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Study On Drug Solubilisation and Synergism Using Prominently Used Non Ionic Surfactants and Sodium Lauryl Sulphate

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ABSTRACT

In the present study amount of Cefixime and amount of Metronidazole solubilised using PEG 6 K, PEG 20 K, PVP K 30, Brij 30 and Sodium lauryl sulphate alone and in combinations was investigated. Study results showed that drug amount solubilised by single surfactant was higher than water for both drugs and values were noticeable for Brij 30 and Sodium lauryl sulphate. Regarding drug amount solubilised using surfactant combination results showed synergistic effects and the effect was prominent when Brij 30 and Sodium lauryl sulphate were present in combination.

Key words: PEG 6 K, PEG 20 K, PVP K 30, Brij 30, Sodium lauryl sulphate, synergism and drug solubilisation

INTRODUCTION

In practice solubility of water insoluble or poorly water soluble drug imposes a big problem in the pharmaceutical fields and several approaches were undertaken to improve water solubility since many years till today. [1-5] The use of surfactants is one of them and this approach has been regarded as a successful approach especially for targeted drug therapy. The reason behind such success is that surfactants are amphiphilic molecules with structural uniqueness. These molecules consist of a polar head moiety and a non polar tail part. These molecules because of such structural duality can form aggregates with definite shape and size under suitable conditions. These are commonly known as ‘micelles’ and the prerequisite concentration above which micellisation occurs is known as ‘critical micellar concentration’ (cmc). [6,7] These micelles acts like micro-containers which entraps the solute molecule and carries the solute to the target sites escaping the surrounding immiscible media. This is solubilisation. Due to solubilisation the solubility of a hydrophobic solute (apparently) increases and problem of solubility disappears. [6] For a drug with limited or no aqueous solubility fact remains the same. In recent times, therefore use of surfactants in targeted drug therapy has been increased by many folds. Interestingly surfactant propelled drug solubilisation technique although has been investigated a lot but investigation regarding the effect of synergism on drug solubilisation has been done rarely. From pharmaceutical point of view synergism is a much practiced phenomenon especially in case of using excipients like antioxidants, preservatives and colorants. Synergism gives an extra benefit of efficacy than is expected on the basis of their individual activities. Not only that, synergism reduces cost of production and elevates safety level of final product as quantity of an individual excipient becomes less than the calculated amount. [8, 9] Surfactants are claimed to be a pharmaceutical excipient and these may have synergistic effect on drug solubilisation that needs exploration. Polyethylene glycol 6000 (PEG 6K), Polyethylene glycol 20000 (PEG 20K), Polyvinylpyrrolidone K 30 (PVP K 30), Polyethylene lauryl ethers 30 (Brij 30) are mention worthy non-ionic polymeric surfactants. Characteristically these surfactants are non irritant, bio compatible

and being non ionic in nature remains unaffected by solution pH. As such each of these surfactants offers wide range of compatibility with other agents present in formulations and presents uninterrupted medicinal and industrial values. In medicinal fields these surfactants are used for stabilizing formulations and also for imparting viscosity to the formulations. Besides these are used as wetting agents and as solubilisers for hydrophobic drugs. [7,8,10] On the other hand Sodium lauryl sulphate (SLS) is a sulfated chaotropic an ionic surfactant with pharmaceutical and cosmetic values. In pharmaceutical fields SLS has been used as an excipient in tablets and pills. This agent is used to reduce surface tension generated between immiscible phages and can be used to enhance disintegration and dissolution of solid dosage forms in the gastric media. Not only that in pharmaceutical formulations this agent has been used as a binder and as a diluting agent since years. [6, 10] In cosmetic fields this agent is used in dentifrices. [11] In medicinal field this surfactant has been proved to be a potent inhibitor for HIV [12] and a diagnostic agent for haemoglobin estimation as well. [13] This present study therefore aimed at investigating amount of Cefixime and amount of Metronidazole solubilised by these surfactants and synergism caused by them. The rationale behind choosing Cefixime was that this drug is a broad spectrum antibiotic of third generation and is suitable for oral use. This drug is more effective than Cephalosporin against *Escherichia coli*, *klebsiella* spp, *Proteus mirabilis*, *Serratia marcescens* and *Streptococcus pyrogens.* [14-17] Unfortunately Cefixime is poorly water soluble and its aqueous solubility value is 55 mg / L. [18] So, it was felt important to enhance its solubility in preparations where water would be a vehicle. Likewise Metronidazole is another anti-bacterial agent and is extremely useful for the treatment of serious infection caused by anaerobic bacteria. [19-22] Unfortunately this is another sparingly water soluble drug and needs to be investigated for enhancing its water solubility. Therefore this work aimed firstly at investigating extent of solubilisation of Cefixime and Metronidazole in water in presence of PEG 6 K, PEG 20 K, PVP K 30, Brij 30 & SLS and secondly to observe synergistic effect of these surfactants on solubilisation of these two drugs, if any.

MATERIALS AND METHODS

Polyethylene glycol 6000 and Polyethylene glycol 20,000 (Merck), Polyvinylpyrrolidone 30 (Merck) were gifts from Incepta Pharmaceuticals, Polyethylene lauryl ethers 30 (Merck) and Sodium lauryl sulphate were locally purchased. Cefixime and Metronidazole were gifts from Square Pharmaceuticals, Dhaka

Method

Drug solubilisation study was conducted at normal day temperature following the method as described by T Arnarson and PH Elworthy, (1980) with slight modification. In the method the model drug (a few mcg) was mixed with aqueous surfactant solution (2%, 5 ml) for 48 hours (with a fashion like 12 hours rotation followed by 12 hours pause) using a rotary mixture at a slow rpm. [23, 24] Assuming the state of equilibrium was attained, the mixture was centrifuged for 5 minutes at a speed of 2,000 rpm. The clear, supernatant of the drug-surfactant dispersions was removed and was filtered using 22 micron Millipore filter paper. A definite quantity of the clear filtrate following dilution using a solvent system (methanol and water = 50:50) was taken and its absorbance was read using a UV/visible spectrophotometer (SHIMADZU-1601PC). The amount of drug solubilized was determined from standard calibration curve drawn with absorbance versus seven concentration values ranging from 1 mcg / ml to 64 mcg / ml. For studying surfactant induced synergism, volume adjustment technique using 4% of respective surfactant solutions were used.

RESULTS AND GENERAL DISCUSSIONS

Our study was involved with determining amount of Cefixime and amount of Metronidazole solubilised by PEG 6K, PEG 20K, PVP K 30, Brij 30 and SLS. At the same time our study aimed at looking into the synergistic effect of surfactant combination(s) on drug solubilisation (if any). Results of solubilisation have been shown in different figures and tables. Figure 1 represents amount Cefixime solubilised by PEG 6K, PEG 20K, PVP K30, Brij 30, SLS and water; while figure 2 represents amount Metronidazole solubilised by them. In the study water was used as control. Our results showed that amount Cefixime solubilised by each surfactant was higher than water except glycols. Here SLS showed highest solubilisation for Cefixime followed by Brij 30 and then PVP K 30. Solubilisation values obtained with SLS was 3.17 mg /ml and values obtained with Brij 30 and PVP K 30 were 0.71 mg/ml and 0.60 mg/ml respectively. For PEG 6K and PEG 20K the values were 0.52 mg/ml and 0.50 mg/ml respectively; while amount Cefixim solubilised by water was 0.50 mg/ml. Thus in the study PEGs failed to exhibit an ehancement in Cefixim solubilisation. Considering the trend of Cefixim solubilisation by the surfactants (i.e. solubilisers) and water, it became like water ≤ PEG 20K ≤ PEG 6K < PVP K 30 < Brij 30 < SLS (fig 1).

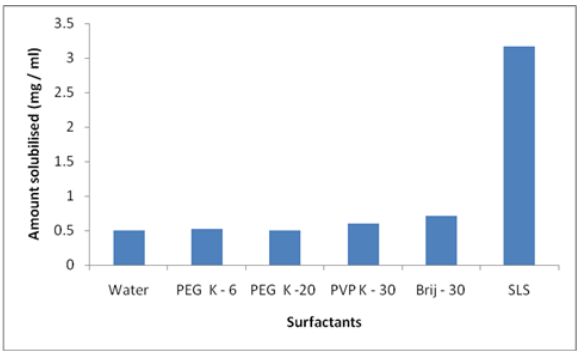

Fig 1 : Amount Cefixim solubilised by surfactants

Regarding solubilisation of Metronidazole results are shown in fig 2 and here results also showed higher amount of drug solubilisation than water in presence of surfactants. Amount Metronidazole solubilised was the highest with Brij 30 followed by SLS and then PVP K 30 and it was the least with PEG 6K. For instances amount Metronidazole solubilised by Brij 30 was 9.24 mg /ml. For SLS and PVP K 30 values were found to be 7.18 mg/ml and 6.48 mg/ml respectively. For PEG 6 K value was 5.07 mg/ml and for PEG 20 K the value was 5.63 mg/ml; while for water it was 4.38 mg/ml. Thus the trend of solubilisation of Metronidazole by the solubilisers became water < PEG 6K < PEG 20 K< PVP K 30 < SLS < Brij 30 (fig 2). Such results were as was expected and our results were in line with others. AA Ismail *et al.*, 1970 conducted solubilisation studies on barbitone, phenobarbitone and cyclobarbitone using a series of surfactants and noticed many folds increase in drug solubilisation when surfactants were in use. [1] Sakina, 2001 conducted a similar study on drugs like Testosterone, Griseofulvin, Phenylbutazone and Betamethasone using non ionic polymeric surfactants and noticed several folds increase in solubilisation of those drugs in presence of surfactants. [2] Likewise Jasimuddin *et al.*, 2003 conducted drug solubilisation study on Paracetamol. Here the surfactants in use were SLS and PEG 6K. The workers noticed an increase in drug solubilisation in presence of surfactants and solubilisation was better with SLS than PEG 6K. [3]

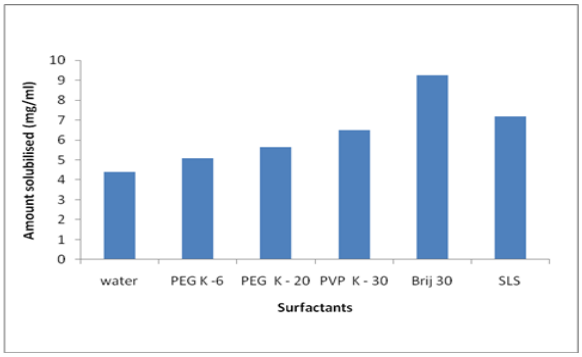

Fig 2 : Amount Metronidazole solubilised by surfactants

In our study synergistic effects of surfactant combinations on drug

solubilisation was investigated. For the purpose combinations used were PVP K 30 + Brij 30, PEG 6k + PEG 20k, PEG 6k + Brij 30, PEG 20k + Brij 30, PEG 6k + SLS, PEG 20k + SLS and drugs used were Cefixime and Metronidazole. Results are presented in table 1 and table 2 and results showed the values was higher than the amount solubilised by the individual (table 1) and (table 2).

Table 1: Cefixim solubilisation in surfactant combinations

Surfactants	Solubilisation (mg^{-mL})	Surfactants in combinations	Solubilisation (mg^{-mL})	Comments On drug solubilisation
PVP K 30	0.60	PVP K 30 + Brij 30	0.73	Increased
PEG 6k	0.52	PEG 6k + PEG 20k	0.67	Increased
PEG 20k	0.50	PEG 6k + Brij 30	0.80	Increased
Brij 30	0.71	PEG 20k + Brij 30	0.82	Increased
SLS	3.17	PEG 6k + SLS	1.65	Decreased With respect to SLS
		PEG 20k + SLS	1.65	Decreased With respect to SLS
Water	0.50			

Table 2: Metronidazole solubilisation in surfactant combinations

Surfactants	Solubilisation (mg^{-mL})	Surfactants in combinations	Solubilisation (mg^{-mL})	Comments On drug solubilisation
PVP K 30	6.48	PVP K 30 + Brij 30	12.20	Increased
PEG 6k	5.07	PEG 6k + PEG 20k	12.52	Increased
PEG 20k	5.63	PEG 6k + Brij 30	9.07	Increased
Brij 30	9.24	PEG 20k + Brij 30	10.29	Increased
SLS	7.18	PEG 6k + SLS	12.53	Increased With respect to SLS
		PEG 20k + SLS	9.65	Increased With respect to SLS
Water	4.38			

For instances with the combination of PVP K 30 + Brij 30 amount Cefixim solubilised was 0.73 mg/ml (table 1); but with PVP K 30 solubilisation value was 0.60 mg / ml and with Brij 30 the value was 0.71 mg /ml. Again with the same combination amount Metronidazole solubilised was 12.20 mg/ml; but with PVP K 30 value was 6.48 mg / ml and with Brij 30 value was 9.48 mg /ml (table 2). Thus for Cefixime and Metronidazole, surfactant combination exhibited higher solubilisation than that as obtained with the individual surfactant. This is synergism. The higher values of solubilisation caused by surfactant combinations therefore was due to synergistic effect and the effect was positive. Similar was the case with the combination of PEG 6k + PEG 20k. Here amount solubilised by this combination for Cefixim was 0.67 mg/ml (table 1) and for Metronidazole the solubilisation value was 12.52 mg/ml (table 2). Both the values were higher than the value as exhibited by the individual PEG 6K & PEG 20K (table 1) and (table 2). Such results were also due to positive synergistic effect. Considering the case of combinations of PEG 6k + Brij 30 and PEG 20k + Brij 30 results were as was got earlier. Here also surfactant combinations exhibited higher extent of drug solubilisation than the extent caused by individual ones (table 1) and (table 2). Unfortunately in our study when SLS was present in combination results depicted a different picture. Here combinations containing SLS were PEG 6k + SLS, PEG 20k + SLS. For Cefixime amount solubilised by the combinations of PEGs and SLS was less than the individual SLS. For instances amount Cefixime solubilised by the combinations of PEG 6k + SLS was 1.65 mg / ml and that for combinations of PEG 20K + SLS was also 1.65 mg / ml; while value obtained with SLS was 3.17 mg / ml. This is called negative synergism as

stated by Jannatul *et al*., 2014 [24]. On the other hand for Metronidazole solubilisation the same combination showed positive synergism (table 1) and (table 2). Here amount Metronodazole solubilised by the combination of PEG 6k + SLS was 12.53 mg / ml and by the combination of PEG 20k + SLS, amount solubilised was 9.73 mg / ml; while SLS when was used alone solubilised the drug in an amount of 7.18 mg / ml. Here the combination containing SLS successfully enhanced solubilisation of Metronidazole. This is positive synergism. Thus our results showed an anomaly which can be explained on the fact that surfactant induced drug solubilisation is an entrapment phenomenon caused by aggregation of surfactant molecles among themselves. Interestingly such aggregation process is not a simple and straight forward phenomenon. It depends on several factors and among the factors nature of solute whether non polar or polar, and nature of surfactant (i.e. ionic or non ionic), site of residence of the incoming solute molecule into / onto the micelles and number of participating molecules in the aggregation process are the major ones. Upon summing up the influences of the factors it is reported that usually a hydrophobic solute encourages micellasation and *vice versa*. [3, 6-8, 25] In the present study Cefixim and Metronidazole were used as model drugs. Although these two were hydrophobic by nature yet they might have different polarities causing such anomaly in the results. In the study Metronidazole exhibited many folds higher amount of solubilisation than Cefixm. It was reported earlier in that hydrophobicity encourages aggregation of surfactant molecules and hence entrapment of the hydrophobic solute molecule. The more is the hydrophobicity of solute molecule, the more would be the aggregation and more would be the probability of the solute molecule to be within the micellar core leading to enhanced solubilisation. It was expected that Metronidazole was located inside the micellar core and hence solubilisation was higher. Secondly SLS is an inoic surfactant. This surfcatnt has got ionisable SO4= group in its molecule. In water this surfactant undergone rapid ionisation and such ionic behaviour maight have changed solution pH and ultimately changed the site of location of the incoming hydrophobic solute molecule. Usually a micelle offers three sites (with varying polarities) where the incoming solute molecule can reside. These are micellar core, micellar surface and palisade layer. In general the micellar core reprents a central region of the micelle and it is hydrophobic; hence represents the best location for the incoming hydrophobic solute for entrapment. If it happens then solubilisation becomes optimum. [25] Therefore it might be assumed that influence of ionic moiety of SLS on Cefixim in presence of PEGs was higher than Metronidazole and such higher influence might have prevented Cefixim molecule from entering into the micellar core resulting low lesser solubilisation than Metronidazole. However this is a speculation and therefore needs further study for confirmation.

CONCLUSION

From our study it may be concluded that surfactant molecules enhances solubilisation of hydrophobic drugs and synergism prevails with surfactant combinations when situation permits.

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REFERENCES

1. Ismail AA, Gouda MW, Motawi MM. Micellar solubilization of barbiturates I: Solubilities of certain barbiturates in polysorbates of varying hydrophobic chain length. Journal of pharmaceutical sciences. 1970; 59: 221-223
2. Sultana S. Comparison between polyvinyl pyrrolidone – base and polyoxazoline nonionic surfactants: their physico-chemical and solubilisation behaviour. Ph. D thesis. Department of Pharmacy, King's College London, University of London. 2001
3. Ahmed JU, Rahman T, Sultana S. Comparison of drug solubilising behaviour between

sodium lauryl sulphate and polyoxyethylene glycol. Bangladesh Journal of Life sciences. 2003; 15(2): 151-155
4. Sultana S, Farooq ATMO, Kamruzaman M, Imtiaz MF. Solubilising capacity of PEG 6000, PVP 30 and Polysorbate 80 for Cortisone acetate. Journal of Bangladesh Society for Pharmaceutical Professionals. 2011; (1): 51-54.
5. Fardous J, Perveen FF, Saifuddin A, Sultana S. A comparative study on solubilising capacity at different concentration levels of PVP K 30 and PEG 6000 and theophylline solubilisation in them and in their combinations with other surfactants. Journal of Bangladesh Society for Pharmaceutical Professionals. 2013; 2(2): 48-54.
6. Liebermann HA; Reiger MM; Banker GS. Pharmaceutical dosage forms. Disperse system. Volume I. Marcel Dekker Inc. Newyork and Basel. 1988; pp: 199, 319 -324
7. Rawlins EA (ed). Betley's textbook of Pharmaceutics. 8th edition. Bailliere Tindall. London. 2004; pp: 44, 51-59.
8. Liebermann HA; Reiger MM; Banker GS. Pharmaceutical dosage forms. Disperse system. Volume II. Marcel Dekker Inc. Newyork and Basel. 1989; pp: 350 -354, 363
9. Sahu SN (ed). The technology of preparation and distribution of drugs and cosmetics. 1st edition. Kislay Book House. India. 1990; pp: 38.
10. Academy of Pharmaceutical Sciences, & Pharmaceutical Society of Great Britain. Handbook of pharmaceutical excipients. Washington, D.C., American Pharmaceutical Association. 1986.
11. http: // www. Mayoclinic.com / health / canker-sore / DS00354/DSECTION = causes. Accessed on August 30, 2011 as cited in http: // www.drugs.com/ inactive/sodium –lauryl-sulfate-124. html Accessed on August 3, 2018
12. Piret J, Lamontagne J, Bestman-Smith J, Roy S, Gourde P, Désormeaux A, et al. In vitro and in vivo evaluations of sodium lauryl sulfate and dextran sulfate as microbicides against herpes simplex and human immunodeficiency viruses. Journal of clinical microbiology. 2000;38(1):110-9.
13. Oshiro I, Takenaka T, Maeda J. New method for hemoglobin determination by using sodium lauryl sulfate (SLS). Clinical biochemistry. 1982;15(2):83-8.
14. https:// www.drugbank.ca/ drugs/ DB00671
15. Naqvi SH, Bhutta ZA, Farooqui BJ. Therapy of multidrug resistant typhoid in 58 children. Scandinavian journal of infectious diseases. 1992; 24(2):175-9.
16. Neu HC. In vitro activity of a new broad spectrum, beta-lactamase-stable oral cephalosporin, cefixime. The Pediatric infectious disease journal. 1987; 6: 963-970
17. Bhutta ZA, Khan IA, Molla AM. Therapy of multidrug-resistant typhoid fever with oral cefixime vs. intravenous ceftriaxone. The Pediatric infectious disease journal. 1994;13(11):990-4.
18. https:// pubchem.ncbi.nlm.nih.gov/ compound/ cefixime/ 2018
19. JA O'Donnell. Anti-infectives In : Remington : The Science and Practice of Pharmacy Alfonso, R Gennaro. Editor. Remington : The Sc and Practice of Pharmacy. 21st edition. Lippincott Williams and Wilkins. Philadelphia. 2006. pp 1669. Chapter 90.).
20. Löfmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. Clinical infectious diseases. 2010;50(Supplement_1): S16-S23. https://doi.org/10.1086/647939
21. Shahidi RU (ed). Quick Index of medical Products and Problems (QUIMP-17). Dhaka, Bangladesh. 2015. pp: 104-105.
22. https: // en.wikipedia.org/wiki/Metronidazole/2018
23. Arnarson T, Elworthy P. Effects of structural variations of non-ionic surfactants on micellar properties and solubilization: surfactants based on erucyl and behenyl (C22) alcohols. Journal of Pharmacy and Pharmacology. 1980;32(1):381-5.
24. Fardous J, Perveen FF, Ohidullah M, Saifuddin A, Sultana S. Effects of concentration and synergism on drug solubilising behaviour of PVP K 30 and PEG 6000. Jahangirnagar University Journal of Biological Sciences. 2014;3(2):49-55.
25. Attwood D and Florence AT. Surfactant systems – their chemistry, pharmacy and biology. Chapman and Hall, London. 1983

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