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Electrodes for Estimation of Nimesulide Drug using Voltammetry Technique: A Revisit

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Abstract—Nimesulide is a pain-killer and falls in the category of non-steroidal anti-inflammatory drug. It can reduce different types of pain. Nimesulide is a safe drug but uncontrolled use of this medicine creates many problems. So detection and estimation of nimesulide is very important. Electro analytical methods are good choice for detection and estimation. Among them, voltammetry is one of the good method in this twenty-first century. In this review, different electrode materials for voltammetric study have been presented with detection limit.

Keywords: *Nimesulide, electrode, cyclic voltammetry, scan rate, peak potential, nanoparticle.*

INTRODUCTION

Nimesulide is a medicine which lowers the different types of pain, and this drug has wonderful application in the case of osteoarthritis and rheumatoid arthritis. Antipyretic along with analgesic properties make this drug very attractive (Bernareggi 2001). The molecular structure and formula of Nimesulide, N-(4-nitro-2-phenoxyphenyl) methane sulfonamide is shown in figure 1. This is a good example of NSAID (non-steroidal anti-inflammatory drug). Nimesulide inhibits the enzyme cyclo-oxygenase (COX), thereby blocking the generation of prostaglandins. Prostaglandins are important in pain and inflammatory pathways and COX is the key enzyme in the biosynthesis of prostaglandins. Nimesulide is selctive for COX-2 (cyclo-oxygenase-2). Due to free radical scavenger property of the drug, it helps to protect against the tissue damage that occurs during inflammation. Normally nimesulide is safe, but it has also side effects due to over dosage or excess use. Some of them are:

- ***Gastrointestinal:*** Nausea, vomiting, diarrhea, abdominal discomfort, heartburn, abdominal cramps.
- ***Central Nervous-System:*** Dizziness and drowsiness, Headache.
- ***Genitourinary:*** Blood in urine, decrease in urination and kidney failure.

Thus, sensitive determination of nimesulide at trace level is highly recommended (Bukkitgar *et al*. 2016; Maltese *et al*. 2004; Pereira *et al*. 2013).

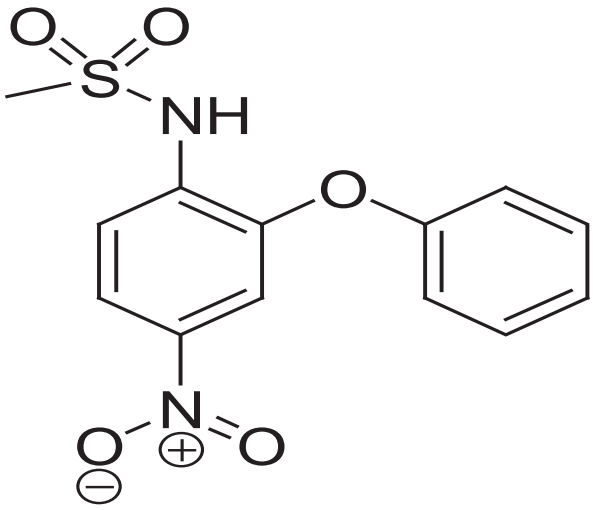

Fig. 1: Nimesulide

It is very exciting that nimesulide was never sold in the USA but has been marketed in many countries without any restriction. In India, it is banned in children below twelve years of age.

TECHNIQUE FOR DETECTION OF NIMESULIDE

Techniques for detection and estimating of nimesulide include chromatography (Maltese *et al.* 2004; Zacharis *et al.* 2009), electrochemical methods (Catarino *et al.* 2003;

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Furlanetto *et al*. 2000; Wang *et al*. 2006; Zhang *et al*. 2010) and spectrometry (Constantinescu *et al*. 2009; Hemmateenejad *et al*. 2008). However, chromatography and spectrometry require time-consuming steps and expensive instruments. Electrochemical methods have been widely applied, and the tremendous progress in electrochemical methods in the field of the analysis of drugs is due to their simplicity, cost-effective, accurate and relatively short analysis time when compared with the other methods (Chatterjee 2017; Farghaly *et al*. 2014). Apart from these, other advantages consist of large temperature window, simultaneous analysis of multiple substances, it offers kinetic and mechanistic properties and it needs very little amount sample volumes, often in the microliter range, various solvents along with electrolytes may be used (Xu *et al*. 2009). Electrochemical techniques serve the pharmaceutical and drug analysis centres since 1960s. Among them voltammetric analysis is the flagship technique (Patriarche *et al*. 1987).

VOLTAMMETRIC METHOD

This method is based on potential given to an electrode and measurement of the resulting current. Potential is the key parameter which controls the electrochemical process occurs in the solution **(**reduction or oxidation) at the electrode. Above current is called diffusion current and is used for the quantitative estimation of different analytes ranging from organic to inorganic materials, biomaterials (Barker 1958; Lawrence *et al*. 2002). Voltammetry provides information about oxidation–reduction behaviour, adsorption process, kinetics of electron transfer processes; thermodynamic properties of solvated species (Hefnawey *et al*. 2004). There are different types of voltammetry techniques. Each technique has some merits over others. Some of them are briefly discussed.

PULSE VOLTAMMETRY

Polarography has been extensively applied for the estimation of many drugs since nineteenth century (Gilpin 1979). Barker and co-workers at Harwell developed the Pulse voltammetry technique (Barker *et al*.1952). It is also called pulse polarography and was originally given for the DME (dropping mercury electrode). The pulse method provides a series of pulses of increasing amplitude. The Square-wave voltammetry (SWV) is a large-amplitude differential technique (Clough 1992; Hamm 1958).

STRIPPING VOLTAMMETRY

Stripping voltammetry method is an extremely sensitive electrochemical technique (Kissinger *et al*. 1996; Wang 1985). There are different categories of stripping voltammetry like anodic stripping voltammetry, cathodic stripping voltammetry, and adsorptive stripping voltammetry etc. Each technique has some advantages and disadvantages. Among different electrochemical techniques, voltammetry methods have been very popular and have made valuable contributions in drug industry. Recent voltammetric methods are sophisticated and easy to handle due to advancement in instrumentation, computer accessories. In voltammetric method, we need an electrode (working electrode) where electrode reaction occurs. Solid or mercury based electrodes act as working electrodes. Solid electrodes have advantages over mercury based electrodes. It is easy to handle, mechanically stable and has large anodic potential window (Uslu *et al*. 2007; Uslu *et al*. 2007; Wang *et al*. 1999).

From Table 1, we see that different kinds of electrodes have been used for nimesulide determination, and Table 2, represents the detection limit and linear range of different electrodes.

Table 1: Electrochemical Techniques and Different Electrodes

Type of Electrodes	Technique	Reference
TiO2 nanoparticles/GCE	DPV (differential pulse voltammetric)	(Bukkitgar *et al*. 2016)
Cysteic acid/MWCNTs	DPV	(Wang *et al*. 2006)
MWCNTs/GCE	Cyclic voltammetry and linear sweep voltammetry	(Zhang *et al*. 2010)
Fe3O4 magnetic nanoparticles/GCE	DPV	(Jin lei *et al*. 2011)
ER-GONRs/SPCE	Voltammetry,amperometry	(Govindasamy *et al*.2017)
MWCNTs/CPE	Voltammetry	(Ağin F *et al*. 2016)
Gold electrode	Cyclic and differential pulse Voltammetry	(Malode *et al*. 2013)
Glassy Carbon Electrode	Voltammtric method and linear sweep voltammtry	(ElSayed *et al*.2009)
Carbon paste electrode	DPV	(Malode *et al*. Z. Phys. Chem 2013)
Silicon carbide nanoparticles/GCE	Voltammetry and Chronoamperometry	(Ghavami *et al*. 2012)

Table 2: Different Electrodes and Detection Limit and Linear Range

Type of Electrode	Limit of Detection	Linear Range/M	Reference
TiO2 nanoparticles/GCE	3.37 nM	$1.0*10^{-7}$ to $4.0*10^{-5}$	(Bukkitgar *et al*. 2016)
Cysteic acid/MWCNTs	50 nM	$1.0 * 10^{-7}$ to $1.0 *10^{-5}$	(Wang *et al*. 2006)
MWCNTs/GCE	160 nM	$3.2*10^{-7}$ to $6.5*10^{-5}$	(Zhang *et al*. 2010)
Fe3O4 magnetic nanoparticles/GCE	130 nM	$2.6*10^{-6}$ to $1.0*10^{-4}$	(Jin lei *et al*. 2011)
ER-GONRs/SPCE	3.5 (+-1.57) nM	$1.0*10^{-8}$ to $1.5*10^{-3}$	(Govindasamy *et al*. 2017)
MWCNTs/CPE	1.07 nM	$6*10^{-8}$ to $1*10^{-5}$	(Ağin F *et al*. 2016)
Gold electrode	1.1 nM	$2.0*10^{-7}$ to $1.2*10^{-6}$	(Malode *et al*. 2013)
Glassy Carbon Electrode	32 nM	$4.0*10^{-7}$ to $5.0*10^{-5}$	(ElSayed *et al*.2009)
Carbon paste electrode	8.6 nM	$0.5*10^{-6}$ to $10*10^{-6}$	(Malode *et al. Z. Phys. Chem* 2013)
Siliconcarbide nanoparticles/GCE	30 nM	$0.09 * 10^{-6}$ to $8.7*10^{-6}$	(Ghavami *et al*. 2012)

MECHANISM OF NIMESULIDE REACTION ON ELECTODES

Redox properties of drugs can be described from electrochemical study. Redox characteristics of drug molecules can provide metabolic destiny of the drug (or their in vivo redox processes or pharmaceutical activity).

Reduction Mechanism

Nimesulide follows nitrite reduction mechanism (scheme1) during electrochemical process (Govindasamy *et al*.2017). Cyclovoltammetric experiments corroborate the following type of mechanism.

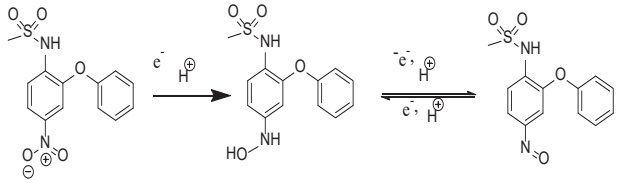

Fig. 2: Nimesulide, Hydroxy Nimesulide, Nitrosonimesulide

Scheme 1. Pathway for the electroreduction of nimesulide onto ER-GONRs/SPCE electrode (Govindasamy *et al*.2017).

Govindasamy *et al*. (Govindasamy *et al*. 2017) found that cathodic peak appears in the forward sweep (- 0.60V vs Ag/AgCl) which was due to irreversible reduction of nitro group to hydroxyl amine. During the reverse sweep and second cycle, reversible redox peaks were found, which indicates redox reactions of hydroxyl amine to nitroso. Thus, the electrocatalytic reduction mechanism of nimesulide follows nitrite reduction pathway as given in Scheme 1.

OXIDATION MECHANISM

According to Malode *et al.* (Malode *et al*. 2013), nimesulide offers one sharp anodic peak in all pH range in their investigation. As per their explanation and reaction mechanism, this is probably due to methyl sulfonamide group oxidation.

Cyclic Voltammetry (CV) study on different electrodes–effect of scan rate, and pH variation:

CV is the most powerful tool for the study of the electrocatalytic activity of drug molecules.

At first, we consider a research paper of Lueje *et al*. (Lueje *et al*. 1997). They used droping mercury electrode as the working electrode and nimesulide in solution showed cathodic response in a range of pH (2-12). This peak corresponds to the nitro group reduction in position 4. Patil *et al*. optimised the experimental parameters using the differential pulse polarography (DPP) for the characterization of Nimesulide (0.1 M NaOH as the supporting electrolyte, scan rate 6mV/sec). The calibration curves for Nimesulide were linear with the limit of detection (LOD) 5.02X 10^{-6} M obtained by the DPP method (Patil *et al*. 2018). Modified electrodes are gaining importance and tremendously applied in pharmaceutical companies. Govindasamy *et al*. (Govindasamy *et al*. 2017) investigated the electrocatalytic behavior of ER-GONRs/SPCE electrode towards reduction of nimesulide by cyclic voltammetry in the potential window, +0.40 V to -0.80V. Their study indicates that the crest current (Ipc or peak current) increases as the rate of scan increases and the corresponding potential (peak potential) is negatively shifted. The electrochemical process is diffusion controlled as the square root of scan rate has linear dependence with peak current (Ipc). Their

study also reveals that electrocatalytic reduction process of nimesulide is chemically irreversible {E_p vs log (scan rate) confirmed chemical irreversibility}. This group (Govindasamy *et al*.2017) also studied the influence of pH on the electroreduction process of nimesulide. With increasing pH of the solution, reduction peak current increases and reaches maximum at pH 7.0, so reaction occurs smoothly at pH 7. Afterwards, the decreasing trend of current is observed. Thus, the electrode is not a good choice at alkaline pH. But on gold electrode surface, the electrochemical responses of nimesulide in 0.2 M phosphate buffer solution with different pH values and at a scan rate of 0.05 Vs^{-1} were studied (Malode *et al*. 2013) and the highest peak current was found at pH 6.5. After proper selection of pH, they varied the scan rates ranging between 10 and 200 mVs^{-1} and peak current versus square root of the scan rate gave a linear relationship. Their observation shows that the electrode reaction is diffusion controlled. The peak potential shifted to positive values with increasing scan rates. Further, calculated value of the number of electron (n) in the electro oxidation of nimesulide was 2. ElSayed *et al*. studied the nimesulide reduction process at GCE with the help of cyclic voltammetry in B-R buffer (Britton-Robinson buffer) of different pH values (ElSayed *et al*.2009) and it was observed that reduction peak at all pH related to the reduction of the nitro group, along with a small anodic peak in the anodic direction appeared. The difference between E_{pc} and E_{pa} was about 640 mV and *I*pa/*I*pc was about 0.18. Thus, the nimesulide reduction onto this electrode is quasi reversible in nature. On increasing the pH of the solution, the cathodic peak potential shifted to more negative potentials indicating the involvement of hydrogen ions in the reduction process and anodic part was nearly vanished on increasing pH. The reduction peak is due to the four-electron reduction of nitro group to the corresponding hydroxylamine (ElSayed *et al*.2009). Again reduction on GCE is adsorption controlled.

Cyclic voltammograms of nimesulide at bare GCE and Fe_3O_4/GCE were compared by Jin lei research group (Jin lei *et al*. 2011). They found a reduction peak at about –0.683 V on the bare GCE and at –0.625 V on Fe_3O_4/GCE electrode at pH 5.0 (acetic acid-sodium acetate). On the backward scan, there was no oxidation peak either on bare GCE or on Fe_3O_4/GCE which confirms that the electrochemical reaction was a totally irreversible process. These magnetic nanoparticles increase the sensitivity towards nimesulide estimation around three times compared to normal electrode. These are due to the high surface area and the electrocatalytic effect of Fe_3O_4 nanoparticles. According to their study nimesulide reaction was an adsorption controlled. Similar findings were observed when nimesulide reduction happened on multiwalled carbon nanotubes (MWCNTs) modified glassy carbon electrode (MWCNTs/GCE) in PBS buffer solution of pH 6.6 and the MWCNTs/GCE showed a good catalytic response to reduction of the nimesulide (Zhang *et al*. 2010). In this case, the sensitivity of the electrode increased around seven times compared to GCE (Zhang *et al*. 2010) whereas sensitivity of the nanoparticle based electrode increased around three times compared to GCE (Jin lei *et al*. 2011). The reduction process on to MWCNTs/GCE electrode at different scan rates confirmed that it is also an adsorption controlled because a linear relation exist between the peak current and the scan rate(scan rate varies between 0.02 to 0.2Vs^{-1}). Glassy carbon modified with Silicon carbide nanoparticles were used for the determination of nimesulide by Ghavami *et al*. (Ghavami *et al*. 2012). Electro reduction was happened at a potential -526 mV (at the bare GCE) and at -387 mV on the modified electrode at pH 2. But surface fouling on unmodified electrodes during voltammetric quantification is a major drawback, and Santos da Silva etal adapted new approach for nimesulide quantification in the anodic region (Santos da Silva *et al*. 2013) and overcome the problem.

CONCLUSION

From the above review, it is seen that nano based electrode materials are good choice for nimesulide detection. Scan rate study showed that with increasing scan rate, peak current increases. pH study reveals that pH of the medium is a vital for detection of the said drug and alkaline regions are not suitable for any kind of electrodes. To detect the trace amount of nimesulide, new electrode to be prepared and it is a big challenge for the scientists.

ABBREVIATIONS

CV-cyclic voltammetry, DPV-differential pulse voltammetry, MWCNTs-Multiwalled carbon nanotubes, ER-GONRS-Electrochemically reduced grapheme oxide nanoribbons, SPCE-Screen printed carbon electrode; GCE-Glassy carbon electrode; CPE-Carbon paste electrode.

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