Variation of Functional Monomers for The Preparation of Imprinted Polymers for Selective Analysis of Glibenclamide

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Abstract. The Molecular imprinting technology has been applied for glibenclamide, an antidiabetic drug. Synthesis was conducted on bulk polymerization method. The component of polymers is: trimethylolpropane trimethacrylate (TRIM) as crosslinker, chloroform and methanol as the porogen solvent, benzoyl peroxide as initiator and methacrylic acid (MA), ithaconic acid (ITA) were the various functional monomer. Soxlet extraction was conducted on the mixture of acetic acid: methanol (15:85). Physical characterization included functional group identification using Fourier Transform Infrared (FTIR) spectrophotometer, showed that the polymers met the qualification of imprinted polymer- new peaks found indicated that analyte has been successfully grafted to the polymers. Morphology elaboration using Scanning Elctron Microscope (SEM). Adsorption performace was represent by imprinting factor (IF) and α (analogue selectivity). Imprinting factor for MA and ITA found respectively: 1.22 and 1.30 The α points showed those three polymers are selective for glibenclamide better than those for analogue molecules.

Keywords: Functional monomer, glibenclamide, molecular imprinting technology.

1 Introduction

Glibenclamide is the antidiabetic drug of sulfonylurea group that used in the treatment of type 2 of diabetes mellitus. Glibenclamide is commonly used and favorable because of its low cost and helpful for diabeticspatients, with the small dose, less than 5 mg, glibenclamide (**Figure 1**) are effective in lowering blood glucose level with no appreciable increase in effect with higher dose[1]**.** For the Glibenclamide is used for a long time period of therapy, and also mostly found in the complex matrix in biological fluid, a proper analysis is an important to be prepared. Molecularly imprinted polymers (MIP) are synthetic receptors for a targeted molecule. This

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techique, which is still in its infancy, entails creating synthetic target molecule receptor sorbents on a polymer network.

MIP is emerging as a very promising method for controlled release and targeted delivery system with certain advantages.

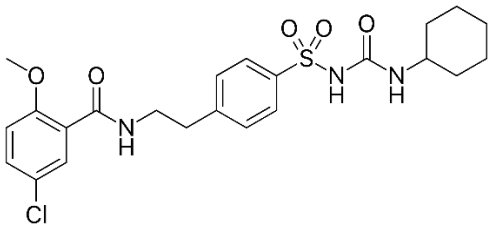

Fig.1. Molecular structure of glibenclamide.

Functional monomer provides a suitable complementary pre-polymerization complex with the a complementary way, such as H-bond donor with H-bond acceptor, in order to maximize the target molecules and substrates by binding their functional groups [2]. It is important to match the functionality of the template molecule with the functionality of the functional monomer information of the pre-polymerization complex and the imprinting effect. A functional monomer typically consists of two units: a polymerizable unit and a recognition unit.

In this work, we elaborate the characteristic of polymers formed from two different functional monomer, methacrylic acid (MA) and ithaconic acid (IA). MA is used with many drugs or templates to manage several acute or chronic disorders like cancer, asthma, opthalmic, etc. A comprehensive study of physicochemical and binding properties compiled deliberately to the biodegradability of MA gave the good result for drug delivery studies [3], Previous study showed that IA produced high affinity polymers toward to metronidazole that was reflected in the higher drug uptake [4]. The right choose of functional monomer on synthesis molecularly imprinted polymer is very crucial for selectivity, the main point of molecularly imprinting.

2 Methods

2.1 Material

The chemicals used in this study were glibenclamide (IFAR Pharmaceuticals laboratories), methacrylic acid (MMA), ithaconic acid (ITA), trimethylpropane trimethacrilate (TRIM), ethyleneglycol dimethacrylate (EGDMA) and benzoyl peroxyde (BPO) (Sigma Aldrich), metformin, ramipril (Dexa Medica), acetic acid, chloroform, methanol, acetic acid (Merck Chemicals), and nitrogen.

The Binder Laboratory model heater was used for polymer synthesis; FTIR (Shimadzu IRSpirit) was used to investigate the functional groups of polymers; UV-visible spectrophotometer (Thermoscientific Genesys 150) 8453 G1103A); morphology of surface analysis was performed using scanning electron microscope JEOL IT 300 SEM, shaker.

2.2 Procedures

Synthesis of polymer. The polymers shyntesized were: MP-MA, NP-IA, MP-IA, NP-IA, MP-MA was synthesized using this protocol **:** 50 mg of the template molecule, glibenclamide dissolved in porogen (chloroform : methanol (1.5 : 8.5) then functional monomer 211 µL of MMA, 3.19 mL of TRIM added together, the compound was homogenized with *magnetic stirrer* for 20 minutes. 125 mg of BPO were added then and homogenized for 15 minutes, followed by nitrogen stream for 5 minutes. It was the polymer solution. Polymer solution then heated at 65°C for 5 hours. NP-MA were synthesized with the same protocol, without glibenclamide as template molecule.

MIP-IA was synthesized using this protocol : 247 mg of glibenclamide dissolved in chloroform, followed by addition of 260 mg ITA as functional monomer and 3.19 mL of TRIM as crosslinker agent, all materials were homogenized with magnetic stirrer for 20-25 minutes to form polymer solution at room temperature, then 125 mg of BPO were added to the solution followed by N_2 gas sstreamed to the mixture. The mixture heated at 65-70°C to form bulk polymer. NP-IA was synthesized with the same protocol to the MP-IA, without the presence of glibenclamide as template molecule.

After the solid polymers formed, polymers were washed with distilled water and methanol to minimize the impurities; then crumbled at 16-20 mesh, weighted and placed in certain flask.

Extraction of analyte from the polymer. The templates were extracted from the polymer MP-MA and MP-IA by soxlet extraction where a mixture of methanol: acetic acid (85:15 v/v) was used as the solvent to construct polymers imprinted glibenclamide from MA (Mex-MA) and polymers imprinted glibenclamide from ITA (Mex-IA). Since the NP-NA and NP-IA had no analyte molecule on its body, no extraction procedure needed to these two polymers. To make sure the template molecules were completely removed from the polymer, the extraction was monitored using a UV spectrophotometer at λ = 240–250 nm.

Physical Characterization of Polymers. The functional group and structure in MP-MA, NP-MA, Mex-MA, MP-IA, NP-IA and Mex-IA were observed using an FTIR spectrophotometer from 4,000 to 500 cm^{-1}; morphology of the polymers was also observed using SEM with 2,000 times of magnitude for each polymer.

Adsorption Tests. The stock solution of 1000 mg/L of glibenclamide was prepared fresh daily before the analysis with methanol. From stock solution, a-50 mg/L is pipetted to a certain flash of 25mL, then 30 mg of Mex-MA, Mex-IA added to the flask, contacted for 24 hours with shaking. The final concentration and capacity were then calculated using the equation

$$Q = \frac{(C0 - Ct)}{m} V \quad (1)$$

where Q = adsorption capacity (mg/g), C_0 = analyte concentration before adsorption (50 mg/L), Ct = analyte concentration after adsorption (mg/L), m = mass of sorbent (mg), and V = solution volume (mL).

Selectivity was represented by the imprinting factor (IF) and selectivity coefficient α, defined as

$$IF = \frac{Q\ Mex-MA}{Q\ NP-NA} \quad (2)$$

for polymers built from MA, and

$$IF = \frac{Q\ Mex-IA}{Q\ NP-IA} \quad (3)$$

for polymers built from IA, selectivity coefficient which other molecules considered, determined as follows :

$$\alpha = \frac{Q\ glibenclamide}{Q\ analogue\ molecul} \quad (4)$$

where analogue molecules chosen were: metformin and ramipril, metformin is also antidiabetic drug; ramipril is antihypertension drug that commonly consumed by the patient together with the antidiabetic drugs.

3 Result and discussion

The synthesis of MP-MA, NP-MA, MP-IA and NP-IA was conducted through bulk polymerization method. This method was the simple and easy te be prepared. Methanol and chloroform were chosen as the porogen.

(a) (b)

Fig. 2. Polymer solution polymer product.

Nonpolar and less polar organic solvent are often used for non-covalent imprinting to achieve maximum imprinting efficacy [2]. The polymers as the product of the synthesis were white crystal and odorless. The synthesis used a noncovalent method, which involved crushing and sifting a macroporous polymer to small particle sizes following the final polymerization. [5] The total amount of MP-MA, NP-MA, MP-IA and NP-IA respectively were : 5.84; 4.82; 1.8; and 064 g.

The extraction was conducted to remove the analyte from the body of polymers through soxlet extraction. The glibenclamide content that should reduce by the time of extraction, controlled by the absorbance at λ = 245 nm, the λ for glibenclamide in the methanol:acetic acid (85:15), the extraction solvent for glibenclamide from the polymer backbone. The goal of extraction is to take the template out of the polymer so that it becomes a template mold. Zero absorbance indicated that all molecule glibenclamide has been thrown out from the polymers, leave the

imprinted pore that mimic the structure of the template, glibenclamide. This product then became the Mex-MA and Mex-IA (**Figure 2**).

Functional group investigation for MP-MA and MP-IA gave the significant difference at the peak of 1560 cm^{-1} that indicated the primary amine which is only found in MP-MA but not NP-MA; glibenclamide has been successfully grafted to the body of polymer. For the polymer of MP-IA and NP-IA, the difference peak found at 2358cm^{-1} (MP-IA) that indicated the primary amine; no structure in NP-IA has primary amine.

The surface morphology of MP-MA, NP-MA, MP-IA, NP-IA was characterized by SEM with 2000 times of magnification (Fig. 3). According to the SEM image, there were notable variations in the morphologies of the two polymers (made of ithaconic acid, NP-IA and methacrylic acid, NP-MA), Polymers produced after extraction, Mex-MA and Mex-IA, clearly showed a porous surface due to the pores after extraction).

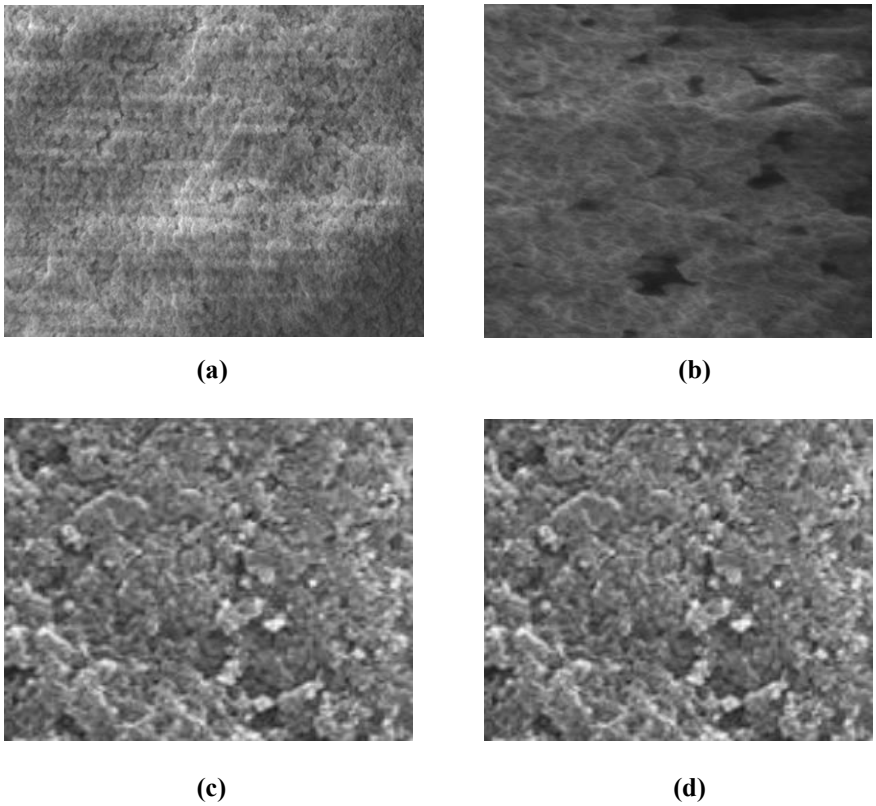

Fig. 3. SEM image of (a) Mex-MA (b) NP-MA, (c) Mex-IA and (d) NP-IA

The surface of MP-MA and MP-IA were bulky because of the presence of glibenclamide in the formation of the polymer. The increased adsorption of the analyte glibenclamide should be supported by the more porous surfaces of Mex-MA and Mex-IA.

Table 1. Imprinting factor (IF) of polymers.

Polymer	Q (mg/g)	IF
Mex-MA	8.14	1.22
NP-MA	6.67	
Mex-IA	2.89	1.44
NP-IA	2.01	

Adsorption capacity testing gave the result as shown in **Table 1**. As seen on table, the adsorption capacity of extracted polymers (Mex-MA and Mex-IA) is higher than NP-MA and NP-IA. It is connected to the binding ability of polymer given the specific and selective site after the extraction. When the IF is equal to 1, there is no change in the polymers' adsorption capacities or selectivity between the polymers with and without the analyte. The higher IF value, the more selectivity of the polymers [6].

Both compared IF value between Mex-MA to NP-MA and Mex-IA and NP-IA bind the template at different capacities; of which the resulting difference can be attributed to either templating effect [7]**.** The parameter of α for the two different kind polheymers also investigated. **Table 2** showed the result. From the table it can be seen that the polyners were more selective for glibenclamide better than those to the analogue molecules : metformin and ramipril.

Table 2. Selectivity factor, α, for extracted polymers.

Polymer	α to glibenclamide	α to ramipril
Mex-MA (1)	1.86	1.33
	1.83	1.38
	1.84	1.30
	1.84 ± 0.02	1.34 ± 0.04
Mex-IA	2.15	1.30
	2.10	1.24
	2.12	1.25
	2.12 ± 0.02	1.26 ± 0.03

Both polymers showed that the result that indicated that the adsorption amounts of glibenclamide was high compared to the adsorption to metformin and ramipril. This resulted from their structural similarity to ramipril, but different compared to metformin. Mex-MA and and Mex-IA had low affinity for ramipril; this might be because the more similar structure to glibenclamide. Metformin has different structure to glebenclamide, that's why metformin has bigger selectivity factor to glibenclamide.

4 Conclusion

Molecular imprintied glibenclamide has been successfully synthesized through bulk polymerization method. Polymer produced from ithaconic acid as functional monomer gave the higher imprinting factor (IF) than that from methacrylic acid. Selectivity to metformin is higher than to ramipril for both polymers applied. To obtain higher adsorption of adsorption and

selectivity, some optimation should be taken, such as: pH, mass of adsorbent, initial concentration, and time of contact.

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