –OH groups interact with drug molecules by electrostatic interactions, and the hydrophobic alkyl chain of the surfactant resides at the interface of a micelle. The encapsulation of the drug also depends on the shape and size of the drug molecule. The solubility enhancement of Glibenclamide by non-ionic Gemini surfactants (1a-1c) and by carbohydrate derived surfactants (2a -2c) is documented in Table 2. Sugar surfactants are non-toxic and biodegradable in nature. The sugar moiety of these surfactants accelerates the encapsulation power of the surfactants many folds. As sugar moiety linked to these surfactants is dextrorotatory in nature, this character can be used for chiral recognition of enantiomers of chiral drugs. The stereochemistry plays an important role in encapsulation of drug. All these factors are responsible for the fact that, the sugar derived surfactants encapsulate drug more effectively as compared to non-ionic Gemini surfactants without sugar moiety.

Sugar surfactants (2a – 2c) have more HLB values (Table 1) as compared to non-ionic Gemini surfactants. The higher the surfactant HLB value, the more hydrophilic it is. The more the HLB value of the surfactants, more it acts as solubilizing agent. This is also one of the main factors which explain the more encapsulation efficiency of sugar surfactants as compared to non-ionic Gemini surfactants (Series 1; 1a -1c). CMC of sugar surfactants (Series 2: 2a – 2c) is less than the CMC value of non-ionic surfactants (1a -1c). Lesser the CMC value of the surfactants means at very low concentration it can form micelle and encapsulate hydrophobic entity.

CONCLUSION

The above investigation revealed that both non-ionic Gemini surfactants and carbohydrate derived surfactants enhanced the solubility of poorly water-soluble drug viz. glibenclamide many folds by micellization. But carbohydrate derived surfactants encapsulate more effectively as compared to non-ionic Geminis, due to the presence of sugar moiety in the former. Moreover, the CMC of sugar surfactants is lower and HLB values are higher than non-ionic Gemini surfactants without sugar moiety. This might be the reason for the better performance of carbohydrate derived surfactants.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise

REFERENCES

- [1] 1. Sharma L, Singh S. Synthesis, characterization, and reverse-micellar studies of some N-substituted derivatives of 6-amino-6-deoxy-1,2-O-isopropylidene-D-glucose. Vol. 270, Carbohydrate Research. 1995.
- [2] 2. Singh N, Sharma L. Synthesis of Carbohydrate Derived Non-ionic Gemini Surfactants and Study of Their Micellar and Reverse Micellar Behavior - A Review. Lett Org Chem. 2019;16(8):607–14.
- [3] 3. Aveyard R, Binks BP, Chen J, Esquena J, Fletcher PDI, Buscall R, et al. Surface and Colloid Chemistry of Systems Containing Pure Sugar Surfactant. Langmuir. 1998;14(17):4699–709.
- [4] 4. Bazito RC, El Seoud OA. Sugar-based cationic surfactants: Synthesis and aggregation of methyl 2-acylamido-6-trimethylammonio-2,6-dideoxy-D-glucopyranoside chlorides. J Surfactants Deterg. 2001;4(4):395–400.
- [5] 5. Bazito RC, El Seoud OA. Sugar-Based Surfactants: Adsorption and Micelle Formation of Sodium Methyl 2-Acylamido-2-deoxy-6-O-sulfo-d-glucopyranosides. Langmuir. 2002 May 28;18(11):4362–6.
- [6] 6. Neimert-Andersson K, Sauer S, Panknin O, Borg T, Söderlind E, Somfai P. Synthesis of new sugar-based surfactants and evaluation of their hemolytic activities. J Org Chem. 2006;71(9):3623–6.
- [7] 7. Caussanel F, Andre-Barrès C, Lesieur S, Rico-Lattes I. A comparative study of sugar-based surfactants for the solubilization of phosphatidylcholine vesicles. Colloids Surf B Biointerfaces. 2001;22(3):193–203.
- [8] 8. Gao C, Millqvist-Fureby A, Whitcombe MJ, Vulfson EN. Regioselective synthesis of dimeric (gemini) and trimeric sugar-based surfactants. J Surfactants Deterg. 1999;2(3):293–302.
- [9] 9. Mohammed AI, Abboud ZH, Alghanimi AHO. Synthesis of d-mannitol substituted ether-linked bis-1,2,3-triazoles as models of gemini surfactants. Tetrahedron Lett. 2012 Sep 19;53(38):5081–3.
- [10] 10. Cecutti C, Focher B, Perly B, Zemb T. Glycolipid Self-Assembly: Micellar Structure. Langmuir. 1991;7(11):2580–5.
- [11] 11. Ware AM, Waghmare JT, Momin SA. Alkylpolyglycoside: Carbohydrate Based Surfactant. J Dispers Sci Technol. 2007;28(3):437–44.
- [12] 12. Bunton CA, Robinson L, Stam MF, Schaak J. Catalysis of Nucleophilic Substitutions by Micelles of Dicationic Detergents. Journal of Organic Chemistry. 1971;36(16):2346–50.
- [13] 13. Zana R, Talmon Y, Zana R, Talmon Y. Dependence of aggregate morphology on structure of dimeric surfactants. Natur. 1993;362(6417):228–30

- [14] 14. Menger FM, Littau CA. Gemini Surfactants: A New Class of Self-Assembling Molecules. *J Am Chem Soc.* 1993 Nov 1;115(22):10083–90.
- [15] 15. Zana R. Critical Micellization Concentration of Surfactants in Aqueous Solution and Free Energy of Micellization. *Langmuir.* 1996;12(5):1208–11.
- [16] 16. Sakai K, Umezawa S, Tamura M, Takamatsu Y, Tsuchiya K, Torigoe K, et al. Adsorption and micellization behavior of novel gluconamide-type gemini surfactants. *J Colloid Interface Sci.* 2008 ;318(2):440–8.
- [17] 17. Deng W, Zhang Y, Zhong Y, Peng J. Synthesis and Thermodynamic Properties of Rosin-Based Cationic Gemini Surfactants. *J Surfactants Deterg.* 2014;17(3):453–8.
- [18] 18. Han F, Zhang G. Synthesis and characterization of glucosamide-based trisiloxane gemini surfactants. *Journal of Surfactants and Detergents* 2004;7(2):175–80
- [19] 19. Mine Y, Fukunaga K, Samejima KI, Yoshimoto M, Nakao K, Sugimura Y. Preparation of gemini-type amphiphiles bearing cyclitol head groups and their application as high-performance modifiers for lipases. *Carbohydr Res.* 2004;339(3):493–501.
- [20] 20. Patil S, Bapat A, Madankar CS. Synthesis of novel cationic Gemini surfactant and its utilization in fabric softeners. In: *Materials Today: Proceedings.* 2023.
- [21] 21. Cabana Saavedra LC, Pachón Gómez EM, Oliveira RG, Fernández MA. Aggregation behaviour and solubilization capability of mixed micellar systems formed by a gemini lipoamino acid and a non-ionic surfactant. *Colloids Surf A Physicochem Eng Asp.* 2017 Nov 20;533:41–7.
- [22] 22. Khodsiani M, Kianmehr Z, Brycki B, Szulc A, Mehrbod P. Evaluation of the antiviral potential of gemini surfactants against influenza virus H1N1. *Arch Microbiol.* 2023;205(5).
- [23] 23. Liao R, Shi L, Zhou Y, Jia C, Feng J, Zhang W, et al. Synthesis, physicochemical property, and antibacterial activity of novel nonionic 1-alkylaminoglycerol Gemini surfactants. *Arabian Journal of Chemistry.* 2023;16(10).
- [24] 24. Zhang X, Yan X, Chen P, Zhang P, Kang X, Ma J, et al. Selective and Efficient CO₂ Electroreduction to Formate on Copper Electrodes Modified by Cationic Gemini Surfactants. *Angewandte Chemie - International Edition.* 2024;63(9).
- [25] 25. ELWORTHY PH, LIPSCOMB FJ. The effect of some non-ionic surfactants and a polyoxyethylene glycol on the dissolution rate of griseofulvin. *J Pharm Pharmacol.* 1968;20(12):923–33.
- [26] 26. Sant VP, Smith D, Leroux JC. Enhancement of oral bioavailability of poorly water-soluble drugs by poly(ethylene glycol)-block-poly(alkyl acrylate-co-methacrylic acid) self-assemblies. *J Control Release.* 2005;104(2):289–300.
- [27] 27. Bromberg L. Polymeric micelles in oral chemotherapy. *Journal of Controlled Release.* 2008 Jun 4;128(2):99–112.
- [28] 28. Gaucher G, Satturwar P, Jones MC, Furtos A, Leroux JC. Polymeric micelles for oral drug delivery. *Eur J Pharm Biopharm.* 2010;76(2):147–58.
- [29] 29. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. *J Pharmacol Toxicol Methods.* 2000;44(1):235–49.
- [30] 30. Choi YK, Poudel BK, Marasini N, Yang KY, Kim JW, Kim JO, et al. Enhanced solubility and oral bioavailability of itraconazole by combining membrane emulsification and spray drying technique. *Int J Pharm.* 2012;434(1–2):264–71.
- [31] 31. Pokhrel DR, Sah MK, Gautam B, Basak HK, Bhattarai A, Chatterjee A. A recent overview of surfactant-drug interactions and their importance. Vol. 13, *RSC Advances.* 2023.
- [32] 32. 2016 Annual International Conference on Chemical Processes, Ecology & Environmental Engineering (ICCPEE'16) Pattaya, Thailand April 28-29, 2016
- [33] 33. Singh Nirmal SL. Synthesis and Use of novel carbohydrate derived non-ionic surfactants for enhancing Aqueous solubility of Norfloxacin by Micellization. *Trends in Carbo research.* 2016;3(8 (3)).
- [34] 34. Sharma L, Saroj, Singh N. Micellar encapsulation of some polycyclic aromatic hydrocarbons by glucose derived non-ionic gemini surfactants in aqueous medium. *Tenside, Surfactants, Detergents.* 2014;51(5).