ION SELECTIVE ELECTRODES IN PHARMACEUTICAL ANALYSIS – A REVIEW

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CONTENTS

ABSTRACT

The applications of Ion-Selective Electrodes (ICE) in pharmaceutical analysis have been described. A compilation for different types of drugs analysed by this method is given in tabular form. The review covers the literature of the last 6 years.

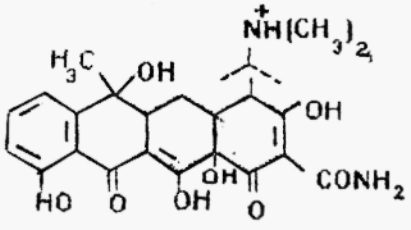
INTRODUCTION

Ion Selective Electrodes are widely used in analytical chemistry and in the fields of clinical, biochemical and environmental analysis. Solid ISE have longer life time compared to liquid ion selective electrodes.

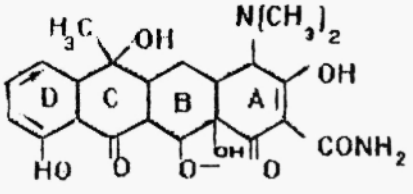
Ion selective electrodes are devices that permit the activity of a given ion in a solution to be determined potentiometrically despite the presence of other ions. A large number of membrane ion selective electrodes have been developed and recommended for the analytical applications /1-8/, and many of them have become commercially available.

The application of the ISE in pharmaceuticals have been summarized in Table 1 /9-33/ Ion selective electrodes for the analysis of the drugs viz. perbutalosulphate, betapresin, novacaine sulphamethoxazole, sulphathiazine, ciprofloxacine, tizanidine, pilocarpine, benzyl pencillin, cloxacillin etc. are summarised in this review. A thiamine ISE has been used for vitamin B_1 which shows least interference by other vitamins. Most of the electrodes reported have been applied for the estimation of the drugs in various pharmaceutical preparations.

Electrodes that are sensitive to both cationic and anionic species of tetracycline have been reported /9/, in which the cation sensitive electrode responds to monoprotoned tetracycline over the range of pH 1.9 - 3.2, the anion sensitive between pH 8 - 11 to the singly charged tetracycline anion resulting from dissociation of the enolic group of the B ring.



Cation



Anion

Tetracycline is widely used in the treatment of a large number of infections, including plague and some disease caused by large viruses, because of its wide spectrum of activity. It is also used in the treatment of staphylococcal and streptococcal infections in pencillin sensitive patients whose tetracycline resistance is not a problem. A solid state tetracycline silicotungstate electrode is reported/10/ , for the potentiometric determination of 0.1 - 4.2 mg/ml tetracycline hydrochloride. Microgram quantities of tetracycline hydrochloride in very small sample volumes (Ca 20-50 μl) can also be determined by using an inverted solid state tetracycline silicotungstate electrode with average recovery 99.4% (standard deviation 1.9%). The potentiometric analysis of tetracycline tablets (each containing a normal amount of 250 mg) with the tetracycline silicotungstate electrode gave a value of 241 $\pm$ 5 mg per tablet. The result by the pharmacopoeial method was 245 mg/tablet.

A cloxacillin electrode is being characterized and applied for penicillins /10/. The response time is 30 sec with advantageous detection limit of $5x10^{-5}$ M and relatively higher selectivity coeffecients for inorganic ions makes it useful for cloxacillin determination. The selectivity coefficients of the cloxacillin electrode for penicillins decrease in the order cloxacillin > benzyl pencillin > ampicillin > amoxicillin and this order can be explained in terms of the change of substituent character in the penicillin side chain. Of the penicillins examined, cloxacillin has the strongest affinity for the ion exchanger owing to the presence of heterocyclic isoxazolyl substituents. Amoxicillin, with amine and hydroxyl groups as substituent, has the lowest affinity for the ion exchanger while the affinity of ampicillin, which has only an amine group as the substituent, is slightly higher. The affinity of benzyl pencillin is only slightly smaller than that of cloxacillin.

Cloxacillin was determined with the electrode in both pure preparation of penicillin and in solutions corresponding to commercial formulations containing cloxacillin and ampicillin. The selectivity was sufficient for determination of cloxacillin in such mixtures. The potentiometric determination of cloxacillin creates new possibilities for application of ISEs. it has been satisfactory used for the determination of cloxacillin in serum, and also used for control of cloxacillin production.

Selective determination of thiamine (vitamin B_1) in pharmaceutical preparations by direct potentiometric titration with use of the silver-silver sulfide ion selective electrode, was described /11/ based on direct titration in alkaline media ($\geq$ 0.5 M) in which a chemical transformation takes place, creating two acidic groups, the protons of which are replacable by silver ions. The potentiometric titration curves display two consecutive potential breaks specific for thiamine. The second break is reproducible and corresponds to a 2:1 reaction ratio of silver to thiamine. No interference was caused by other vitamins, active ingredients and inactive excipients normally present in multivitamin preparations /11/. The results obtained for determination of thiamine in pure powders, pharmaceutical tablets and ampoules showed an average recovery of 98.2% of the values and a mean standard deviation of 0.5%, and agreed fairly well with data obtained by the British Pharmacopoeia (BP) procedure. A serious disadvantage of the BP method is that silicotungstic acid gives sparingly soluble precipitates with organic bases generally used in multivitamin preparations and prior separation of vitamin B_1 is necessary.

A polymeric membrane electrode selective to cholate, based on

benzydimethyl ethyl ammonium cholate was prepared, characterised and applied for the determination of cholic acids in real matrices /12/ and the results were compared with liquid membrane sensor/15/. The experimental results show that quasi-Nernstian slope values, fast responses, linear concentration ranges (of about 1.5 decades), good precision, accuracy and selectivity were obtained. The main advantages of the polymeric membrane are the life of the electrode; a membrane can last several months if the matrices are not particularly complex. The electrode is also very easy to handle its method of assembly avoids the formation of air gaps which sometimes remain on the liquid membrane electrode /15/.

The potentiometric method reported for determination of naproxene /18/ using a naproxinate electrode has the advantage of simplicity and rapidity and it can be used for the direct assay of formulations without any interference from excipients. The electrode which responds to ciprofloxacin ions has been prepared /19/ by coating a silver wire conductor with PVC based film which was applied for evaluation of ciprofloxacin in pure solutions and in Cenin$^{(R)}$ 500 tablets; showing a relative standard deviation of 0.16%.

The electrochemical study of three important β-agonist drugs at modified and Nafion-modified carbon paste electrodes was carried out /25/. All the compounds were oxidized irreversibly at higher positive potentials at a base carbon paste electrode, giving rise to sharp, well defined peaks. A secondary oxidation process was observed at pH values above 6. The rate determining step was investigated for each compound at two concentration levels. Electrochemical oxidation procedures were optimized to ensure reproducible signals for the construction of calibration graphs.

The modification of the carbon paste with a Nafion film allowed a preconcentration process to take place for all compounds, such that higher sensitivities were achieved compared with the base surface. Such modification resulted in limits of detection for the compounds down to 2.5×10^{-8} M. Optimum accumulations was obtained at low pH values (pH 2 -3). Cyclic voltmetry at two Nafion film thickness demonstrated that a diffusion controlled process exists within the Nafion layer. Salbutamol showed a higher affinity for Nafion than the Fenoterol and Metaproterenol.

The compounds are oxidised at high positive potentials on carbon paste electrodes (pH 4.0; Salbutamol, 0.84 V; fenoterol, 0.78 mV; metaproterenol, 0.89 V) giving rise to two processes. Similiar behaviour has been reported for other compounds in this class (clenbuterol and mabuterol) on carbon paste electrodes /26/. The rate controlling step is mainly governed by diffusion, although adsorption processes were observed for salbutamol and metaproterenol in low concentrations, close to the limit of detection of the technique. An ion exchange mechanism between the protonated (positively charged) compounds and the negatively charged Nafion membrane have also been explained and studies were carried out at various pH ranges/26/.

The signal enhancement at low pH values may be explained by the additional partition equilibrium (Donnan equilibrium), which occurs when the Nafion membrane, saturated with protons, remains neutral ($SO_3^-H^+$) and the analyte forms an ion pair with a back ground electrolyte anion. Cyclic voltametric results showed that the oxidation process on Nafion films is diffusion controlled.

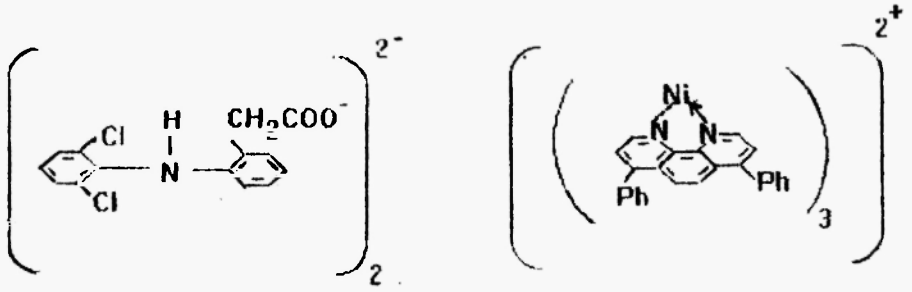
Such a phenomenon has also been reported by Hoyer /27/ in relation to metal ions on Nafion modified glassy carbon electrodes. The higher affinity of salbutamol for Nafion films is an interesting finding. This compound differs structurally from fenoterol and metaproterenol in the positioning and number of the hydroxyl group (or groups) on the aromatic ring and it was thought that this difference causes higher accumulation of salbutamol without saturating the electrode.

Epinephirine and isoproterenol, two compounds in this class possessing a similiar ring structure to salbutamol, were then evaluated for their ability to preconcentrate at Nafion films. The use of Nafion modified carbon paste electrode provides a low cost and sensitive determination technique for selected β_2 - agonists. These electrodes are proved to be very much selective for these compounds in presence of extracts from biological matrices.

The plastic membrane ion selective electrode for determination of diclofenac anion consists of diclofenac-nickel(II) bathophenanthroline as an ion exchanger site in a poly(vinyl chloride) matrix plasticized with o-nitrophenyl phenyl ether /28/ in borate buffer solutions of pH 8-12, the electrode exhibited a fast, stable and linear response.

Potentiometric selectivity measurements revealed negligible interferences from 14 different anions including aromatic and aliphatic carboxylic acid salts. The electrode displayed useful analytical characteristics for the direct determination of diclofenac in various pharmaceutical preparations. Results with an average recovery of 98 $\pm$ 0.6% of the normal value were obtained /28/.

The diclofenac anion reacts with the nickel(II) tris (bathophenanthroline) cation to form a stable 2:1 water insoluble ion association complex with the composition:



The complex was isolated, charactrized, incorporated with a suitable solvent mediator in a PVC membrane. The critical electrochemical performance characteristics of the electrode were systematically evaluated according to IUPAC recommendations /29/.

The response of the electrode was also examined in the presence of a number of organic and inorganic anions. The potentiometric selectivity coefficients ($K^{pot}_{DCe,B}$) were used to evaluate degree of interference. No adverse effect on the reponse of the electrode was observed for up to a 100-fold excess of many pharmaceutical excipients and diluents commonly used for diclofenac drug formulations such as glucose, lactose, maltose, mannitol, starch, talc and magnesium stearate

Three different models of electrodes selective for tizanidine were constructed /30/ containing an ion-pair of the drug either with sodium tetraphenylborate, phosphotungstic acid or silicotungstic acid. The use of

halogenated tetraphenylborate derivatives, namely tetrakis (4-chlrophenyl)-borate and tetrakis [3,5-bis(trifluoromethyl) phenylborate as ion exchangers in the preparation of electrode membranes sensitive to pilocarpine has been reported /31/ which operates without an inner reference solution favouring an increased lifetime and reproducibility responsibility to the electrodes. These electrodes are used for determination of pilocarpine in ophthalmic solutions and ointments. An ion-selective electrode based on Ferroin- picrolonate salt has been used /32/ for the direct potentiomentric determination of picrolonates and for the indirect determination of calcium and piperazine in pharmaceuticals and serum.

A graphite electrode coated with a PVC matrix membrane containing the benzyl dimethyltetradecyl ammonium- phospho tungstate ion association complex as electroactive material and dioctyl phthalate as plasticizer was constructed /33/ for the determination of micro-amounts of vitamine B1 by direct potentiometric titration in aqueous medium with a standard phophotungstic acid solution. The method was applied for the determination of thiamine hydrochloride in tablets and injections Riboflavin, nicotinamide and calcium panthothenate upto 4 mg and cyncobalamin up to 0.1 mg were found not to interfere in the titration of 2 mg of thiamine hydrochloride. However, pyridoxine hydrochloride interferes, giving high results.

Conclusions

This review covers certain useful ion-selective electrodes for pharmaceutical analysis. We hope that this will be a guideline and hence boost for further advanced application of ion-selective electrode systems in the field of applied chemistry The low cost and easily operable conditions are of course, as well known, the added advantages.

Table 1:

Membrane sensor	Type of drug	Response time	Slope, mv / decade	pH range
I) Tetracyclin silicotungstate II) Dipicryl aminate III) Tetraphenyl borate	Tetracycline, both anions and cations	60 sec	I) 59.7 II) 58.7 III) 58.7	1.9-3.2 for cations 8-11 for anions

Application of ISE in Pharmaceuticals

Interferences	Selectivity Coeff., k	Life time	Range / det. limit	Ref.
Cation-sensitive electrode		2 months	I) $3x10^{-5}$ - 10^{-2} M	9
i) Sulphamic acid	-1.36		II) 10^{-4} - 10^{-2} M	
ii) Urea	-1.47		III) $8x10^{-5}$-10^{-2}M	
iii) Citric acid	-1.46			
iv) Amino acetic acid	-1.55			
v) Glucose	-1.48			
vi) Thiourea	-1.38			
vii) Sulphosalicylic acid	-1.39			
viii)) Ammonium chloride	-1.38			
ix) Lithium sulphate	-1.45			
x) Sodium chloride	-1.38			
xi) Rubidium sulphate	-0.96			
xii) Caesium sulphate	-0.61			
xiii) Beryllium sulphate	-2.99			
xiv) Magnesium chloride	-2.88			
xv) Calcium chloride	-2.78			
xvi) Strontium chloride	-2.62			
xvii) Barium chloride	-2.46			
xviii)Tetramethyl ammonium iodide	-1.05			
xix) Tetraethyl ammonium iodide	-0.18			
xx) Tetrabutyl ammonium iodide	2.66			
xxi) Tetraoctyl ammonium iodide	5.31			
Anion-sensitive electrode				
i) Sodium chloride	-0.96			
ii) Sodium sulphate	-2.37			
iii) Potassium thioyanate	2.53			
iv) Urea	-0.35			
v) Ammonium aminoacetate	-0.95			
vi) Ammonium aminopropionate	-1.14			
vii) Thiourea	-0.92			
viii) Glucose	-1.50			

Table 1

Membrane sensor	Type of drug	Response time	Slope, mv / decade	pH range
336-Cloxacillin complex	Cloxacillin (penicillins)	30 sec	60.2	5-6
Silver Silver sulphide	Thiamine (Vitamin B_1)	–	–	–
Benzyl dimethyl cetyl ammonium cholate	Drugs contain chenodeoxy cholic acid & usrodeoxy cholic acid	15 sec	56	–
Dinonylnaphthalene sulphate	Perbutalol sulphate, Betapresin	–	–	–
Benzoquinone modified cauliflower tissue based	Ascorbic acid	–	–	–
Benzyl penicillin & qua - ternary amine	Benzyl penicillin	–	–	–
Dinonyl naphthalene sulphonic acid	1. Methadone 2. Methyl amphetamine 3. Cocaine 4. Protriptylene	–	–	–
Tetraheptyl ammonium naproxenate in p-nitro-cumene	Naproxene	2.5 sec	58 - 61	9

Continued

Interferences	Selectivity Coeff., k	Life time	Range / det. limit	Ref.
Benzyl penicillin Ampicillin Amoxicillin 6-APA acid Penicilloate Nitrate Chloride Acetate	0.096 0.014 0.005 0.15 0.0 5 0.0018 0.001	3 months	10^{-5} - 10^{-1} M / 7 x 10^{-6} M	10
No interference by other vitamins	–	–	–	11
Benzoate Acetate Citrate Oxalate Nitrate Sulphate Chloride Hydroxyl	0.26 $1.05x10^{-2}$ $5.8x10^{-4}$ $1.17x10^{-3}$ $3.80x10^{-2}$ $1.24x10^{-3}$ $1.87x10^{-2}$ 0.11	Several months	8 x 10^{-5} to 5 x 10^{-3} M	12
–	–	–	$5x10^{-6}$ - 10^{-3} M	13
–	–	At least 30 days	$5.66x10^{-4}$ $5.66x10^{-2}$ M	14
–	–	–	$5x10^{-3}$ – $5x10^{-1}$ M	16
–	–	–	$10^{6.5}$ – $10^{5.5}$ M	17
Acetate Sulphate Hydrogen phosphate Chloride	0.0048 0.0045 0.0059 0.029	2 months	10^{-1} – 10^{-1} M	18

Table 1

Membrane sensor	Type of drug	Response time	Slope, mv / decade	pH range
i) Ciprafloxacine PVC-coated ISE based on 4-quinolines	Ciprafloxacine	2-5 min	50	
ii) Ciprafloxacine-tetraphenyl borate	Ciprafloxacine	0.5-2 min	50-54	4.5-7.0
iii) Norfloxacine	Ciprafloxacine	0.5-2 min	54-62	4.5-7.0
iv) Perfloxacine	Ciprafloxacine	2-5 min	50	4.5-7.0
Respective electrode array	i) Sulpha meth-oxazole ii) Sulpha thiazinc iii) Sulpha thiazole			
PVC-sebacate containing benzyl dimethyl ethylammonium cholate	Chemo- or deoxy-cholic acid content in common drugs and crit. micellar concentration			
Organic cation heteropoly complex (HPC)	Phenothiazine			
Phenyl ephedrinic tetraphenyl borate	Determination of ephedrine hydro-chloride			
Lead salicylaldoxime complex	Lead in carbimaxole	50-60		
Nafion modified carbon paste	Salbutamol Fenoterol Metaproterenol	30 sec	50.7-60	2-12

Continued

Interferences	Selectivity Coeff., k	Life time	Range / det. limit	Ref.
		1 week	1×10^{-4} to 1×10^{-2} M / 5×10^{-5}	19
Acetate Chloride Penicilline Ampicillin	-0.61 -0.14 -0.97	2 months	1×10^{-4} to 1×10^{-2} M/ 7.9×10^{-5}	
Acetate Chloride Pencilline Ampicillin	-0.66 -0.16 -0.73 -.068	2 months	1×10^{-4} to 1×10^{-2} / 5×10^{-5}	
Penicillin Ampicillin Acetate Chloride	-0.98 -0.81 -0.46 -0.14		$1 \times 10^{0-4}$ to 1×10^{-2} / 5×10^{-5} M	
				20
				21
				22
			2×10^{-5} - 10^{-1} for Ep^{+} & 10^{-5} - 10^{-1} for Ag^{2+}	23
			10^{-6} - 10^{-1} M	24
			2.5×10^{-8} M	25

Table 1

Membrane sensor	Type of drug	Response time	Slope, mv / decade	pH range
Diclofenac nickel (II) bath phenanthroline	Diclofenac (Voltaren) anion detn.		55.5 ± 0.2	8-12
Tizanidine ion-paired with i) sodium tetraphenyl borate ii) phosphotungstic acid iii) silicotungstic acid	Tizanidine	 i) 53 ii) 55 iii) 57	2 min	4.6

Continued

Interferences	Selectivity Coeff., k	Life time	Range / det. limit	Ref.
Benzoate	8.1×10^{-3}	3 months	1×10^{-2}	28
Aminobenzoate	7.8×10^{-3}		5×10^{-5}	
Anthranilate	6.0×10^{-3}			
Salicylate	4.7×10^{-3}			
Aminosalicylate	6.3×10^{-3}			
Phthalate	7.8×10^{-3}			
Citrate	9.3×10^{-3}			
Tartrate	7.7×10^{-3}			
Oxalate	9.3×10^{-3}			
Acetate	8.5×10^{-3}			
Formate	1.0×10^{-3}			
Phosphate	7.8×10^{-3}			
Sulfate	7.5×10^{-3}			
Nitrate	1.5×10^{-3}			
2,1,3-Benzothiadiazole	1×10^{-4}	4 months		30
4-Amino-2,1,3-benzo-diazole	1×10^{-4}		(i) $1x10^{-5}$ - $1x10^{-2}$ /$6.3x10^{-6}$ M	
Mephenesine	1×10^{-4}		(ii) $3.5x10^{-6}$ - $1x10^{-2}$ M/ $3.2x10^{-6}$ M	
Thiocholchicoside	1×10^{-4}			
Chloromemzanone	1×10^{-4}			
Dantrolene	1×10^{-4}		(iii) $3.9x10^{-6}$ - $1x10^{-2}$ M/ $2.5x10^{-6}$ M	
Acetylsalicylic acid	1×10^{-4}			
Paracetamol	1×10^{-4}			
[2-Imidazolidone]				
Pyruvic acid	1×10^{-4}			
Glutamic acid	1×10^{-4}			
Ascorbic acid	1×10^{-4}			
Caffeine	1×10^{-4}			
Urea	1×10^{-4}			
Benzidine	7.9×10^{-2}			
Ephedrine-HCl	1.9×10^{-2}			
Phenazone	3.0×10^{-3}			
Promethazine - HCl	56			
Methixene - HCl	457			
Trazodone	3.9×10^{-3}			
Pyridoxine - HCl	4.0×10^{-3}			
L-cysteine ethyl ester - HCl	1×10^{-4}			
Sodium ion	1×10^{-4}			
Potassium ion	1×10^{-4}			

Table 1

Membrane sensor	Type of drug	Response time	Slope, mv / decade	pH range
Pilocarpine and i) tetrakis 4-chlorophenyl borate	Pilocarpine	i) 59	i) 6 sec	i) 2.5-6.6
ii) tetrakis[3,5-trifluoro-methylphenyl borate		ii) 60	ii) 10 sec	ii) 2.5-6.5
Ferroin-picrolonate in 2-nitro toluene	Picrolonates (direct method) Piperazine (indirect method)	42.5	2 min	3 - 10
Benzyldimethyl tetradecyl ammonium phosphctungstate	Triamine	36		

Continued

Interferences	Selectivity Coeff., k	Life time	Range / det. limit	Ref.
(i) Calcium Sodium Ammonium Potassium Ephedrine Atropine Strychnine Quinidine	-3.6 -1.6 -1.7 -1.6 -0.2 +0.4 +1.3 +1.7	(i) 7 months	(i) 3.0×10^{-5} - 1.0×10^{-1} M / 5.7×10^{-6} M	31
(ii) Calcium Sodium Ammonium Potassium Ephedrine Atropine Strychnine Quinidine	-3.4 -1.6 -1.4 -1.4 -0.1 +0.3 +1.0 +1.8	(ii) 7 months	(ii) 5.7×10^{-5} - 1×10^{-1} M / 9.3×10^{-6} M	
Iodide Chloride Periodate Benzoate Picrate 3,5-Dinitrosalicylate 2,4-Dinitrophenolate 4-Nitrophenolate	6.2×10^{-2} 1.0×10^{-3} 0.95 2.4×10^{-3} 3.39 2.56 0.73 1.10		1.0×10^{-4} - 1×10^{-2} m	32
Malate Citrate Acetate Fluoride Thiocyanate Sulfate Sulfite Phosphate	1.8×10^{-4} 4.2×10^{-4} 3.1×10^{-4} 7.3×10^{-4} 1.8×10^{-3} 2.0×10^{-3} 2.2×10^{-4} 4.6×10^{-5}			
			3×10^{-5} - 1×10^{-1} M / 1×10^{-6} M	33

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