International Journal of Advanced Research in Chemical Science
Volume 7, Issue 6, 2020, PP 1-6
ISSN No.: 2349-0403
DOI: https:// doi.org/10.20431/2349-0403.0706001
www.arcjournals.org

Improve the Role of Ibuprofen in the Biological Field: Short Review

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Abstract: *Ibuprofen is an anti-inflammatory medication (NSAID) and it is also a non-steroidal, which might be providing relief from symptoms of inflammation and pain. However, Ibuprofen can cause risks such as stomach pain, heartburn, nausea, vomiting, gas, constipation and diarrhea. In order to decrease the side effect and enhance the role of Ibuprofen, the researcher improves different methods such as metal-Ibuprofen complexes synthesized and developed Ibuprofen-delivery systems.*

Keywords: *Ibuprofen, NSAID, Drug-delivery system.*

1. Introduction

1.1. History of Ibuprofen

Chemically Ibuprofen is (2RS)-1[4-(2-methyl propyl) phenyl] propionic acid (figure 1) [1]. In 1961 Adams and Nicholson filed a patent for the Ibuprofen as analogue of aspirin that might be suitable for long-term use for rheumatoid arthritis [2]. The first clinical trials of Ibuprofen were performed by Dr Tom Chalmers in six patients with rheumatoid arthritis in 1966. From the results which have been reported, Ibuprofen produced enhancement in pressure tolerance (a measure of joint tenderness) with fewer marked enhancement in joint size [3]. It is non-steroidal anti-inflammatory drug (NSAID), which is antipyretic, analgesic which is used in mild to fever [4].

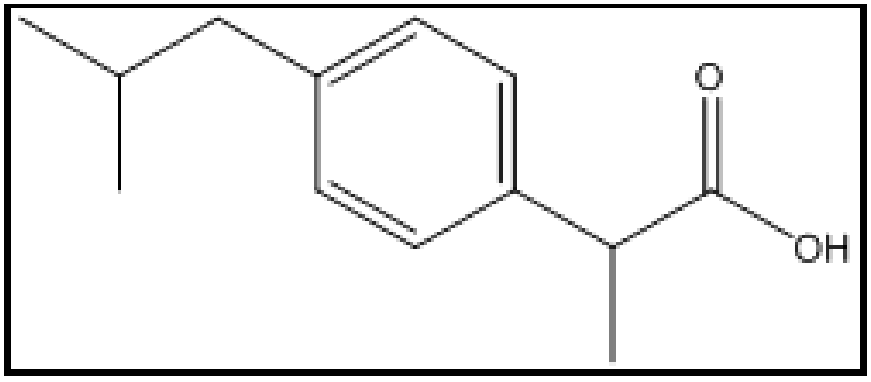

Figure1. *Structure of Ibuprofen*

2. Experimental Work Review

2.1. Synthesis of Ibuprofen

Ibuprofen (5) has been synthesized by reducing compound (1) utilizing sodium borohydride (0.30 g) in methanol as a solvent giving compound (2) 1-(4-isobutylphenyl)ethan-1-ol (2) as shown in Figure 2. It was used separatory funnel to shake compound (2) with HCl to give 1-(1-chloroethyl)-4-isobutylbenzene (3). After that the last compound was converted to compound (4) Grignard reagent using turning magnesium in dry THF. Then 1,2-dibromoethane was added and about one litter of CO_2 was bubbled inside the reaction mixture. The reaction was worked up by extraction and the solvent was evaporated by rotary evaporator to give pure Ibuprofen (5) see Figure 2 [5].

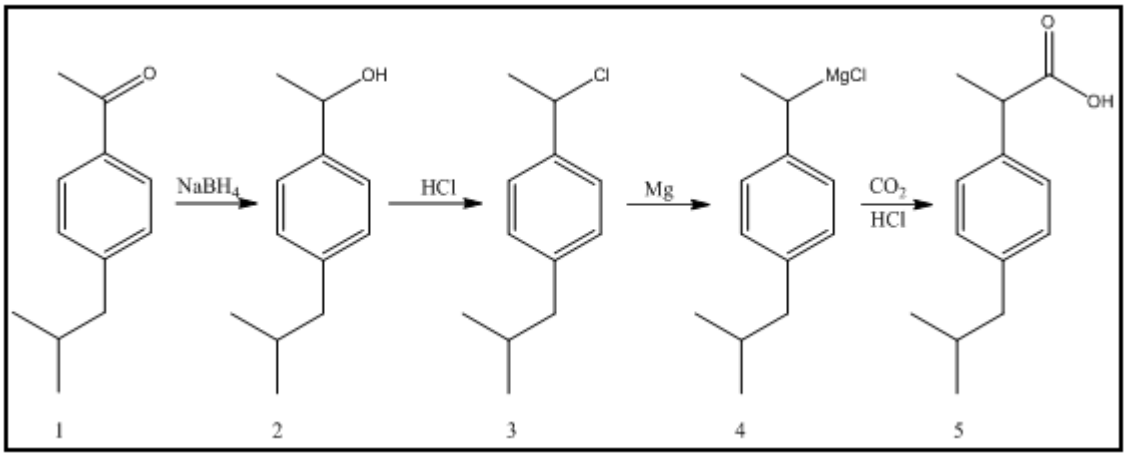

Figure2. *Synthesis of Ibuprofen [5]*

2.2.Characterization of Ibuprofen

Ibuprofen has been characterized by Fourier transform infrared (FTIR) spectroscopy (Figure 3) [6]. The O–H stretching noticed in the 3600–3300 cm^{-1}. The *ν*(C=O) of the carboxylic acid group showed at 1719 cm^{-1}. Several peaks noticed at 1506 cm^{-1} (Ring mode), 1461-1419 cm^{-1} (asymmetry CH_3), 1379-1329 cm^{-1} (symmetry CH_3 isopropyl), 1266 cm^{-1} (phenyl, p-substituted), 1183 cm^{-1} (CH isopropyl) [7].

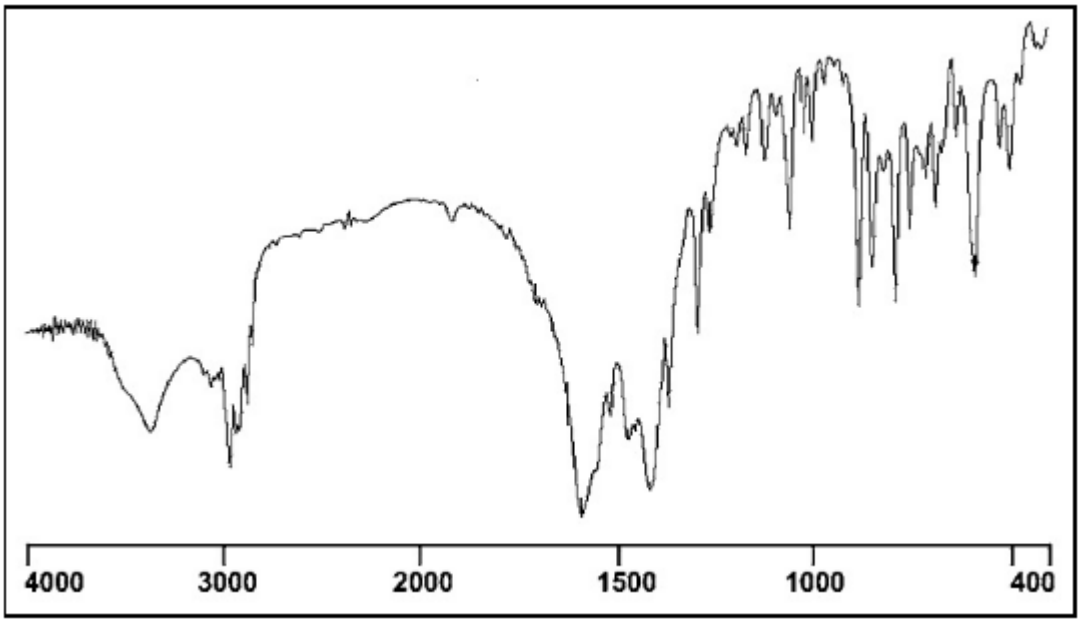

Figure3. *FTIR spectrum of Ibuprofen [6]*

According to nuclear magnetic resonance (^{1}H-NMR) spectroscopy, Ibuprofen characterized and reveals several chemical signals (figure 4) [8]. ^{1}H-NMR spectrum show proton resonance at 3.72 (q, 1H, H-2), 1.5 (d, 3H, H-3), 7.23 (d, 2H, H-5, 5′), 7.11 (d, 2H, H-6, 6′), 2.46 (d, 2H, H-8), 1.85 (m, 1H, H-9), 0.91 (d, 6H, H-10,10′); [9].

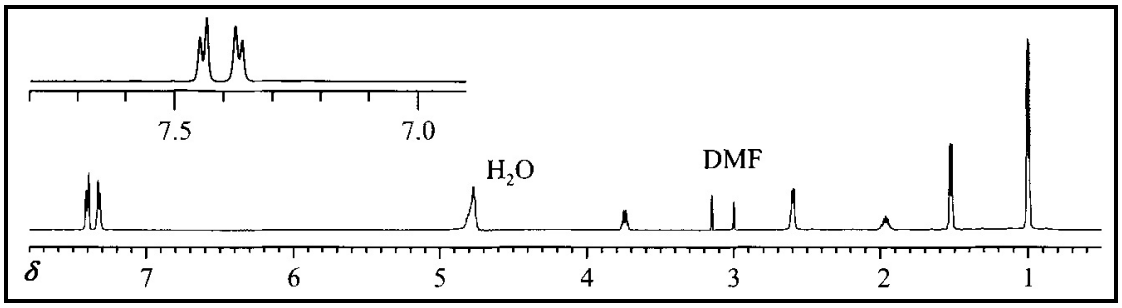

Figure4. *^{1}H-NMR spectrum of Ibuprofen [8]*

It is worth mentioning that Ibuprofen characterized by scanning electron microscopy. Figure 5 show the crystal morphology of Ibuprofen [10].

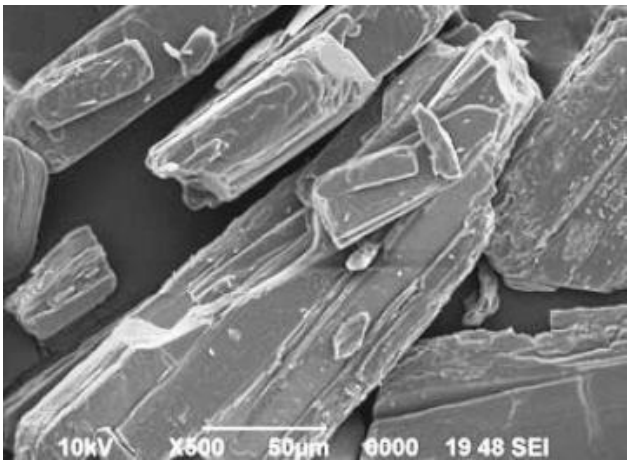

Figure5. *SEM image of Ibuprofen [10]*

2.3. Side Effects of Ibuprofen

Like any drug [11], Ibuprofen can cause risks, such common side effects are [12]:

- stomach pain
- heartburn
- nausea
- vomiting
- gas
- constipation
- diarrhea

3. METAL-IBUPROFEN COMPLEXES USES

Recently, Diphenyltin-, dibutyltin- and tributyltin-Ibuprofen complexes have been synthesized and characterized. Docking study carried out of these complexes and performed the capability of ligand (Ibuprofen) to cooperate within the active site of cyclooxygenases, which significant enzymes of the inflammatory process. Pharmaceutically, might be provide relief from symptoms of inflammation and pain [13]. In another study, Three complexes of Zr(IV)-, Ce(III)- and Th(IV)-Ibuprofen were synthesized and performed their activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Bacillus cereus*, *Aspergillus niger* and *Aspergillus flavus* organisms [14]. While M-Ibuprofen complexes (M= Na^{+}, Ag^{+}, Ca^{2+}, Mg^{2+}, Cu^{2+}, Zn^{2+} and Hg^{2+}) exhibited antibacterial activity against the Gram-positive bacteria (*Staphylococcus aureus* and *Listeria monocytogenes*) (Figure 6) [15,16].

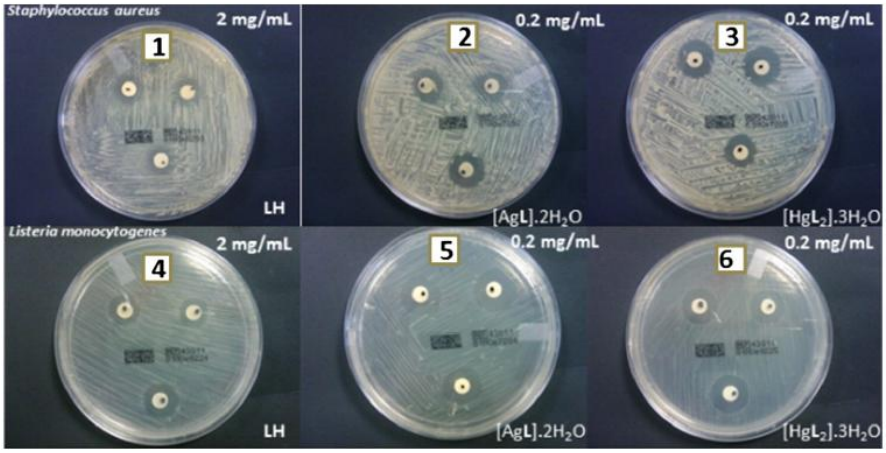

Figure6. *Antibacterial, Ag-Ibuprofen (plots 2 and 5) and Hg-Ibuprofen (plots 3 and 6) complexes [15]*

In the same field of antibacterial and antifungal, M-Ibuprofen complexes (M= Cu(II), Fe(II), Mn(II) and Co(II)) proved their activity *versus Escherichia* Coli (Gram -ve), *Bacillus subtilis* (Gram +ve) and antifungal (tricoderma and penicillium activities) [17]. On other hand, Ni(II)-, Mn(II)- and Pd(II)-Ibuprofen complexes potential evaluated against leishmanicidal [18].

4. IBUPROFEN-DELIVERY SYSTEMS

According to adsorption phenomena, Cu(II)-Ibuprofen complex has been synthesized and immobilized by adsorption on magnesium–aluminum dual hydroxides (Mg_3Al-LDH), in order to simulate the adsorption of the Cu(II)-Ibuprofen complex on an antacid drug transporter may also be an effective substitute to decrease gastric irritation [19]. Furthermore, polymeric Ibuprofen prodrug of was synthesised by chemo-enzymatic procedure with molecular weight reached 2.126×10^4 (figure 7). *In vitro* studies, polymeric prodrug released at pH 7.4 buffered solution at 37 °C and evaluated by HPLC, which used for the qualitative analysis of the released product [20].

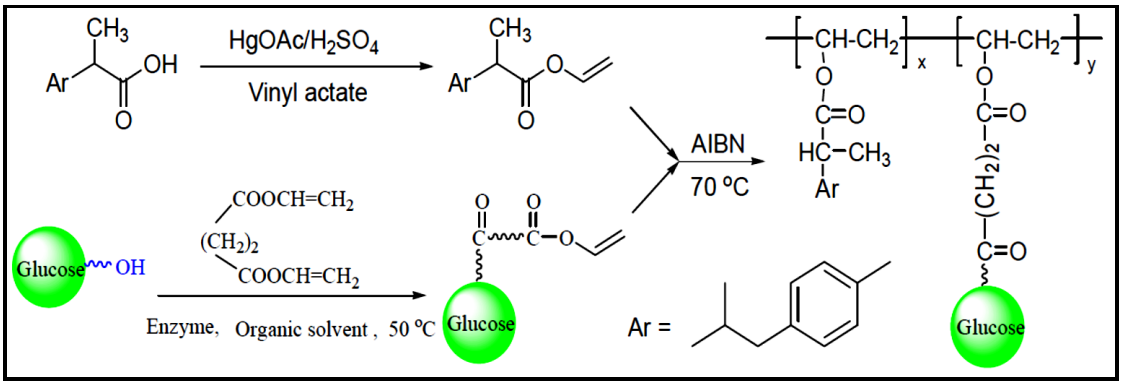

Figure7. *Structure of polymeric prodrug of Ibuprofen*

In recent study, two biocompatible Zinc-MOF-74 and UTSA-74 synthesized for ibuprofen delivery (Figure 8) in presence of phosphate buffer saline (PBS) solution [21]. In a previous study, MOF-74 and UTSA-74 have been prepared [22,23]. Zn MOF-74 was the higher biocompatible MOF for medication transport compare to UTSA-74 according to HPLC measuring.

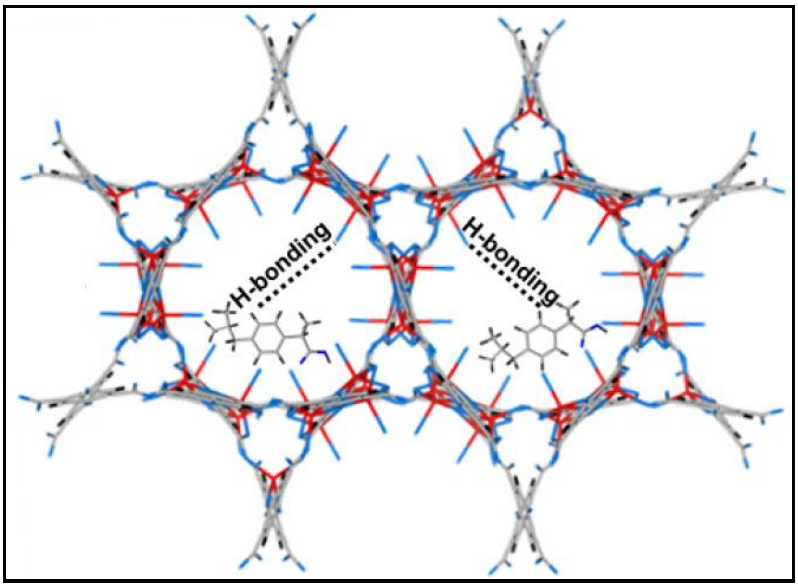

Figure8. *Drug loaded MOF*

Another drug-delivery system for Ibuprofen was Ibuprofen-phosphathidylcholine association (IPA) which induced the medication amorphous nature. That leads to enhance the Ibuprofen solubility in pH 7.2 of phosphate buffer medium [24]. Polydopamine (PDA) coverings functionalized on titanium dioxide nanotube layers (TNTs) were effectively synthesized. TNTs-PDA loaded IBU was applied on MC3T3 cell line. It was demonstrated that the prolonged medication release and Ibuprofen loading were significantly enhanced by the dopamine-modification TNTs. The medication loading improved by the interaction between Ibuprofen and the existence multifunctional groups [25].

5. CONCLUSION

Improving methods were enhanced the role of Ibuprofen in biological field. Where used as relief from symptoms of inflammation, pain, antibacterial and antifungal

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Citation: *Mohammed H. Al-Mashhadani, et.al, "Improve the Role of Ibuprofen in the Biological Field: Short Review", International Journal of Advanced Research in Chemical Science, 7(6), pp. 1-6. DOI: https://doi.org/10.20431/2349-0403.0706001*