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# Cetrimonium Surfactants with Biologically Active Counter Ions as Self-Immolative Drug Delivery Systems

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## ABSTRACT

Novel derivatives of cationic surfactant cetyltrimethylammonium bromide (CTAB) possessing anions of ibuprofen and naproxen as hydrophobic counterions were synthesized and characterized using Fourier transform infrared and differential electronic absorption spectroscopy. The self-assembly of each surfactant was investigated using surface tensiometry. The self-immolative nature of these compounds was analyzed by studying their behaviour in response to a trigger such as medium pH. ADMET-SAR (adsorption, distribution, metabolism, excretion, and toxicity – structure-activity relationship) profiles of synthesized surfactants were generated using admetSAR (v. 1.0). The cetrimonium drugs exhibited better profiles than the corresponding pure drugs, saving the aqueous solubility, which was reduced due to the hydrophobicity of counterions.

**Keywords:** *Cetrimonium, NSAIDs, drug delivery, ADMET*

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## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a major class of drugs used to treat inflammation and pain. In addition, they reduce fever and prevent clotting of blood. NSAIDs retard the action of cyclooxygenases COX-1 and COX-2 [1,2] and consequently inhibit the formation of prostaglandins (responsible for inflammation) and thromboxanes (that promote clotting of blood). NSAIDs may selectively inhibit COX-1 or COX-2 [3]. The commonly known over-the-counter NSAIDs are aspirin, naproxen, and ibuprofen [1]. Figure 1 shows the *ovine* COX-1 complexed with ibuprofen and COX-2 complexed with naproxen.

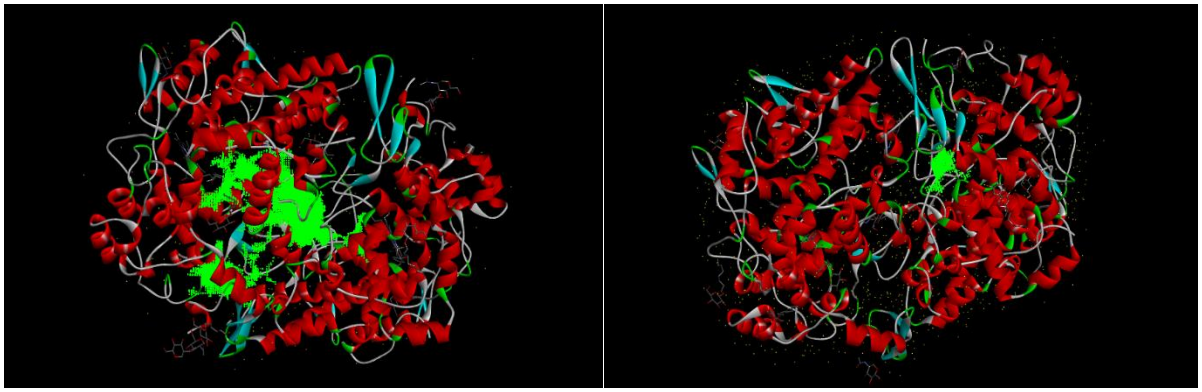

**Figure 1:** Ovine COX-1 complexed with ibuprofen [4] (left) and naproxen:COX-2 complex [5] (right). The cavities or binding sites are highlighted in bright green color

Ibuprofen belongs to the propionic acid class of NSAIDs prescribed in fever [6], menstrual pain, migraine and inflammation in the diseases such as rheumatoid/osteoarthritis [7]. Naproxen is also employed in treatment of inflammation and pain in migraine [8], rheumatoid arthritis [9], kidney stones [10], osteoarthritis [11], tendinitis [12,13], bursitis [14] and gout [15]. Long term use of NSAID can cause adverse effects such as gastrointestinal problems, kidney diseases, adverse cardiovascular events, photosensitivity, raised liver enzymes, headache and allergies [16]. Their role in different degenerative diseases is also of interest [2].

These drugs are water-insoluble, and controlled release systems have been employed to tune their bioavailability and minimize their adverse effects [17–21]. However, these systems are not devoid of limitations, and new ways are sought to effectively deliver the drugs at the target site [22,23]. One of the better strategies is to use self-immolative polymers [24], which is the depolymerization that releases the active monomeric segments [25].

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In the present work, self-immolative surfactants based on cetyltrimethylammonium surfactants have been developed, which carry carboxylates of ibuprofen and naproxen as counterions. These surfactants are expected to undergo self-immolation and release the drugs after crossing the biological barriers. In the absence of hydrophobic drug counterions, CTA+ ions exhibited high hydrophilicity and were expelled out of the membrane in a very short period [26]. Besides characterization and self-assembly, the molecular ADMET-SAR profiles were generated for each synthesized surfactant. The triggering of self-immolation by medium pH has also been investigated.

## EXPERIMENTAL

### *Materials*

Naproxen and ibuprofen were obtained from Shaigan Pharmaceuticals (Pakistan). Cetyl-trimethylammonium bromide was acquired from Alfa Aesar. All products were of purity ≥ 98 % and used without further purification. Dimethyl sulfoxide (HPLC grade, Aldrich) and doubly distilled deionized water were used in solution preparation.

### *Synthesis of Silver Salt of Drugs*

According to the reported method, Naproxen and ibuprofen were converted to sodium salts by treatment with sodium hydroxide in 50 % methanol [21]. The sodium salts were treated with silver nitrate in a 1:1 molar ratio. Silver naproxenate (CN) and silver ibuprofenate (CI) immediately precipitated out of the solution upon mixing. However, the solution was further stirred for 60 minutes, and products were collected by filtration to ensure completion. The solid was washed with aqueous methanol to remove sodium nitrate and dried in a vacuum oven at room temperature [27-29].

### *Synthesis of Cetrimonium Drugs*

An aqueous suspension of silver salts of drugs was added to an aqueous solution of cetyltrimethylammonium bromide (CTAB) in a 1:1 ratio, containing small amounts of dimethyl sulfoxide and stirred at room temperature for 48 h. The pale-yellow precipitate of silver bromide was removed by filtration, and the excess solvent was removed slowly under vacuum at low temperature to avoid decomposition, and the final product was collected after freeze-drying [30].

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### *Characterization and Analysis*

FT-IR spectra were recorded with Varian/Digilab FTS7000 spectrometer. Electronic absorption spectra in the differential mode were measured using the free drug as a reference on the Perkin Elmer lambda 25 double beam spectrophotometer. Thermo Star laboratory lyophilizer/freeze dryer (TSFD-3KG) was employed to dry samples. The self-aggregation experiments were performed using the digital tensiometer DST 30. The temperature was controlled within ±0.1 °C using a water thermostat. The critical micelle concentration of each synthesized surfactant was determined from the breakpoint in the surface tension-concentration plot. Melting points were determined on Gallenkamp Melting Point Apparatus. ADMET-SAR profiles were generated using admetSAR v.1.0 [31].

## RESULT AND DISCUSSION

### *Characterization of Cetrimonium Surfactants*

The FT-IR spectrum of cetrimonium naproxenate (CN) is provided in Figure 2. When compared with that of pure naproxen [32], the peak representing of C=O of the carboxylic acid group of naproxen was shifted from 1729 $cm^{-1}$ to 1682 $cm^{-1}$ in CN, showing assocation between $-COO^-$ of drug with tetralkylammonium cation of the surfactant [33]. The frequencies in the range 1461-1480 $cm^{-1}$ are due to $C-N^+$ stretching vibrations [34]. The other peaks in the region 1025-1075 $cm^{-1}$ were representative of Ar-O-R bond stretch. The peaks around 2847-2974 $cm^{-1}$ are characteristic peaks of C-H vibrations of hydrocarbon chain [34].

In the FT-IR spectrum of cetrimonium ibuprofenate (CI) (Figure 3), the frequency due to stretching vibrations of C=O localized at 1703 $cm^{-1}$ was originally present at 1721$cm^{-1}$ in pure ibuprofen [35]. This shift reveals assocation between $-COO^-$ of drug with tetralkylammonium cation of the surfactant [33]. The peaks around 2847-2974 $cm^{-1}$ are characteristic peaks of C-H vibrations of hydrocarbon chain. The peak at 1461 $cm^{-1}$ is attributed to $C-N^+$ stretching vibrations of ammonium ion [34].

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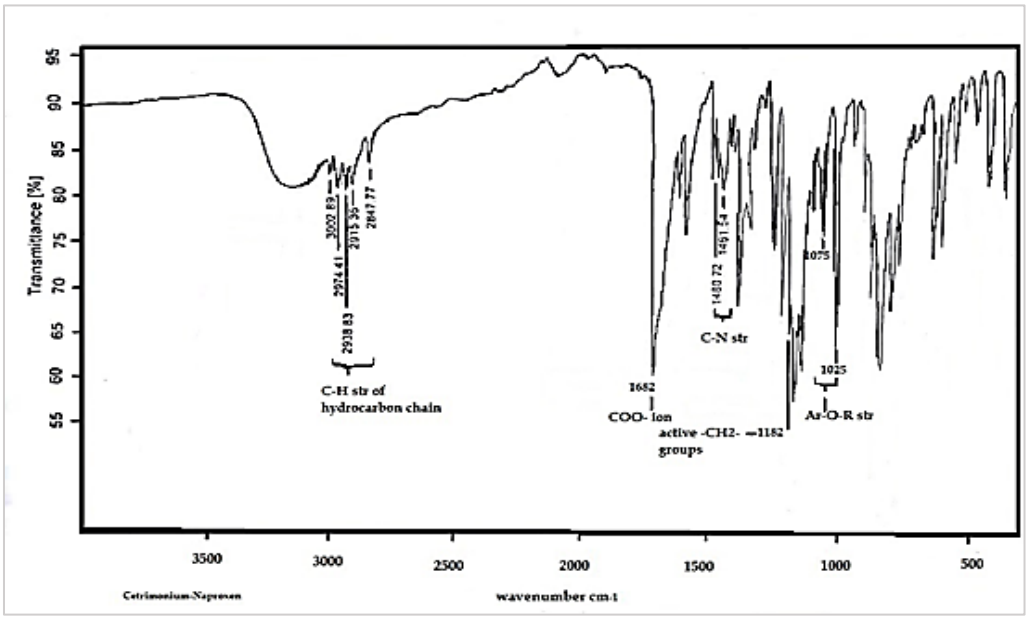


**Figure 2:** FT-IR spectrum of cetrimonium naproxenate (CN)

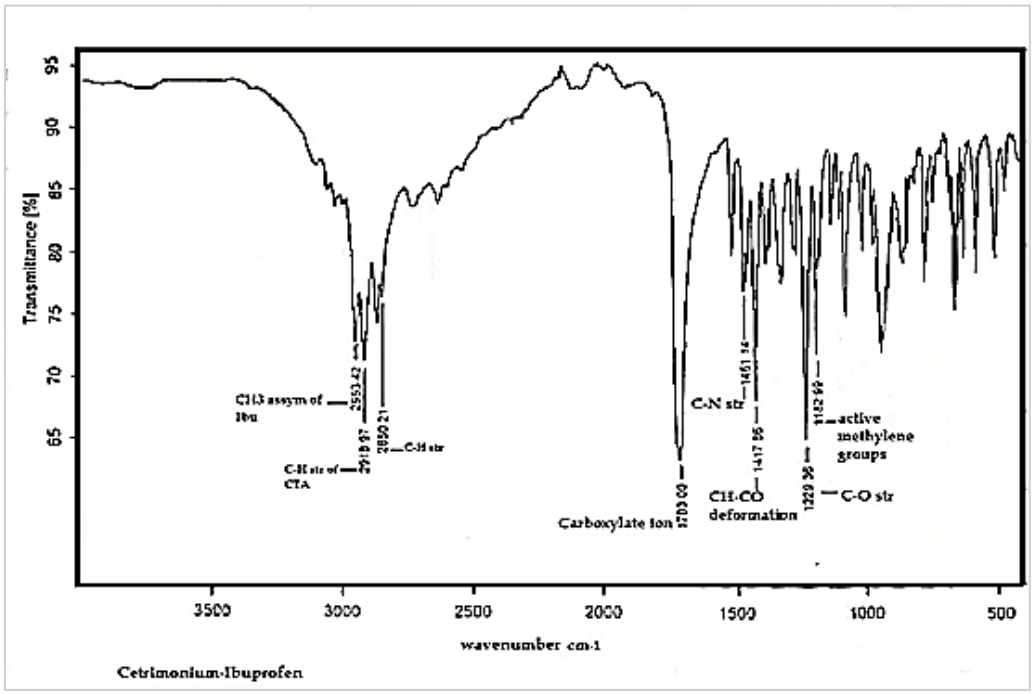


**Figure 3:** FT-IR spectrum of cetrimonium ibuprofenate (CI)

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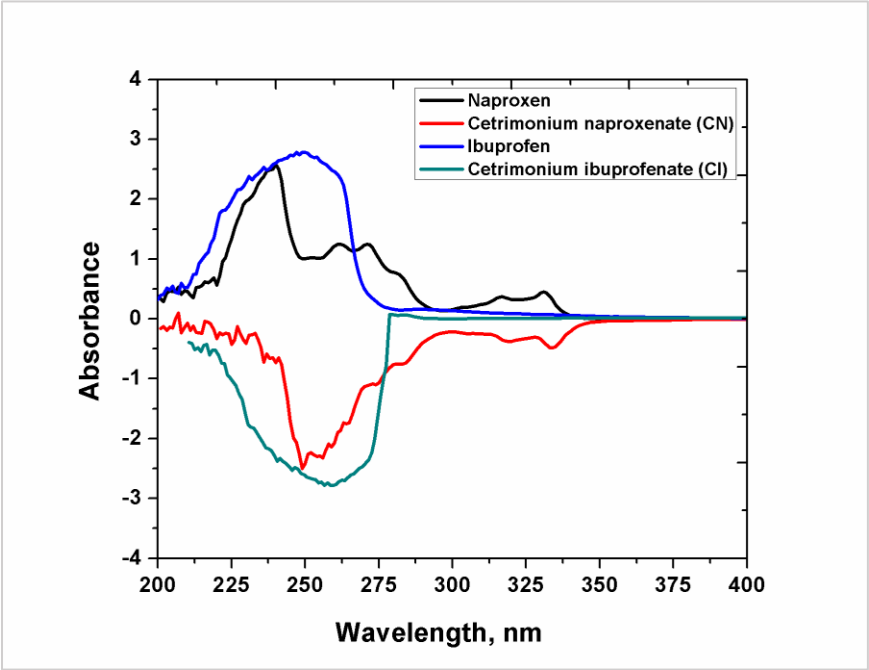


**Figure 4:** Electronic absorption spectra of pure drugs (naproxen and ibuprofen), and differential electronic spectra of corresponding cetrimonium surfactants (CN and IN)

Further characterization of the synthesized surfactants was done through differential electronic absorption spectroscopy. A complete inversion of the spectrum was observed in case of cetrimonium drugs (Figure 4), clearly indicating that in surfactants, the drug molecules exist in the bound state. The $\lambda_{max}$ value of pure naproxen is 240 nm, but other peaks were also seen in the higher wavelength region. These peaks appear at wavelengths of 262 nm, 271 nm, and 331 nm. These additional absorptions may arise due to possibility of self-association [36]. In the difference spectrum (i.e., the one with negative absorbance) the $\lambda_{max}$ is shifted to 248 nm. The peak that appeared at 331 nm in the UV-spectrum of pure naproxen suffered a red shift of 3 nm in CN. These red shifts are indicative of the presence of drug as anion and show the existence of more than one complexation modes between drug and tetraalkylammonium cation [37].

The $\lambda_{max}$ value of ibuprofen is 250 nm, which is shifted to 259 nm in the difference spectrum recorded for CI. This $\Delta\lambda$ (= 9 nm) reflects the presence of ibuprofen as anion, which absorbs at lower frequency compared to corresponding drug molecule in the neutral state. Here, no new peaks are emerged that shows only one complexation mode of drug anion with surfactant [37,38].

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### *Physicochemical Properties and ADMET-SAR Predictions*

The physicochemical properties of CN and CI are provided in Table 1. The melting point of surfactants was lower than that of CTAB, showing the absence of compactness due to drug counterion. The drug counterions do not allow the close packing of alkyl chains of the surfactant, and consequently, lattice energy is reduced [39]. Both surfactants showed high lipophilicity, as revealed from their significantly high positive logP values.

There are at least three stages involved in the biophysical and biochemical transformation of drugs: (1) pharmaceutical that relates to form and release of the drug; (2) pharmacokinetic that involves the transport of drug; and (3) pharmacodynamic stage during which an interaction takes place between drug and receptor. The pharmacokinetics of drugs depends on lipophilicity as it reflects the permeability of drugs across biological barriers such as cell membranes related to their action and fate in the human body [40]. Drugs with high lipophilicity undergo clearance through metabolites, whereas drugs with low lipophilicity experience renal clearance. The bromide replacement by hydrophobic drug anions also reduced the water solubility in the synthesized surfactants as negative values of logS were exhibited by CN and CI.

**Table 1:** Physicochemical properties of cetrimonium surfactants (CN, CI)

| Property | Cetrimonium naproxenate (CN) | Cetrimonium ibuprofenate (CI) |
|---|---|---|
| Melting point (°C) | 160-161 | 82-84 |
| AlogP (lipophilicity) | 9.21 | 9.25 |
| logS (water solubility) | -4.101 | -2.908 |
| CMC (critical micelle concentration)[a] | 0.78 mM | 0.71 mM |

[a] in aqueous dimethyl sulfoxide

Table 2 shows the ADME properties obtained for pure drugs and corresponding cetrimonium surfactants using admetSAR v. 1.0 [31]. The subcellular localization of original drugs (i.e., mitochondria) is not altered in CN and CI. Subcellular localization of molecules is related to their activity and function [41]. Most of the properties of original drugs are retained in their cetrimonium derivatives. However, some important differences must be highlighted. First, the human intestinal absorption (HIA) is compromised in CN and CI, but the absorption through intestinal epithelial and blood-brain barriers remains possible. There are several ways a drug molecule is transported from the intestinal tract to the blood circulation. It could diffuse passively under the mere effect of concentration gradient or aided by carriers such as P-glycoprotein (i.e., the efflux process) in intestinal permeation [42].

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**Table 2:** ADMET-SAR predictions (classification) for pure drugs and corresponding cetrimonium surfactants (CN, CI)

| Model | Naproxen | Cet. nap (CN) | Ibuprofen | Cet. ibu (CI) |
|---|---|---|---|---|
| **Absorption** | | | | |
| Blood-Brain Barrier | BBB+ | BBB+ | BBB+ | BBB+ |
| Human Intestinal Absorption | HIA+ | HIA- | HIA+ | HIA- |
| Caco-2 Permeability | Caco2+ | Caco2+ | Caco2+ | Caco2+ |
| P-glycoprotein Substrate | Non-substrate | Substrate | Non-substrate | Substrate |
| P-glycoprotein Inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |
| OATP2B1 inhibitor | Non-inhibitor | Inhibitor | Non-inhibitor | Non-inhibitor |
| Renal Organic Cation Transporter | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |
| **Distribution** | | | | |
| Subcellular localization | Mitochondria | Mitochondria | Mitochondria | Mitochondria |
| **Metabolism** | | | | |
| CYP450 2C9 Substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate |
| CYP450 2D6 Substrate | Non-substrate | Non-substrate | Non-substrate | Non-substrate |
| CYP450 3A4 Substrate | Non-substrate | Substrate | Non-substrate | Substrate |
| CYP450 1A2 Inhibitor | Inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |
| CYP450 2C9 Inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |
| CYP450 2D6 Inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |
| CYP450 2C19 Inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |
| CYP450 3A4 Inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor | Non-inhibitor |
| CYP Inhibitory Promiscuity | Low CYP Inhibitory Promiscuity | Low CYP Inhibitory Promiscuity | Low CYP Inhibitory Promiscuity | Low CYP Inhibitory Promiscuity |
| **Toxicity** | | | | |
| Human Ether-a-go-go-Related Gene Inhibition | Weak inhibitor | Weak inhibitor | Weak inhibitor | Weak inhibitor |
| AMES Toxicity | AMES toxic | Non AMES toxic | Non AMES toxic | Non AMES toxic |
| Carcinogens | Non-carcinogens | Non-carcinogens | Carcinogens | Non-carcinogens |
| Fish Toxicity | High FHMT | High FHMT | High FHMT | High FHMT |
| Tetrahymena Pyriformis Toxicity | High TPT | High TPT | High TPT | High TPT |
| Honeybee Toxicity | High HBT | High HBT | High HBT | Low HBT |
| Biodegradation | Not readily biodegradable | Not readily biodegradable | Readily biodegradable | Readily biodegradable |
| Acute Oral Toxicity | II | III | III | III |

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In contrast to original drugs, which are non-substrates, their corresponding cetrimonium adducts are expected to act as substrates for P-glycoprotein. Their impaired HIA also endorses this. Cetrimonium naproxenate (CN) inhibits OATP2B1, which is an organic anion uptake transporter. Naproxen is an inhibitor of CYP450 1A2, an enzyme from cytochrome proteins involved in the metabolism of xenobiotics. However, CN does not inhibit the respective enzyme. Instead, the metabolism of CN and CI involves CYP450 3A4, an enzyme found in the liver and intestine that is responsible for the oxidation of small foreign molecules. Hence, clearance of CN and CI is expected to occur through different pathways from those of original drugs. Another significant change in property is the absence of DNA mutagenesis potential in CN.

The original drug naproxen possesses AMES toxicity, whereas CN appears to be non-toxic in the AMES test. So, CN and CI can be considered much safer than the original drugs. Similarly, ibuprofen is carcinogenic, but the corresponding surfactant is non-carcinogenic. The naproxen belongs to class II, whereas cetrimonium naproxenate belongs to class III in terms of actual oral toxicity, unravelling that the latter is safer than the original drug. In addition, CI has much lower honeybee toxicity than pure ibuprofen.

**Table 3:** ADMET-SAR predictions (regression) for pure drugs and corresponding cetrimonium surfactants (CN, CI)

| Model | Naproxen | Cet. nap (CN) | Ibuprofen | Cet. ibu (CI) |
|---|---|---|---|---|
| **Absorption** | | | | |
| Aqueous solubility | -4.0976 | -4.4007 | -3.9041 | -2.9081 |
| Caco-2 Permeability ($LogP_{app}$, cm/s) | 1.2775 | 0.9659 | 1.7486 | 1.0980 |
| **Toxicity** | | | | |
| Rat Acute Toxicity (LD50, mol/kg) | 2.4579 | 2.6724 | 2.3092 | 2.5977 |
| Fish Toxicity (pLC50, mg/L) | 0.8696 | 0.6704 | 1.3122 | 1.5133 |
| Tetrahymena Pyriformis Toxicity (pIGC50, ug/L) | 1.3533 | 1.4742 | 1.3858 | 0.9653 |

The regression allows the quantification of absorption and toxicity profiles, and the results are gathered in Table 3. The Caco-2 permeability was reduced in the surfactant bound drugs in both cases. The movement across Caco-2 cell monolayers relates to intestinal absorption. Thus, reduction in Caco-2 permeability reflects the compromised intestinal absorption of the drug [43]. The aqueous solubility was slightly altered in the case of naproxen, but the marked change was observed for ibuprofen. Nearly comparable results were obtained for acute rat toxicity. The fish

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toxicity of naproxen was reduced in CN, and Tetrahymena Pyriformis toxicity of ibuprofen was reduced upon conversion to CI.

### *Self-immolation Behaviour of Cetrimonium Drugs Triggered by pH*

The effect of pH on the self-immolation behaviour of CN and CI was recorded in aqueous dimethyl sulfoxide due to the low solubility of surfactants in water. The differential electronic spectra of CN at different pH values are shown in Figure 5(a and b). The absorbance at wavelengths 249 nm and 332 nm, which represent surfactant associated naproxen, either diminished or positive absorbance was regained at non-neutral pH values indicating the dissociation of drug counterions from surfactant cation (Figure 4a).

A bathochromic shift of about 7 nm is also observed for a peak at 332 nm at pH > 8. Hence, any shift from neutral pH would trigger the release of a drug. A small alteration in spectral patterns originating from a change in pH is significant as electronic spectra of pure naproxen are nearly pH-independent [44]. Besides, the stabilization of large anions is markedly reduced in dimethyl sulfoxide, simply because it cannot act as a hydrogen donor [45]. DMSO competes as a proton acceptor because its *O*-protonated form is 37 kcal mol-1 more stable than the corresponding neutral form [46]. Again, in Figure 4b representing ibuprofenate (CI), the peak representing the CTA+ bound drug localized at wavelength 269 nm is diminished with the emergence of new peaks at wavelengths 203 nm and 340 nm at pH < 7, reflecting the detached drug. At pH > 7, the peak at 340 nm is seen, showing the absence of a protonated form of drug and free drug anions in solution.

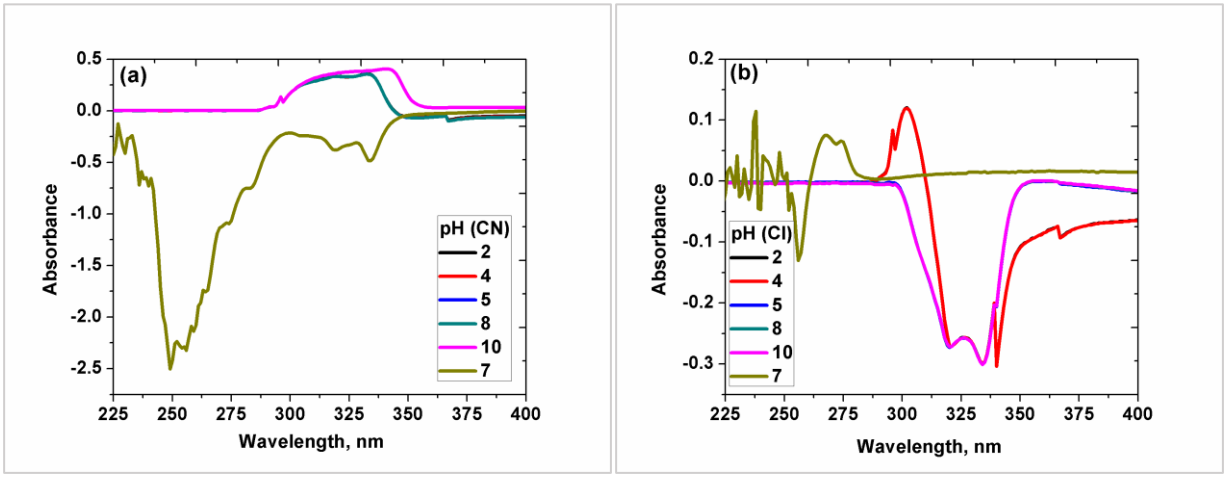


**Figure 5:** (a) Effect of pH on differential electronic spectra of CN; and (b) Effect of pH on differential electronic spectra of CI

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## CONCLUSION

NSAIDs, naproxen and ibuprofen, were successfully converted to cetrimonium surfactants bearing drug anions. FT-IR and differential electronic absorption patterns showed the presence of surfactant bound drugs. The bound drugs were metabolized through a different pathway than the free drug molecules. ADME profiles revealed the absence of carcinogenicity and DNA mutagenesis in pure drugs. However, the aqueous solubility was reduced due to the replacement of bromide ion in CTAB by hydrophobic drug anions. It was also identified that change in pH could trigger the self-immolation of cetrimonium surfactants and hence they could act as a drug delivery system.

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## AUTHOR'S CONTRIBUTION

Sabat Yousaf carried out the research. Syed Waqar Hussain Shah and Iram Bibi wrote and revised the article. Syed Waqar Hussain Shah and Iram Bibi designed the research and supervised research progress. All authors collectively approved the article submission.

## CONFLICT OF INTEREST STATEMENT

The authors agree that this research was conducted in the absence of any self-benefits, commercial or financial conflicts and declare absence of conflicting interests with the funders.

## REFERENCES

[1] Scales, C. (2021) Know your NSAIDs. *The Veterinary Nurse*. 12 (4), 193–199. https://doi.org/10.12968/vetn.2021.12.4.193

[2] Kaduševičius, E. (2021). Novel Applications of NSAIDs: Insight and Future Perspectives in Cardiovascular, Neurodegenerative, Diabetes and Cancer Disease Therapy. *International Journal of Molecular Sciences*, *22*(12), 6637. https://doi.org/10.3390/ijms22126637

[3] Díaz- González, F., & Sánchez- Madrid, F. (2015). NSAIDs: learning new tricks from old drugs. *European Journal of Immunology*, *45*(3), 679-686. https://doi.org/10.1002/eji.201445222

[4] Selinsky, B. S., Gupta, K., Sharkey, C. T., & Loll, P. J. (2001). Structural analysis of NSAID

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Vol. 16(1) JANUARY 2022

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DOI: 10.24191/sl.v16i1.14547

binding by prostaglandin H2 synthase: time-dependent and time-independent inhibitors elicit identical enzyme conformations. *Biochemistry*, *40*(17), 5172-5180. https://doi.org/10.1021/bi010045s

[5] Duggan, K. C., Walters, M. J., Musee, J., Harp, J. M., Kiefer, J. R., Oates, J. A., & Marnett, L. J. (2010). Molecular basis for cyclooxygenase inhibition by the non-steroidal anti-inflammatory drug naproxen. *Journal of Biological Chemistry*, *285*(45), 34950-34959. https://doi.org/10.1074/jbc.M110.162982

[6] McCullough, H. N. (1998). Acetaminophen and ibuprofen in the management of fever and mild to moderate pain in children. *Paediatrics & Child Health*, *3*(4), 246-250. https://doi.org/10.1093/pch/3.4.246

[7] Davies, N.M. (1998). Clinical pharmacokinetics of ibuprofen. The first 30 years. *Clinical Pharmacokinetics*. 34 (2), 101–154. https://doi.org/10.2165/00003088-199834020-00002

[8] Pardutz, A., & Schoenen, J. (2010). NSAIDs in the acute treatment of migraine: a review of clinical and experimental data. *Pharmaceuticals*, *3*(6), 1966-1987. https://doi.org/10.3390/ph3061966

[9] Gøtzsche, P. C. (1989). Methodology and overt and hidden bias in reports of 196 double-blind trials of nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Controlled clinical trials*, *10*(1), 31-56. https://doi.org/10.1016/0197-2456(89)90017-2

[10] Davenport, K., & Waine, E. (2010). The role of non-steroidal anti-inflammatory drugs in renal colic. *Pharmaceuticals*, *3*(5), 1304-1310. https://doi.org/10.3390/ph3051304

[11] Pelletier, J. P., Martel-Pelletier, J., Rannou, F., & Cooper, C. (2016, February). Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: Evidence from real-life setting trials and surveys. In *Seminars in Arthritis and Rheumatism* (Vol. 45, No. 4, pp. S22-S27). WB Saunders. https://doi.org/10.1016/j.semarthrit.2015.11.009

[12] Su, B., & O'Connor, J. P. (2013). NSAID therapy effects on healing of bone, tendon, and the enthesis. *Journal of Applied Physiology*, *115*(6), 892-899. https://doi.org/10.1152/japplphysiol.00053.2013

[13] Warden, S. J. (2010). Prophylactic use of NSAIDs by athletes: a risk/benefit assessment. *The Physician and Sportsmedicine*, *38*(1), 132-138. https://doi.org/10.3810/psm.2010.04.1770

[14] Nurkovic, J., Jovasevic, L., Konicanin, A., Bajin, Z., Ilic, K. P., Grbovic, V., Skevin, A.J., & Dolicanin, Z. (2016). Treatment of trochanteric bursitis: our experience. *Journal of physical therapy science*, *28*(7), 2078-2081. https://doi.org/10.1589/jpts.28.2078

[15] Burns, C. M., & Wortmann, R. L. (2012). Latest evidence on gout management: what the clinician needs to know. *Therapeutic Advances in Chronic Disease*, *3*(6), 271-286. https://doi.org/10.1177%2F2040622312462056

[16] Klas, J., Kluz, N., & Piwowar, K. (2021). NSAIDs and PPIs-review of new reports. *Journal of Education, Health and Sport*, *11*(9), 462-472. https://doi.org/10.12775/JEHS.2021.11.09.060

[17] Miranda, G. M., Bessa, J. R., Teles, Y. C., Yahouédéhou, S. C. M. A., Goncalves, M. S., & Ribeiro-Filho, J. (2021). Inclusion complexes of non-steroidal anti-inflammatory drugs with

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DOI: 10.24191/sl.v16i1.14547

cyclodextrins: a systematic review. *Biomolecules*, *11*(3), 361. https://doi.org/10.3390/biom11030361

[18] Gliszczyńska, A., & Sánchez-López, E. (2021). Dexibuprofen Therapeutic Advances: Prodrugs and Nanotechnological Formulations. *Pharmaceutics*, *13*(3), 414. https://doi.org/10.3390/pharmaceutics13030414

[19] Auriemma, G., Cerciello, A., & Aquino, R. P. (2017). NSAIDS: design and development of innovative oral delivery systems. *Nonsteroidal Anti-Inflammatory Drugs*, *33*.

[20] Haley, R. M., & von Recum, H. A. (2019). Localized and targeted delivery of NSAIDs for treatment of inflammation: A review. *Experimental Biology and Medicine*, *244*(6), 433-444. https://doi.org/10.1177%2F1535370218787770

[21] Menagen, B., Pedahzur, R., & Avnir, D. (2017). Sustained release from a metal-Analgesics entrapped within biocidal silver. *Scientific Reports*, *7*(1), 1-11. https://doi.org/10.1038/s41598-017-03195-w

[22] Wen, H., Jung, H., & Li, X. (2015). Drug delivery approaches in addressing clinical pharmacology-related issues: opportunities and challenges. *The AAPS journal*, *17*(6), 1327-1340. https://doi.org/10.1208/s12248-015-9814-9

[23] Moshikur, R. M., & Goto, M. (2021). Ionic Liquids as Active Pharmaceutical Ingredients (APIs). In *Application of Ionic Liquids in Drug Delivery* (pp. 13-33). Springer, Singapore. https://doi.org/10.1007/978-981-16-4365-1_2

[24] Xiao, Y., Tan, X., Li, Z., & Zhang, K. (2020). Self-immolative polymers in biomedicine. *Journal of Materials Chemistry B*, *8*(31), 6697-6709. https://doi.org/10.1039/D0TB01119C

[25] Yardley, R. E., Kenaree, A. R., & Gillies, E. R. (2019). Triggering depolymerization: Progress and opportunities for self-immolative polymers. *Macromolecules*, *52*(17), 6342-6360. https://doi.org/10.1021/acs.macromol.9b00965

[26] Leila, B., Zahia, Z., Mustapha, H., & Abdellatif, B. (2014). Determination of selected cetyltrimethylammonium halide parameters by molecular modeling. Study of their adsorption on montmorillonite. *Journal of Cheminformatics*, *6*(1), 1-1. https://doi.org/10.1186/1758-2946-6-S1-P1

[27] Ameer, A.A., Ibrahim, F.M., Ameer, A.A., & Yousif, E.A. (2014). Synthesis , Characterization and Spectroscopic of Some Transition Metal Complexes With2- ( 6-Methoxynaphthalen-2-Yl ) Propanoic Acid. *International Journal for Research in Pharmacy and Chemistry*. 4 (2), 299–302.

[28] e Silva, I. M. P., de Moraes Profirio, D., de Paiva, R. E. F., Lancellotti, M., Formiga, A. L. B., & Corbi, P. P. (2013). A silver complex with ibuprofen: Synthesis, solid state characterization, DFT calculations and antibacterial assays. *Journal of Molecular Structure*, *1049*, 1-6. https://doi.org/10.1016/j.molstruc.2013.06.034

[29] Hasan, M.S., & Das, N. (2017). A detailed in vitro study of naproxen metal complexes in quest of new therapeutic possibilities . *Alexandria Journal of Medicine*. 53 (2), 157–165. https://doi.org/10.1016/j.ajme.2016.06.003

[30] Liu, X.H., Luo, X.H., Lu, S.X., Zhang, J.C., & Cao, W.L. (2007). A novel cetyltrimethyl ammonium silver bromide complex and silver bromide nanoparticles obtained by the

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Vol. 16(1) JANUARY 2022

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DOI: 10.24191/sl.v16i1.14547

surfactant counterion. *Journal of Colloid and Interface Science*. 307 (1), 94–100. https://doi.org/10.1016/j.jcis.2006.11.051

[31] Shen, J., Cheng, F., Xu, Y., Li, W., & Tang, Y. (2010). Estimation of ADME properties with substructure pattern recognition. *Journal of Chemical Information and Modeling*. 50 (6), 1034–1041. https://doi.org/10.1021/ci100104j

[32] Akbari, J., Saeedi, M., Morteza-Semnani, K., Rostamkalaei, S. S., Asadi, M., Asare-Addo, K., & Nokhodchi, A. (2016). The design of naproxen solid lipid nanoparticles to target skin layers. *Colloids and Surfaces B: Biointerfaces*, *145*, 626-633. https://doi.org/10.1016/j.colsurfb.2016.05.064

[33] Parohaa, S., Dubeyb, R.D., & Mallick, S. (2014). Interaction Of Naproxen with Calcium Carbonate: Physicochemical Characterization and In Vitro Drug Release Studies. *Química Nova*. 37 (1), 81–84. https://doi.org/10.1590/S0100-40422014000100015

[34] Orendorff, C.J., Alam, T.M., Sasaki, D.Y., Bunker, B.C., & Voigt, J.A. (2009). Phospholipid-Gold Nanorod Composites. *ACS Nano*. 3 (4), 971–983. https://doi.org/10.1021/nn900037k

[35] Dasgupta, S. (2017, August). Controlled release of ibuprofen using Mg Al LDH nano carrier. In *IOP Conference Series: Materials Science and Engineering* (Vol. 225, No. 1, p. 012005). IOP Publishing. https://doi.org/10.1088/1757-899X/225/1/012005

[36] Magnusdottir, A., Másson, M., & Loftsson, T. (2002). Self association and cyclodextrin solubilization of NSAIDs. *Journal of inclusion phenomena and macrocyclic chemistry*, *44*(1), 213-218. https://doi.org/10.1023/A:1023079322024

[37] Nachari, Y., & Jabbari, M. (2021). Understanding the Effect of Differently Charged Surfactants on the Protolytic Equilibria of the Drug Naproxen in Micellar Solution. *Journal of Chemical & Engineering Data*, *66*(5), 2096-2104. https://doi.org/10.1021/acs.jced.1c00027

[38] Banti, C.N., Giannoulis, A.D., Kourkoumelis, N., Owczarzak, A.M., Kubicki, M., & Hadjikakou, S.K. (2014). Novel metallo-therapeutics of the NSAID naproxen. Interaction with intracellular components that leads the cells to apoptosis. *Dalton Transactions*. 43 (18), 6848–6863. https://doi.org/10.1039/C3DT53175A

[39] Gamboa, A., Schüßler, N., Soto-Bustamante, E., Romero-Hasler, P., Meinel, L., & Morales, J.O. (2020). Delivery of ionizable hydrophilic drugs based on pharmaceutical formulation of ion pairs and ionic liquids. *European Journal of Pharmaceutics and Biopharmaceutics*. 156 (August), 203–218. https://doi.org/10.1016/j.ejpb.2020.09.007

[40] Czyrski, A. (2019) Determination of the Lipophilicity of Ibuprofen, Naproxen, Ketoprofen, and Flurbiprofen with Thin-Layer Chromatography. *Journal of Chemistry*. 2019. https://doi.org/10.1155/2019/3407091

[41] Rovira-Clavé, X., Jiang, S., Bai, Y., Zhu, B., Barlow, G., Bhate, S., Coskun, A.F., Han, G., Chin-Min, K.h., Hitzman, C., Shin-Yu, C., Bava, F-A.,& Nolan, G. P. (2021). Subcellular localization of biomolecules and drug distribution by high-definition ion beam imaging. *Nature Communications*, *12*(1), 1-18. https://doi.org/10.1038/s41467-021-24822-1

[42] Varma, M.V.S., Sateesh, K., & Panchagnula, R. (2005). Functional role of P-glycoprotein

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Vol. 16(1) JANUARY 2022

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eISSN: 2682-8626
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DOI: 10.24191/sl.v16i1.14547

in limiting intestinal absorption of drugs: Contribution of passive permeability to P-glycoprotein mediated efflux transport. *Molecular Pharmaceutics*. 2 (1), 12–21. https://doi.org/10.1021/mp0499196

[43] Ross, A. M., Walsh, D. R., Cahalane, R. M., Marcar, L., & Mulvihill, J. J. (2021). The effect of serum starvation on tight junctional proteins and barrier formation in Caco-2 cells. *Biochemistry and Biophysics Reports*, *27*, 101096. https://doi.org/10.1016/j.bbrep.2021.101096

[44] Kumar, L., Suhas, B. S., Pai, G., & Verma, R. (2015). Determination of saturated solubility of naproxen using UV visible spectrophotometer. *Research Journal of Pharmacy and Technology*, *8*(7), 825-828. https://doi.org/10.5958/0974-360X.2015.00134.1

[45] Bordwell, F.G. (1988). Equilibrium Acidities in Dimethyl Sulfoxide Solution. *Accounts of Chemical Research*. 21 (12), 456–463. https://doi.org/10.1021/ar00156a004

[46] Rasul, G., Prakash, G.K.S., & Olah, G.A. (2000). Protonated and methylated dimethyl sulfoxide cations and dications. DFT/GIAO-MP2 NMR studies and comparison with experimental data. *Journal of Organic Chemistry*. 65 (25), 8786–8789. https://doi.org/10.1021/jo001366x