Asian Journal of Chemical Sciences

Volume 14, Issue 6, Page 98-105, 2024; Article no.AJOCS.125549
ISSN: 2456-7795

Utilization of Hydrotropes on Solubilization of Tenoxicam in Aqueous Solution

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajocs/2024/v14i6337

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/125549

Original Research Article

Received: 24/08/2024
Accepted: 29/10/2024
Published: 04/11/2024

ABSTRACT

Hydrotropy is a unique solubilization technique utilize to depict the increase in the solubility of a solute by the addition of a second solute (in large amount) resulting in an increase in the aqueous solubility solute of interest. Therapeutic effectiveness of a drug depends on its aqueous solubility and bioavailability. The purpose of the study was to establish tenoxicam solubility in hydrotropes at very low concentrations as well as explore solubilization behavior of the drug in mixed hydrotropic systems at very low concentrations.

The methodology involved the use of rotary flask shaker at room temperature to determine the solubility of tenoxicam in water, hydrotropes (sodium benzoate, sodium citrate, urea) and mixed hydrotropes.

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Cite as: *Gerald, Ugodi W, Mbah J Chika, Nwodo J Ngozi, Ozochi A Oluchi, and Momoh Nafisa. 2024. "Utilization of Hydrotropes on Solubilization of Tenoxicam in Aqueous Solution". Asian Journal of Chemical Sciences 14 (6):98-105. https://doi.org/10.9734/ajocs/2024/v14i6337.*

The results showed that sodium benzoate gave the most increase in the aqueous solubility of tenoxicam when compared to other hydrotropes. However, the highest aqueous solubility fold increase of tenoxicam (about 92 fold-increase) was produced by sodium benzoate and sodium citrate mix at 6:2 ratio. The decrease in standard free energy pointed out the spontaneity of the solubilization process.
In conclusion, the study showed that mixed hydrotropes are better to be utilized in the solubilizing of tenoxicam in aqueous solution.

Keywords: Tenoxicam; hydrotropy; mixed hydrotropy; solubilization.

1. INTRODUCTION

Combinational chemistry, high throughput screening, as well as genomics have accelerated attrition of chemical compounds that lack high probability of successful development. A number of these new chemical compounds are highly hydrophobic and poorly water soluble. Aqueous solubility is a very vital physicochemical property for drug because low aqueous solubility can limit parenteral products development as well as the bioavailability of orally administered dosage forms (Kapetanovic, 2008). Thus, it becomes imperative that finding effective solubilizing systems suitable for a wide range of poorly aqueous soluble drugs will immensely assist in pharmaceutical products development (Yalkowsky and Roseman, 1981). Several solubilizing systems have been utilized to enhance the aqueous solubility of poorly water soluble drugs and they include: (i) particle size reduction (micronization ,nanosuspension) (Khadka and Jieun, 2014), (Samar and Maha, 2015) crystal habit modification (polymorphs, pseudopolymorphs) (Jindal, 2017); complexation (utilization of complexing agents) (Li et al.,1999); drug dispersion in carriers (eutectic mixtures, solid dispersions) (Kumar and Singh, 2016); micellization (utilization of surfactants) (Mbah, 2006), (Dhobale and Dhembre, 2018); cosolvency (utilization of cosolvents) (Mbah and Onah, 2023), (Jagtap and Magdum, 2018); chemical modification (salts, prodrugs) (Zhao et al.,1999), (Tegeli and Thorat, 2010), (Bhosle et al., 2006); microemulsion (Cho et al., 2015); nanoemulsion (Shafiq et al.,2007); self-emulsifying systems (Ahmad, 2022), and hydrotropy (Jain, 2008).

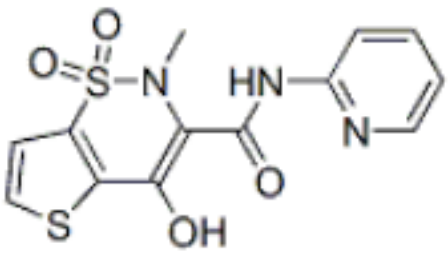
Therefore, the present study was aimed at using hydrotropic systems to enhance the aqueous solubility of tenoxicam.

Hydrotropy is a phenomenon of solubilization entailing addition of large amount of second solute to produce in an increase in the aqueous solubility of another solute (Reddy and Kumar, 2013). It designates increase in aqueous solubility due to the presence of large amount of additives. Additives or salts that increase the solubility of chemical compounds in a given solvent are said to “salt in” the solute whereas those salts that decrease the solubility are said to “salt out” the solute. A good hydrotrope has to have high water solubility while maintaining hydrophobicity. Invariably, an effective hydrotropic solubilization will depend on the balance between these two counteracting properties.

Hydrotropic agents are ionic organic salts (Praveena and Arun, 2020). Typical examples are sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, ibuprofen sodium, sodium acetate, sodium p-toluenesulfonate and N,N-dimethylbenzamide (a nonionic hydrotrope). Nicotinamide or its derivatives (for example N,N-diethylnicotinamide) are the most widely investigated hydrotropes by chemical or pharmaceutical analysts (Lee et al.,2003),(Kim et al., 2010).

Hydrotropes have been classified into: (i) aromatic hydrotropes (nonionic) such as nicotinamide, sodium salicylate, sodium p-toluenesulfonate, N,N-dimethylbenzamide and N,N-diethylnicotinamide, (ii) urea and its derivatives (iii) aromatic alcohols, iv) organic metal salts and organic acids and (v) surfactants.

Hydrotropic solubilization mechanisms have been reported to include: (a) complexation (Sanghvi et al., 2007) (b) molecular self-aggregation (Charman et al., 1993), (c) changes in the nature or structure of the solvent (Bauduin et al., 2005). Mixed hydrotropic solubilization technique enhances the solubility of poorly soluble drugs using blends of hydrotropic agents. The technique provides synergistic enhancement effect on the solubility of poorly soluble drugs, as well as reducing the large total concentrations of hydrotropic agents necessary to produce desired



Scheme 1. Chemical structure of tenoxicam

increase in aqueous solubility (Reddy and Reddy, 2013).

Tenoxicam (Scheme 1), a non-steroidal antiinflammatory (NSAID) agent of the oxicam family, is chemically defined as 4-hydroxy-2-methyl-N-2-pyridinyl2H-thieno (2, 3-e)-1, 2-thiazine-3-carboxamide-1, 1 dioxide) and having a molecular formula of $C_{13}H_{11}N_3O_4S_2$ and molar mass of 337.37 g·mol^{-1}.

It has anti-inflammatory, analgesic, and antipyretic properties, and clinically used in the treatment of rheumatic and arthritic diseases (Todd and Clissold, 1991). Tenoxicam solubility in water is very low (14 µg/ml) thus considered as practically insoluble drug.

To enhance aqueous solubilization of tenoxicam, some approaches such as phenolic cocrystals and salts (Bolla et al., 2013) cosolvency (Yeh et al.,2009), (Shakeel et al., 2016) micellar solubilization (Fetuoh et al., 2002), solid dispersion (Fetuoh et al., 2002), and complexation (Larrucea et al., 2003) have been reported in literature.

Literature review has revealed that tenoxicam is practically insoluble in water and that no study on its aqueous solubility enhancement by hydrotropic technique has been reported.

Therefore, it was considered of interest to investigate the aqueous solubility enhancement of tenoxicam by hydrotropic technique. We envisage that the enhancement of its aqueous solubility could potentially alleviate the drug problems that limit its clinical utilization.

2. MATERIALS AND METHODS

Experimental: Tenoxicam was purchased from Sigma Chemical Company (St. Louis, MO, USA). The water used in this study was highly pure deionized water and obtained from Milli-Q water purification unit (Berlin, Germany). Sodium benzoate, sodium citrate and urea were purchased from Fischer Scientific, USA.

Drug solubility determination: Tenoxicam solubility was determined using saturating shake-flask method. Briefly, an excess amount of drug was added to screw capped 10 ml vials containing 5 ml of purified water, different concentrations of hydrotropes respectively. The vials and the mixtures were shaken for 48 h at room temperature (25 ±1°C) on Rotary Flask Shaker at a speed of 125 rpm to achieve equilibration. Following equilibration, the samples were filtered through 0.45 µm disk filter and the supernatants were suitably diluted. The amount of tenoxicam was determined by measuring absorbance at 281 nm. Triplicate determinations on solubility experiments were carried out.

3. RESULTS

Calibration of tenoxicam: A plot (Fig. 1) of the absorbance versus concentration of tenoxicam is linear curve within the concentration range of 4 – 24 µg/ml. The correlation coefficient of the curve was found to be 0.9942. The regression equation defining the linearity of the curve is A = 0.009C + 0.015.

Tenoxicam solubility in hydrotropes: The experimental aqueous solubility data for tenoxicam as function of the hydrotropes concentrations are given in Tables 1, 2 respectively. Plot of data in Table 1 is presented in Fig. 2. The data show that sodium benzoate gave the most increase in the aqueous solubility of tenoxicam when compared to other hydrotropes (sodium citrate and urea respectively) utilized in the present study. Sodium benzoate at the highest concentration (10% w/v), gave about 82-fold increase in the aqueous solubility of tenoxicam. At the same concentration level, sodium citrate provided about 67-fold increase while urea gave about 9-fold increase in the aqueous solubility of tenoxicam. The correlation coefficients obtained from the curves in Fig. 2 are 0.9918, 0.9905 and 0.9895 for sodium benzoate, sodium citrate and urea respectively.

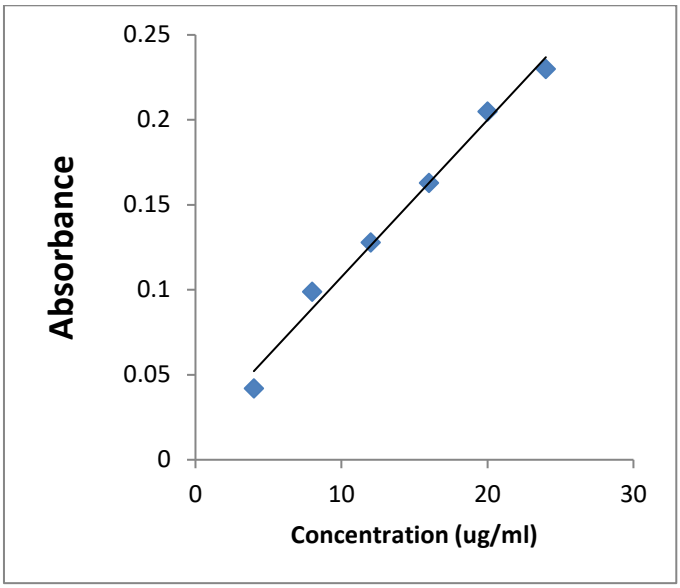


Fig. 1. Calibration curve of tenoxicam

The data in Table 2 provide the aqueous solubility of tenoxicam in mixed hydrotropes. The results show that sodium benzoate and urea mix at a ratio of 6:1 produced 89-fold increase in the aqueous solubility of tenoxicam. At the same mix ratio (6:1), sodium citrate and urea as well as sodium benzoate and sodium citrate gave about 74-fold and 79-fold increase respectively in the aqueous solubility of tenoxicam.

However, the highest aqueous solubility fold increase of tenoxicam (about 92 fold-increase) was produced by sodium benzoate and sodium citrate mix at mix ratio of 6:2. The standard free energy (ΔG^o) involved in the solubilization of tenoxicam in hydrotropes were evaluated and the results presented in Table 3.

4. DISCUSSION

The linearity of the calibration curve of tenoxicam indicates that Beer's law was obeyed in the concentration range of 4-24 µg/ml.

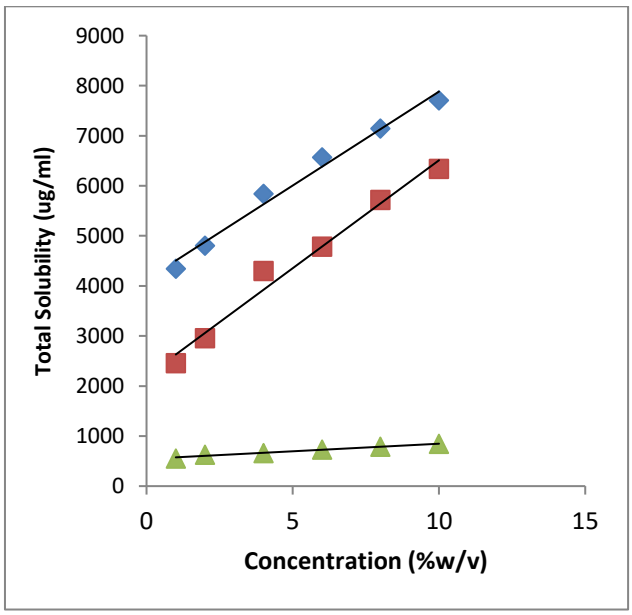


Fig. 2. Plot of total solubility of tenoxicam versus hydrotrope concentration

Table 1. Effect of urea, sodium benzoate, sodium citrate on the aqueous solubility of tenoxicam

Concentration of hydrotropes (% w/v)	Solubility (µg/ml)					
	Sodium benzoate	Enhancement ratio (ER)	Sodium citrate	ER	Urea	ER
0.0	94.06 ±0.29	1.0	94.06 ±0.29	1.0	94.06±0.29	1.0
1.0	4344.12 ±0.53	46.18	2455.67 ±1.49	26.11	553.09±0.53	5.88
2.0	4805.15±1.00	51.09	2954.63±0.49	31.41	631.03±0.26	6.71
4.0	5841.23 ±0.47	62.10	4300.00±3.45	43.72	660.93±0.54	7.03
6.0	6570.12 ±1.00	69.85	4787.89±0.68	50.90	730.02±1.06	7.76
8.0	7143.74 ±0.99	75.95	5717.22±0.59	60.78	785.59 ±0.56	8.30
10.0	7706.18 ±0.70	81.93	6341.23±0.84	67.42	844.43±1.04	8.98

Table 2. Effect of mixed hydrotropes on the aqueous solubility of tenoxicam

Concentration of mixed hydrotropes (% w/v)		Solubility (µg/ml)	Enhancement ratio
Sodium benzoate	**Urea**		
6	1	8372.16±1.06	89.01
1	6	4702.06±1.99	49.99
2	6	4959.79±1.31	52.78
6	2	8846.39±1.12	94.05
Sodium citrate	**Urea**		
6	1	6959.79±0.73	73.99
1	6	3042.27±1.14	32.34
2	6	4124.74±0.56	43.85
6	2	5629.80±0.85	59.85
Sodium benzoate	**Sodium citrate**		
6	1	6341.24±1.01	78.60
1	6	7392.78±1.48	67.42
2	6	5980.00±1.00	63.58
6	2	8609.28±1.55	91.53

Table 3. Solubilization parameters (hydrotrope-water partition coefficient and standard free energy of hydrotropic solubilization)

Concentration of hydrotrope (%w/v)	Sodium benzoate		Sodium citrate		Urea	
	P	Δ G°	P	Δ G°	P	Δ G°
0.0						
1.0	45.18	-9441.16	25.10	-7984.88	4.88	-3927.30
2.0	49.80	-9682.38	30.41	-8460.34	5.71	-4316.47
4.0	61.10	-10189.03	44.72	-9415.81	6.03	-4451.57
6.0	68.85	-10484.90	49.90	-9687.35	6.76	-4734.69
8.0	74.95	-10695.23	59.78	-10134.92	7.35	-4942.01
10.0	80.93	-10885.41	66.42	-10395.88	7.98	-5145.76

Difference in chemical structures of the hydrotropes, were considered to be responsible for the hydrotropic effects on tenoxicam aqueous solubility. Sodium benzoate which produced very strong effect on the solubility enhancement of tenoxicam is the only solute with aromatic moiety out of the three hydrotropes investigated. Previous study has noted that aromatic moieties in the solute significantly favor the hydrotropic effect on the solubility enhancement of poorly aqueous soluble drugs (Lee et al.,2003). The report also pointed out that a good hydrotrope while maintaining hydrophobicity should also have high water solubility.

Mixed hydrotropes at very low concentrations gave much better aqueous solubility enhancement of tenoxicam when compared to single hydrotropes. Previous reports have observed that mixed hydrotropes in lower concentration reduce the use of large total concentration of hydrotropic agents necessary to produce desired increase in solubility (Kadam et al., 2013). Based on Fig. 2, we assume that the relationship between total drug solubility in a hydrotrope solution and hydrotrope concentration could be explained by the following equation:

$$S_{tot} = S_w + kC_{hydro} \text{ ----------} \quad 1$$

where C_{hydro} is the concentration of hydrotrope and k is the solubilization capacity. The solubilization capacity k is determined from the slope of the plot of the total solubility of the drug versus hydrotrope concentration.

Considering the solubilization of tenoxicam in hydrotropes as a thermodynamic process and molecular self-association or formation of micelle-like structure to be the mechanism of solubilization, then the standard free energy (ΔG^o) involved in the solubilization can be evaluated using the following equation (Tavares, 2005):

$$\Delta G^\circ = -RT \ln P \text{ ----------} \quad 2$$

where P is the ratio of the amount of drug in water to the amount of drug in self-associated molecules S_{tot} : is the total drug solubility in hydrotrope; S_w is the drug solubility in water; R is the gas constant; and T is the absolute temperature. The hydrotrope-water partition coefficient (P) can be calculated from the equation below:

$$P = S_{tot} - S_w / S_w \text{ ----------} \quad 3$$

The decrease in standard free energy (Table 3), indicate the spontaneity of the solubilization process.

5. CONCLUSION

Solubility enhancement is one of the advantages of hydrotropes. Sodium benzoate out of the three hydrotropes investigated, showed the best solubility enhancement for tenoxicam. This is probably due to the aromatic moiety in its chemical structure thus explaining different hydrophobicity between sodium benzoate, sodium citrate and urea. Mixed hydrotropes at lower concentrations gave much higher enhancement ratio in comparison with single hydrotropes. Finally, we suggest the utilization of mixed hydrotropes in solubilizing tenoxicam in aqueous solution.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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