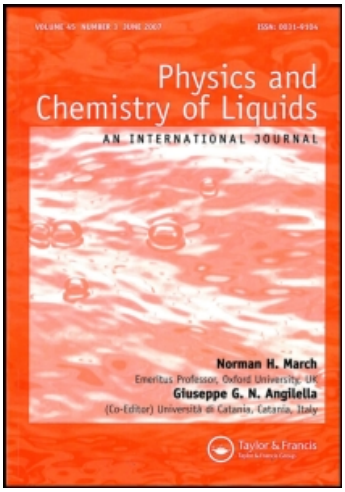
This article was downloaded by:
On: *28 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Physics and Chemistry of Liquids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713646857

Solubilization of non-steroidal anti-inflammatory drugs in the presence of tween series surfactants

Cheng Yiyun[a]; Yang Jiepin[a]
[a] School of Life Science, University of Science and Technology of China, Hefei, Anhui 230027, People's Republic of China

To cite this Article Yiyun, Cheng and Jiepin, Yang(2006) 'Solubilization of non-steroidal anti-inflammatory drugs in the presence of tween series surfactants', Physics and Chemistry of Liquids, 44: 3, 249 — 256
To link to this Article: DOI: 10.1080/00319100500493063
URL: http://dx.doi.org/10.1080/00319100500493063

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Physics and Chemistry of Liquids
Vol. 44, No. 3, June 2005, 249–256

Taylor & Francis
Taylor & Francis Group

Solubilization of non-steroidal anti-inflammatory drugs in the presence of tween series surfactants

CHENG YIYUN* and YANG JIEPIN

School of Life Science, University of Science and Technology of China, Hefei, Anhui 230027, People's Republic of China

(*Received 24 November 2005*)

Downloaded At: 07:40 28 January 2011

The aqueous solubility of non-steroidal anti-inflammatory drugs (NSAIDs) Ketoprofen, Ibuprofen, Diflunisal and Naproxen were measured in the presence of the Tween series surfactants at 37°C. Results showed that the solubility of NSAIDs in the Tween solutions was approximately proportional to Tween concentration; the ability of Tween series surfactants to solubilize NSAIDs in the present study was Tween-80 > Tween-60 > Tween-40 > Tween-20; the order of increased solubility of NSAIDs in Tween series surfactants at a constant Tween series and concentration was Ibuprofen > Ketoprofen > Diflunisal > Naproxen. Under suitable conditions Tween series surfactants can be highly effective used to enhance the solubility of NSAIDs.

Keywords: Tween series surfactants; NSAIDs; Solubility; UV/Vis spectroscopy; Absorption; Micelle; Nanocapsules

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs in the world, primarily for symptoms associated with osteoarthritis and other chronic musculoskeletal conditions [1]. Also, NSAIDs reduce the risk of and mortality from colon cancer by about half and constitute the prototypical colon cancer chemopreventive agents [2]. However, the use of NSAIDs is limited by their significant toxicity. NSAIDs cause a wide variety of reported adverse events, which include gastrointestinal side effects (such as dyspepsia, gastrointestinal bleeding and even perforation), renal side effects and some additional side effects (such as hypersensitivity reactions and distinct salicylate intoxication) [3]. Among patients using NSAIDs, up to 4% per year suffer serious gastrointestinal complications. Many studies have shown that NSAIDs increase the risk of peptic ulcer complications by several

*Corresponding author. Email: yycheng@mail.ustc.edu.cn

Physics and Chemistry of Liquids
ISSN 0031-9104 print: ISSN 1029-0451 online © 2006 Taylor & Francis
DOI: 10.1080/00319100500493063

folds [4]. It is now clear that most NSAIDs can damage the esophagus, stomach, duodenum, small and large intestines and can impair platelet function systemically, with a consequent increase in bleeding from a variety of GI lesions [5].

The side effects of NSAIDs and their potential toxicity has prompted intensive efforts to identify safer alternatives, which will at least maintain their pharmacological properties. Several studies have focused on improving their poor solubility in water [6–8], as poor solubility restricts their use in topical and parenteral applications [9–10]. Also, poor solubility is generally related to a low bioavailability, this presents a major challenge during drug formulation [11]. In order to improve the solubility of NSAIDs in water, technological expedients widely used in pharmaceutics are proposed [6,7,12–14], such as to micronize the drug particles, to form water soluble salts, to modify crystal structure by the formation of various polymorphic forms, to add solubilizing agents or to improve the wettability of the drug powder. However, methods mentioned above have not always been sufficient to achieve this goal.

The non-ionic surfactants are a great class of compounds frequently used in pharmaceutical systems, since their advantages as to compatibility, stability, minimal binding to proteins are rather significant [15–16]. In this present study, we use Tween series surfactants (Tween-20, Tween-40, Tween-60 and Tween-80) to investigate the potential of non-ionic surfactants to increase the solubility of NSAIDs as exemplified by Ketoprofen, Ibuprofen, Diflunisal and Naproxen and to study effect of molecular size and hydrophobic nature of NSAIDs on their solubility in the presence of Tween series surfactants.

Downloaded At: 07:40 28 January 2011

2. Experiments

2.1. *Materials*

Ketoprofen was purchased from Hubei Wuxue Xunda Pharmaceutical Co. (Hubei, China). Ibuprofen and Diflunisal were obtained from Juhua Group Pharmaceutical Factory (Zhejiang, China). Naproxen was a gift from Chetou Pharmaceutical Factory (Zhejiang, China). Quite water soluble non-ionic surfactants, such as the Tween-20, Tween-40, Tween-60 and Tween-80 were used. Tween-20 and Tween-80 were obtained from AMRESCO Co. (America). Tween-40 and Tween-60 were friendly supplied by Shanghai Chemical Co. (Shanghai, China). Double distilled-deionized water was used throughout.

2.2. *Solubility testing experiments*

The phase-solubility of NSAIDs in Tween series surfactant solutions in the range 0–200 mg mL^{-1} was determined. Excess NSAIDs was added to vials containing 5 mL of Tween series surfactants solutions to ensure the drug solution reaching saturation. The vials were then mechanically shaken for 24 h at 37°C and then filtered through a 0.45 μm HA filter (Millipore). The absorbances of NSAIDs test solutions at their characteristic wavelengths (260 nm for Ketoprofen and Naproxen, 251 nm for Diflunisal and 221 nm for Ibuprofen) were tested using the Varian Cary VIII spectrophotometer. Three repeats were conducted.

3. Results and discussion

3.1. *Effect of Tween series surfactant concentration on solubility of NSAIDs*

The solubility of NSAIDs as a function of different concentrations of Tween-20 surfactant, ranging from 0 to 200 mg mL^{-1}, is shown in figure 1. It was observed that the extremely low water solubility of NSAIDs has been significantly improved by Tween-20 surfactant. After interactions with Tween-20 at a concentration of 100 mg mL^{-1}, Ketoprofen solubility increased from 0.88 up to 9.98 mg mL^{-1}; while Naproxen solubility ranged from 0.02 to 3.16 mg mL^{-1}, Ibuprofen solubility ranged from 0.10 to 12.49 mg mL^{-1} and Diflunisal ranged from 0.19 to 3.93 mg mL^{-1}. The apparent solubility of NSAIDs increased linearly as a function of Tween-20 concentration. The same behavior was observed for all the four surfactants (Tween-20, Tween-40, Tween-60 and Tween-80) studied.

Critical micelle concentrations (CMC) for all the Tween series surfactants (Tween-20, Tween-40, Tween-60 and Tween-80) are really small values compared with the concentrations we used in the experiments. The phase-solubility of NSAIDs increasing linearly as a function of the concentration of Tween-20 surfactant was presumably due to the formation of micelles in solution depending on the concentration of surfactant [17]. When the surfactant is above the CMC, the hydrophilic solvents and hydrophobic drugs are partitioned between the polar bulk aqueous phase and the non-polar portions of the micelle, and the solubilization is due to the interactions within the hydrophobic core of the micelles [18].

Downloaded At: 07:40 28 January 2011

3.2. *Effect of different types of Tween surfactant on solubility of NSAIDs*

Different types of surfactants (Tween-20, Tween-40, Tween-60 and Tween-80) on the process were investigated at 37°C. Take Ketoprofen for example, the solubility of Ketoprofen in the presence of Tween series surfactants is shown in figure 2, from

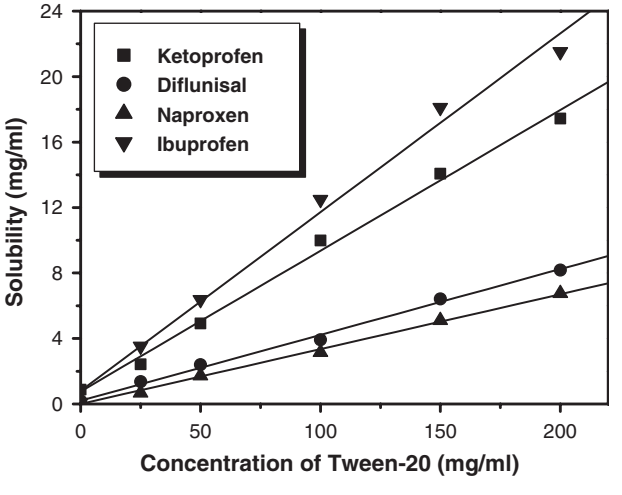


Figure 1. Solubility of NSAIDs in the presence of increasing concentration of Tween-20 surfactant.

Table 1. The characteristic data of Tween series surfactants.

Chemical name	Tween-20	Tween-40	Tween-60	Tween-80
General structure*	$C_{12}S_6E_{20}$	$C_{16}S_6E_{20}$	$C_{18}S_6E_{20}$	$C_{18}S_6E_{20}$
Hydrophobic group	Lauric acid	Palmitic acid	Stearic acid	Oleic aicd
Molecular weight ($g\,mol^{-1}$)	1226	1282	1310	1308
CMC ($mg\,L^{-1}$)	60	29	27	13
HLB	16.7	15.6	14.9	15.0

*S_6 represents for sorbitan ring; E_{20} represents for ethylene oxide group.

which it is clear that the solubility of Ketoprofen was affected by the type of surfactant we used. The increased phase-solubility of Ketoprofen in Tween series surfactants follows the order as Tween-80 > Tween-60 > Tween-40 > Tween-20. This was presumably due to different molecular structures of Tween series surfactants as listed in table 1. It is worthy noting that Tween-80 and Tween-60 have a lower hydrophile-lipophile balance number (HLB) than Tween-40 and Tween-20, Tween-80 and Tween-60 have a lower HLB than Tween-40 and Tween-20. This shows that HLB is also an important parameter on the solubilizing process. Surfactants with low HLB tend to form larger micelles that can physically contain a greater number of molecules of NSAIDs. This indicates that the NSAIDs are probably incorporated within the core of the surfactant micelle rather than in the capsular portion. In this way, we could explain why Tween-80 and Tween-60 could enhance the solubility of NSAIDs more efficiently than Tween-40 and Tween-20.

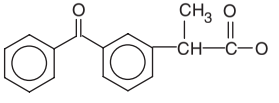
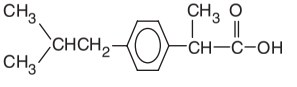
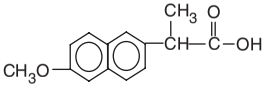
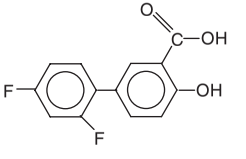
Downloaded At: 07:40 28 January 2011

3.3. *Effect of molecular size and hydrophobic nature of NSAIDs on their solubility in the presence of Tween series surfactants*

Experiments were carried out using four familiar NSAIDs, Ketoprofen, Ibuprofen, Diflunisal and Naproxen. Some important physical and chemical properties of these NSAIDs are given in table 2. The results are also shown in figures 1 and 3–5. The order of increased solubility of NSAIDs in Tween solutions at a constant surfactant concentration and series was Ibuprofen > Ketoprofen > Diflunisal > Naproxen. The molecular size and hydrophilic character of the guest seem to play an important role in the affinity degree for the host. Take Ketoprofen and Ibuprofen for example, the solubilizing of Tween surfactants was more pronounced for Ketoprofen and Ibuprofen than for Diflunisal and Naproxen. The molecular size and hydrophilic character of the drug molecule, which is similar for Ibuprofen and Ketoprofen, lead to a similar solubility enhancement in Tween series surfactants. The solubility of Diflunisal in Tween solutions was the much lower than that of Ibuprofen and Ketoprofen corresponded to that of the hydrophilic character of the guest molecules. It is interesting that the solubility of Naproxen in the Tween solutions was increased least in all the four drugs we used. This adverse result may be deduced to a different interaction mechanism for this molecule. The precise reason for this result will require further investigation.

Downloaded At: 07:40 28 January 2011

Table 2. The characteristic data of the four NSAIDs in our experiment.

Chemical name	Ketoprofen	Ibuprofen	Naproxen	Diflunisal
Molecular structure				
Class	Non-steroidal anti-inflammatory drugs			
Empirical formula	$C_{16}H_{14}O_3$	$C_{13}H_{18}O_2$	$C_{14}H_{14}O_3$	$C_{13}H_8F_2O_3$
Molecular weight ($g\,mol^{-1}$)	254.28	206.28	230.26	250.20
Characteristic wavelengths (nm)	260	221	260	250
Solubility	Extremely low solubility in water			
PK_a	4.5	5.3	4.2	3.3

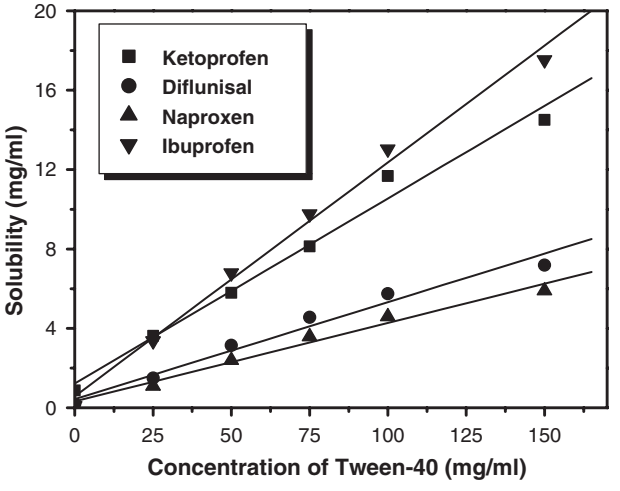


Figure 2. Solubility of NSAIDs in the presence of increasing concentration of Tween-40 surfactant.

Downloaded At: 07:40 28 January 2011

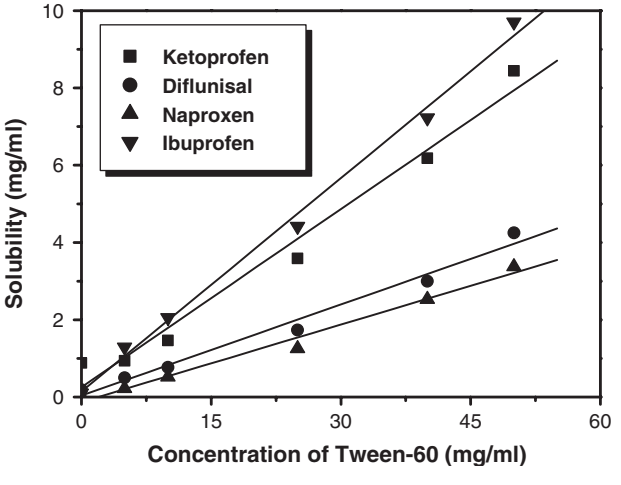


Figure 3. Solubility of NSAIDs in the presence of increasing concentration of Tween-60 surfactant.

4. Conclusion

Tween series surfactants including Tween-20, Tween-40, Tween-60 and Tween-80 have the potential to significantly enhance the solubility of NSAIDs. The higher solubility may contribute to a higher drug bioavailability. The drug solubility depends on the concentration and the HLB of the Tween surfactants. Solubility of NSAIDs in the Tween solutions increase in an approximately linear manner with an increase in surfactant concentration. The order of increased solubility of NSAIDs in Tween solutions at constant concentration and species was Ibuprofen > Ketoprofen > Diflunisal > Naproxen.

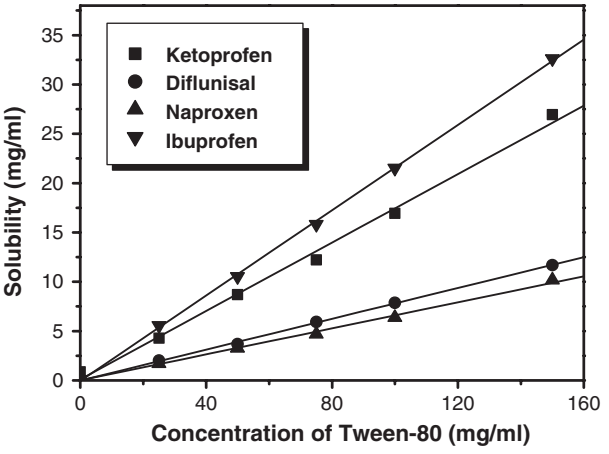


Figure 4. Solubility of NSAIDs in the presence of increasing concentration of Tween-80 surfactant.

Downloaded At: 07:40 28 January 2011

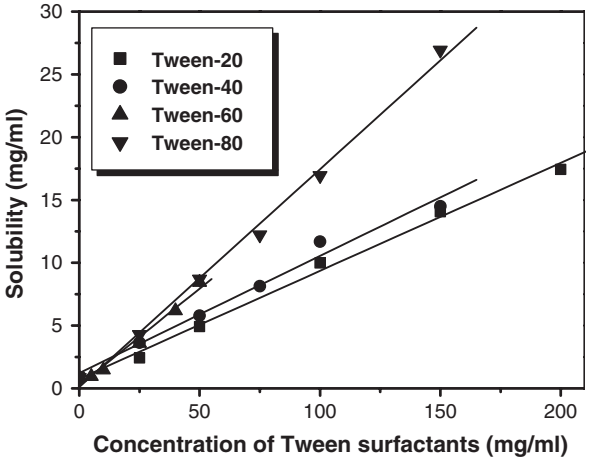


Figure 5. Solubility of Ketoprofen in the presence of increasing concentration of Tween series surfactants.

Acknowledgement

Financial supports from Innovation Foundation of Graduate Student in University of Science and Technology of China (KD2004035) were highly appreciated.

References

[1] R.G. Marie. *The American Journal of Medicine*, **104**, 23S (1998).
[2] A.C. Timothy. *Lancet Oncology*, **3**, 166 (2002).
[3] Y.Y. Cheng, T.W. Xu, R.Q. Fu. *European Journal of Medicinal Chemistry*, **40**, 1390 (2005).
[4] S.E. Gabriel, R.L. Jaakkimainnen, C. Bombarier. *Ann. Intern. Med.*, **115**, 787 (1991).
[5] M.M. Denis. *The American Journal of Medicine*, **107**, 37S (1999).
[6] P. Mura, G.P. Bettinetti, A. Manderioli. *International Journal of Pharmaceutics*, **18**, 189 (1998).
[7] S. Sridevi, P.V.R. Diwan. *European Journal of Pharmaceutics and Biopharmaceutics*, **54**, 151 (2002).

[8] Y.Y. Cheng, T.W. Xu. *European Journal of Medicinal Chemistry*, **40**, 1188 (2005).
[9] E.H. Gesine, C.M. Christel. *Journal of Pharmaceutical Sciences*, **86**, 854 (1997).
[10] J. Simon, T. Lionel, M. Charles. *International Journal of Pharmaceutics*, **268**, 37 (2003).
[11] L. Fabrice, P. Fabienne, M. Myriam. *Journal of Pharmaceutical and Biomedical Analysis*, **23**, 793 (2000).
[12] N. Yumiko, T. Kozo, H. Kimio. *International Journal of Pharmaceutics*, **145**, 29 (1996).
[13] F. Makiko, H. Naohide, S. Kumi. *International Journal of Pharmaceutics*, **205**, 117 (2000).
[14] G.J. Vergote, C. Vervaet, I.V. Driessche. *International Journal of Pharmaceutics*, **219**, 81 (2001).
[15] A.T. Florence, D. Attwood. *Le Basi Chimico-Fisiche Della Tecnologia Farmaceutica*. EdiSES, Napoli (2002).
[16] K. Ikeda, H. Tomida, T. Yotsuyanagi. *Chemical & Pharmaceutical Bulletin*, **25**, 1067 (1977).
[17] S. Tommasini, M.L. Calabro, D. Raneri. *Journal of Pharmaceutical and Biomedical Analysis*, **36**, 327 (2004).
[18] P. Li, L.W. Zhao. *International Journal of Pharmaceutics*, **249**, 211 (2002).

Downloaded At: 07:40 28 January 2011