Maltodextrins as Chiral Selectors in Biomedical Enantioanalysis: A Mini Review

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Abstract: Enantiomers of the same chiral (bio)marker were found to be responsible for different diseases. Therefore, biomedical enantioanalysis is very important for their diagnosis. Enantioselective, potentiometric membrane electrodes were proposed for the enantioanalysis of (bio)markers. Different types of maltodextrins were used for the design of these electrodes. The response characteristics as well as their selectivity and enantioselectivity made possible the reliable diagnosis. The advantage of using such electrodes in biomedical enantioanalysis is high reliability, rapidity and low cost of the analysis.

Keywords: Sensors, chiral recognition, maltodextrins, clinical analysis.

1. INTRODUCTION

Enantioanalysis became very important for clinical analysis as well as for pharmaceutical industry, these fields of analysis being interconnected. The reliable determination of each enantiomer will conclude with the correct diagnosis. Furthermore, utilization of enantioselective electrodes proved to be a good alternative to chromatographic techniques in biomedical enantioanalysis, these comprising analyzing of (bio)markers as well as of the enantiomers of drugs in biological fluids.

Maltodextrins represent a class of very powerful chiral selectors among the chiral selective substances, e.g., cyclodextrins, crown ethers, macrocyclic antibiotics, proteins. Maltodextrins (Fig. **1**) are complex malto-, oligo-, and polysaccharide mixtures formed by hydrolysis of starch, with DE lower than 20 [1-3].

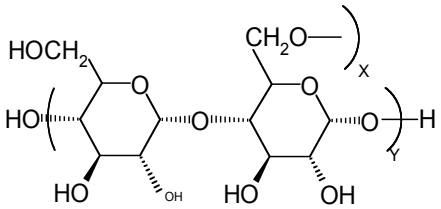

Fig. (1). Maltodextrins structure.

Possible types of maltodextrins have different dextrose equivalent (DE) values [I (4.0-7.0), II (13.0-17.0), and III (16.5-19.5)]. Variations in DE values result in maltodextrins with varying physico-chemical properties: solubility, hydroscopicity, osmolality and their effectiveness to reduce the freezing point increases with increasing DE, while viscosity, cohesiveness and coarse-crystal prevention increase as DE decreases [4, 5]. Maltodextrins were intensively investigated as chiral selectors for enantiomeric separations by capillary zone electrophoresis, the maltodextrins with the highest DE values being the best chiral selectors [2, 3, 6-10], and they were also used in the design of enantioselective, potentiometric membrane electrodes for the enantioanalysis of several drugs.

Maltodextrins were also used as components of the fast dissolving films for the design of the fast-dissolving oral drugs (the drugs which should disintegrate or dissolve within 1 min) [11].

2. ENANTIOSELECTIVE POTENTIOMETRIC MEMBRANE ELECTRODES (EPME) DESIGN

Paraffin oil and graphite powder in a ratio of 1:4 (w/w), were first thoroughly mixed, followed by the addition of an aqueous solution of maltodextrin (solution 10^{-3} mol l^{-1}). A quantity of carbon paste, free of maltodextrin, was also prepared and placed in a plastic pipette peak, leaving 3-4mm empty in the top to be filled with carbon paste containing the chiral selector. The diameter of the EPME was 3mm. Electric contact was obtained by inserting a Ag/AgCl wire into the carbon paste. The internal solution was 0.1 mol l^{-1} KCl. Prior to use, the surface of the electrode was wetted with deionised water and polished with alumina paper (polishing strips 30144-001, Orion).

3. APPLICATIONS IN BIOMEDICAL ANALYSIS

Different types of disease are generated due to inborn errors of metabolism such as organic acidemias, fatty acid oxidation defects, primary lactic acidosis, aminoacido-

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pathies, urea cycle defects, disorders of carbohydrate metabolism, lysosomal storage disorders and peroxisomal disorders. Organic acidemias (e.g., methylmalonic or propionic acidemia, glyceric acidurias, 2-hydroxyglutaric acidurias, carboxylase deficiency) are caused by abnormal metabolism of proteins, fats or carbohydrates and are characterized by marked metabolic acidosis with ketosis, often with elevated lactate and encephalopathy, neutropenia and thrombocytopenia. Chirality plays a very important role in diagnosis of diseases associated with these markers having a chiral moiety (e.g., enantiomers of pipecolic acid, fucose, glyceric acid, 2-hydroxyglutaric acid, vesamicol and lysine), because each enantiomer causes a different phenotype disease associated with different symptoms.

D- and L-glyceric acids (GA) are human metabolites responsible for two different diseases. Excess excretion of D-GA causes D-glyceric academia/acidurias, while excess excretion of L-GA causes hyperoxaluria type 2, PH II. Enantioselective, potentiometric membrane electrodes (EPMEs) based on maltodextrins I (dextrose equivalence (DE) 4.0-7.0), II (DE 13.0-17.0) and III (DE 16.5-19.5) as chiral selectors were proposed for the determination of L- (EPMEs based on maltodextrins I and III) and D-glyceric (EPME based on maltodextrin II) acid (L- and D-GA) [12]. EPMEs based on maltodextrins I and III can be reliably used for the analyses of L-GA using a direct potentiometric method, in the concentration ranges of 10^{-8} to 10^{-6} and 10^{-6} to 10^{-3} mol/L, respectively with very low detection limits (1.19×10^{-9} and 1.0×10^{-7} mol/L, respectively). The EPME based on maltodextrin II was successfully used for the enantioanalysis of D-GA in the 10^{-5} to 10^{-3} mol/L concentration range with detection limit of 1.0×10^{-6} mol/L. The enantioselectivity of EPMEs was determined over L- (or D-) glyceric acid, and their selectivity over creatine, creatinine and some inorganic cations such as Na^+, K^+ and Ca^{2+}.

L-2-Hydroxyglutaric acid (L-2-HGA) may be found in abnormally higher concentrations in urine as a result of genetic errors or metabolic disorders and it is a marker for L-2-hydroxyglutaric aciduria (a rare neurometabolic disorder). Enantioanalysis of L-2-HGA is important for the diagnosis of L-2-hydroxyglutaric aciduria. Three enantioselective, potentiometric membrane electrodes based on maltodextrins with different DE (i.e. DE: 4.0-7.0 (I), 13.0-17.0 (II), 16.5-19.5 (III)), were designed for the enantioanalysis of L-2-HGA [13]. The enantioselective, potentiometric membrane electrodes can be used reliably for enantiopurity assay of L-2-HGA using the direct potentiometric method in the ranges of 10^{-9}-10^{-5}, 10^{-6}-10^{-3} and 10^{-8}-10^{-5} mol/L for the enantioselective, potentiometric membrane electrodes based on maltodextrins I, II and III, respectively, with very low detection limits. A high reliability was obtained when the electrodes were used for the assay of L-2-HGA in urine samples.

L-pipecolic acid is a marker for peroxisomal disorders. Three electrodes based on carbon paste impregnated with different maltodextrins (DE: 4.0-7.0 (I), 13.0-17.0 (II) and 16.5-19.5 (III), respectively) as chiral selectors were reliably used for enantiopurity assay of it using a potentiometric method in the concentration ranges of 10^{-8}-10^{-3}, 10^{-8}-10^{-5} and 10^{-10}-10^{-6} mol/L for the maltodextrins I, II and III, respectively, based electrodes, with very low detection limits (magnitude orders of 10^{-9} for I and II, respectively and 10^{-12} mol/L for III) [14]. The proposed electrodes can be successfully applied for the enantioanalysis of L-pipecolic acid in serum samples.

Maltodextrins (with DE 4.0 - 7.0, 13.0 - 7.0, and 16.5 - 19.5) were proposed as novel chiral selectors for the design of enantioselective, potentiometric membrane electrode for S-captopril assay [15]. The potentiometric, enantioselective membrane electrodes can be used reliably for the assay of S-captopril in serum samples. The best response was obtained when maltodextrin with higher DE was used for the electrode's construction. The best enantioselectivity and stability in time was achieved for the lower DE maltodextrin. L-proline was found to be the main interferent for all proposed electrodes. The surface of the electrodes can be regenerated by simply polishing, obtaining a fresh surface ready to be used in a new assay.

The enantioanalysis of the enantiomers of baclofen was performed using two enantioselective, potentiometric membrane electrodes based on maltodextrins with different value of DE (maltodextrin I: DE 4.0-7.0; maltodextrin II: DE 16.5-19.5) [16]. The slopes of the electrode function of the proposed electrodes were 55.0 mV/pS-baclofen for maltodextrin I-based electrode and 59.0 mV/pR-baclofen for maltodextrin II-based electrode and the detection limits were 1.34×10^{-6} mol/L (S-baclofen) and 2.52×10^{-10} mol/L (R-baclofen), respectively.

The enantioselective, potentiometric membrane electrode based on maltodextrin with DE 16.5-19.5 was proposed for the assay of R-deprenyl [17]. The linear concentration range for the proposed electrode was 10^{-10}-10^{-3} mol/L. The slope of the electrode was 53.1 mV per decade of concentration. The detection limit was 3.6×10^{-11} mol l^{-1}.

Three enantioselective, potentiometric membrane electrodes based on carbon paste impregnated with different maltodextrins (dextrose equivalent DE 4.0 – 7.0 (I), 13 –17 (II), 16.5 -19.5 (III)), were proposed as chiral selectors for the assay of S-flurbiprofen [18]. The best response and enantioselectivity were obtained when maltodextrin with the lowest DE was used for the electrode design. The three EPMEs showed very low detection limits.

Three enantioselective, potentiometric membrane electrodes based on maltodextrin with different values of DE (maltodextrin I: DE 4.0-7.0; maltodextrin II: DE 13.0-17.0; maltodextrin III: DE 16.5-19.5) were proposed for the assay of S-ibuprofen [19]. The linear concentration ranges for the proposed enantioselective, potentiometric membrane electrodes were 10^{-10}-10^{-3}, 10^{-8}-10^{-3} and 10^{-10}-10^{-3} mol/L for the electrodes based on maltodextrin I, II and III, respectively. The slopes of the electrodes were 59.0, 58.4 and 55.6 mV/decade of concentration for maltodextrin I, II and III based enantioselective, potentiometric membrane electrodes, respectively, with detection limits of 5.5×10^{-11}, 8.0×10^{-9} and 4.1×10^{-12} mol/L for the electrodes based on maltodextrin I, II and III, respectively.

Enantioselective, potentiometric membrane electrodes based on maltodextrins of different DE (i.e. DE: 4.0-7.0 (I), 13.0-17.0 (II), 16.5-19.5 (III)) as chiral selectors were used for the assay of S-perindopril [20]. These electrodes can be

successfully used in the assay of S-perindopril in the presence of R-perindopril, D-proline, PVC and inorganic ions such as Na^+, K^+ and Ca^{2+}. The best results were obtained by using maltodextrins I and II in the design of the enantioselective, potentiometric membrane electrodes. Accordingly, these are the electrodes of choice for the enantioselective analysis of S-perindopril. If one compares the results obtained using these maltodextrins based elecrodes and those obtained by using substituted β-CD for the assay of S-perindopril, one can easily observe that there had been improvements in detection limits (lower with maltodextrins as chiral selectors), working concentration ranges, slope and enantioselectivity (higher especially with maltodextrin of lower DE as chiral selector).

Enantioselective, potentiometric membrane electrodes based on carbon paste impregnated with the following maltodextrins having DE 4.0 - 7.0 (I), 13.0 - 17.0 (II) and 16.5 - 19.5 (III) - as chiral selectors were proposed for the assay of L-proline [21]. The response characteristics showed that the proposed electrodes could be reliably utilized in the assay of L-proline, with the best enantioselectivity and time-stability exhibited when the EPME based on malodextrin I was used. The three EPMEs showed very low detection limits (of 10^{-9} mol/L magnitude order).

4. SPECTROSCOPIC METHOD

Chiral discrimination of the enantiomers of fluoxetine was performed using a rapid, simple and selective ^{19}F-NMR spectroscopic method using maltodextrins as chiral selectors [22]. The results obtained showed that the proposed method is reliable.

5. CONCLUSIONS

Maltodextrins were used in biomedical enantioanalysis for three analytical techniques: capillary zone electrophoresis, potentiometric analysis and ^{19}F-NMR. The utilization of them for enantioanalysis, generally, improved the quality of the results by increasing the reliability of the analytical information. The best results were obtained using the enantioselective electrodes, which are well known for the rapidity of analysis, simplicity and high reliability of the analytical information.

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ABBREVIATIONS

β-CD = Beta cyclodextrin

DE = Dextrose equivalent

EPME = Enantioselective potentiometer membrane electrodes

GA = Glyceric acids

HGA = 2-Hydroxyglutaric acid

PH II = Heperoxaluria type 2

REFERENCES

[1] Soini, M.; Stefansson, M.; Riekkola, M.L.; Novotny, N.V. Maltooligosaccharides as chiral selectors for the separation of pharmaceuticals by capillary electrophoresis. *Anal. Chem.,* **1994**, *66*, 3477.

[2] D'Hulst, A.; Verbeke, N. Separation of the enantiomers of coumarinic anticoagulant drugs by capillary electrophoresis using maltodextrins as chiral modifiers. *Chirality,* **1994**, *6*, 225.

[3] D'Hulst, A.; Verbeke, N.J. Chiral analysis of basic drugs by oligosaccharide-mediated capillary electrophoresis. *J. Chromatogr. A,* **1996**, *735*, 283.

[4] Altschul, A.M. Low-calorie foods. *Food Technol.,* **1989**, *43*, 113.

[5] Chronakis, I.S. On the molecular characteristics, compositional properties, and structural-functional mechanisms of maltodextrins: a review. *Crit. Rev. Food Sci. Nutr.,* **1998**, *38*, 599.

[6] D'Hulst, A.; Verbeke, N. Chiral separation by capillary electrophoresis with oligosaccharides. *J. Chromatogr.,* **1992**, *608*, 275.

[7] D'Hulst, A.; Verbeke, N. Quantitation in chiral capillary electrophoresis: theoretical and practical considerations. *Electrophoresis,* **1994**, *15*, 854.

[8] D'Hulst, A.; Verbeke, N. Carbohydrates as chiral selectors for capillary electrophoresis of racemic drugs. *Enantiomer,* **1997**, *2*, 69.

[9] Watanabe, T.; Takahashi, K.; Horiuchi, M.; Kato, K.; Nakazawa, H.; Sugimoto, T.; Kanazawa, H. Chiral separation and quantitation of pentazocine enantiomers in pharmaceuticals by capillary zone electrophoresis using maltodextrins. *J. Pharm. Biomed. Anal.,* **1999**, *21*, 75.

[10] Quang, C.; Khaledi, M.G. Chiral separations of acidic compounds by dextrin-mediated capillary zone electrophoresis. *J. High Resolut. Chromatogr.,* **1994**, *17*, 609.

[11] Cilurzo, F.; Cupone, I.E.; Minghetti, P.; Selmin, F.; Montanari, L. Fast dissolving films made of maltodextrins. *Eur. J. Pharm. Biopharm.,* **2008**, *70*, 895.

[12] Stefan, R.I.; Nejem, R.M. Enantioanalysis of glyceric acid using enantioselective, potentiometric membrane electrodes: applications for the diagnosis of PH II and d-glyceric acidemia/acidurias. *Sens. Actuators B,* **2005**, *106*, 736.

[13] Stefan, R.I.; Nejem, R.M.; van Staden, J.F.; Aboul-Enein, H.Y. Enantioanalysis of L-2-hydroxyglutaric acid in urine samples using enantioselective, potentiometric membrane electrodes based on maltodextrins. *Talanta,* **2005**, *65*, 437.

[14] Stefan, R.I.; Nejem, R.M.; van Staden, J.F.; Aboul-Enein, H.Y. Enantioselective, potentiometric membrane electrodes for the determination of L-pipecolic acid in serum. *Electroanalysis,* **2004**, *16*, 1730.

[15] Stefan, R.I.; van Staden, J.F.; Aboul-Enein, H.Y. Maltodextrins as new chiral selectors in the design of potentiometric, enantioselective membrane electrodes. *Fresenius J. Anal. Chem.,* **2001**, *370*, 33.

[16] Rat'ko, A.A.; Stefan-van Staden, R.I. Determination of baclofen enantiomers in pharmaceutical formulations using maltodextrin-based enantioselective, potentiometric membrane electrodes. *Farmaco,* **2004**, *59*, 993-7.

[17] Stefan-van Staden, R.I.; Mashile, T.R. Determination of R-Deprenyl using a maltodextrin-based enantioselective, potentiometric membrane electrode. *Instrum. Sci. Technol.,* **2007**, *35*, 117.

[18] Stefan-van Staden, R.I.; Bokretsion, R.G.; Ozoemena, K.I. utilization of maltodextrin-based enantioselective, potentiometric membrane electrodes for the enantioselective assay of S-flurbiprofen. *Anal.Lett.,* **2006**, *39*, 1065.

[19] Stefan-van Staden, R.I.; Mashile, T.R. Enantioselective assay of S(+)-ibuprofen using enantioselective, potentiometric membrane electrodes based on maltodextrins. *Sens. Actuators B,* **2006**, *120*, 295.

[20] Ozoemena, K.I.; Stefan R.I.; van Staden, J.F.; Aboul-Enein, H.Y. Utilization of maltodextrin based enantioselective, potentiometric membrane electrodes for the enantioselective assay of S-perindopril. *Talanta,* **2004**, *62*, 681.

[21] Ozoemena, K.I.; Stefan R.I.; van Staden, J.F.; Aboul-Enein, H.Y. Enantioselective, potentiometric membrane electrodes based on maltodextrins: their applications for the determination of L-proline. *Sens. Actuators B,* **2004**, *98*, 97.

[22] Shamsipur, M.; Dastjerdi, L.S.; Haghgoo, S.; Armspach, D.; Matt, D.; Aboul-Enein, H.Y. Chiral selectors for enantioresolution and quantitation of the antidepressant drug fluoxetine in pharmaceutical formulations by ^{19}F NMR spectroscopic method. *Anal. Chim. Acta,* **2007**, *601*, 130.

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