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(Mechano)chemical modification of polyvinyl chloride with azole-based drugs

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Abstract

Polyvinyl chloride (PVC) plays an important role in industry; however, due to its uncontrolled accumulation in the environment, the methods for its utilization are of high demand. Herein we wish to report an approach for the utilization of PVC *via* its use as a carrier for some azole-based drugs, such as 2-mercaptobenzothiazole (multi-activity drug), 4-oxo-1,4-dihydropyrazolo[5,1-*c*]-1,2,4-triazine-3,8-dicarboxylic acid diethyl ester (antidiabetic drug) and 5-methyl-6-nitro-7-oxo-1,2,4-triazolo[1,5-*a*]pyrimidinide (antiviral drug). The abovementioned approach involves the reaction between PVC and potassium or sodium salts of these azole-based drugs either in solution or under ball-milling conditions. The as-obtained PVCs modified with azole-based drugs were isolated for the first time and characterized by means of ^{1}H NMR-spectroscopy as well as gel-permeation chromatography (GPC).

Keywords

polyvinyl chloride
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Supplementary materials

1. Introduction

Polyvinyl chloride (PVC) is a well-known polymer with various uses in the construction, automobile, electrical, medical, and daily goods industries [1]. As a result of using PVC in a wide variety of fields, the uncontrollable release of this polymer into the environment as scraps of various origin or microplastic has become a serious problem. Thermal treatment, such as pyrolysis, gasification or incineration, of PVC-containing waste results in energy recovery, and PVC can be used as a hydrocarbon source [2]. However, a high chlorine content in the PVC (57 wt.% [3]) posts additional drawbacks for this way of utilization. Namely, a higher temperature of heating is needed to prevent the formation of highly toxic dioxins [4], and, due to the release of acidic HCl, its absorption is required [5]. Chemical modification of PVC *via* nucleophilic substitution of chlorine atoms results in its partial or complete dichlorination and, thus, can be used for the utilization of first one [6 – 8]. Along with traditional *S-, O-, N-* nucleophiles some pharmacophoric moieties can be introduced, for instance, *via* reaction of PVC in solution with *N*-sodium salts of pyrazoles and imidazoles [9], triazoles and tetrazoles [10] as well as *in situ* formed *S*-sodium or potassium salts of 2-mercaptobenzothiazole [11], 2-mercaptobenzimidazole [9] or 4-mercaptopyridine [12]. Several azole-appended PVCs were reported as selective ligands for metal cations, including Cu(II) [13], while in case of terpyridine-appended PVC a complexation with transition metals, such as Cd(II), Co(II), Fe(II), Mn(II), Ni(II), Zn(II) and Ru(III), was reported [14] to result in supramolecular complexes.

On the other hand, the introduction of pharmacophoric moieties into the PVC core can be used as an approach to creating so-called polymeric drugs. Polymeric drugs have several advantages over small-molecule-based ones as they can simultaneously act on multiple receptors/binding subsites. And in case of receptors, which are physically not close enough, polymeric drugs can act *via* the mechanism of statistical rebinding *via* binding of the adjacent ligand of polymeric chain to the receptor after the dissociation of previously bound ligand [15]. All this makes polymeric drugs to act faster so as to provide longer and superior pharmacological effect compared with small-molecule-based drugs. In this manuscript we wish to report our attempts on mechanochemical (under solvent-free conditions in ball-milling) and/or chemical (in solution) modification of polyvinyl chloride with some azole-based drugs, such as 2-mercaptobenzothiazole (antifungal drug) [16], 4-oxo-1,4-dihydropyrazolo[5,1-c]-1,2,4-triazine-3,8-dicarboxylic acid diethyl ester (antidiabetic drug) [17] and 5-methyl-6-nitro-7-oxo-1,2,4-triazolo[1,5-a]pyrimidinide (antiviral drug) [18].

2. Experimental part

All reagents were purchased from commercial sources and used without further purification. Silica gel 60 (Kieselgel 60, 230–400 mesh) was used for the column chromatography. NMR spectra were recorded on a Bruker Avance-400 (or Bruker Avance-500) spectrometer, 298 K, digital resolution ± 0.01 ppm, using TMS as internal standard. Ball milling experiments were carried out on a Retsch PM 100 CM ball mill. Elemental analyses were performed on a PE 2400 II CHN-analyzer (Perkin Elmer). GPC measurements were performed using a chromatograph Agilent 1200 with an aerosol light scattering detector (ELSD) (Agilent technologies, USA) and a column Agilent Resipore, 300x7.5 mm – 2 pieces in series. THF (stabilized with 0.0025% BHT) was used as an eluent with a flow rate of 1 ml/min.

2.1. Preparation of azoloazine-functionalized PVCs 3,5

2.1.1. General procedure

PVC powder (0.5 g, 8 mmol chlorine content), corresponding azoloazine sodium salt (2.0 fold molar excess against Cl content) and a few drops of DMF or cyclohexanone were ball-milled in 50 mL stainless-steel milling jar with 4 stainless-steel 10 mm milling balls at 500 RPM for 4 h. The resulting precipitate was suspended in MeOH–H_2O = 2:1 (10 mL), filtered, and washed with MeOH–H_2O = 2:1 (3x10 mL). The obtained residue was dissolved in DMF (2 mL) and extruded into methanol (50 mL) from a syringe. The obtained suspension was filtered off, washed with methanol and dried in air for 24 h.

2.1.2. Polymer 3

White precipitate. Yield 549 mg (79%) (degree of modification 15%). ^{1}H NMR (400MHz, DMF-d_7): δ (ppm) 1.67–1.85 (*m*, 2H, –CH_2–), 2.19–2.62 (*m*, 34H, –CH_2–CHCl–, –CH_2–CH(HetAr), CH_3 (HetAr)), 4.42–4.71 (*m*, 10H, –CH_2–CHCl–, –CH_2–CH(HetAr)), 7.95 (s, 1H, H-3 (HetAr)). M_w = 146.4 kDa, M_n = 104.7 kDa, PDI =1.4.

2.1.3. Polymer 5

White precipitate. Yield 433 mg (49%) (degree of modification 20%). ^{1}H NMR (400MHz, DMF-d_7): δ (ppm) 1.35–1.47 (*s*, 6H, CH_3–CH_2–O–), 1.64–1.82 (*m*, 2H, –CH_2–), 2.19–2.60 (*m*, 20H, –CH_2–CHCl, –CH_2–CH(HetAr), 3.15 (*s*, 6H, CH_3–CH_2–O–), 4.32 (*s*, 4H, CH_3–CH_2–O–), 4.39–4.73 (*m*, 5H, –CH_2–CHCl–, –CH_2–CH(HetAr), 7.95 (s, 1H, H–7 (HetAr). M_w = 114.4 kDa, M_n = 80.4 KDa, PDI =1.4.

2.1.4. Preparation of azole-functionalized PVC 7

Method A. In a solution of cyclohexanone (10 mL) of PVC (0.5 g), nucleophile (25 mg, 0.15 mmol) and K_2CO_3 (20 mg, 0.15 mmol) were heated at 60 °C under Ar for 12 h. The resulting solution was cooled down and poured into a mixture of MeOH–H_2O = 2:1 (150 mL). The resulting precipitate was filtered off, washed with MeOH–H_2O = 2:1 (3x10 mL) and air-dried for 24 h. The residue was dissolved in DMF (2 mL) and extruded into methanol (50 mL) from a syringe. The obtained suspension was filtered off and dried in air for 24 h.

Method B. The procedure was carried out similar to polymers **3, 5**.

White precipitate. Yield 512 mg, 94% (A) (degree of modification 4.1%), 544 mg, 90% (B) (degree of modification 6.8%). ^{1}H NMR (DMF-d_7, δ, ppm): 1.69–1.82 (*m*, 2H, –CH_2–), 2.19–2.60 (*m*, 42H, –CH_2–CHCl, –CH_2–CH(HetAr), 4.39–4.73 (*m*, 25H, –CH_2–CHCl–, –CH_2–CH(HetAr), 6.85–6.89 (*m*, 1H, HetH), 7.02–7.06 (*m*, 1H, HetH), 7.25–7.27 (*m*, 1H, HetH), 7.37–7.39 (m, 1H, HetH). M_w = 161.8 kDa, M_n = 114.5 KDa, PDI =1.4.

3. Results and Discussions

Examples of chemical modifications of PVC with azole moieties in solutions were previously reported. However, no cases of introduction of azine moieties into PVC were described. As possible substrates for such reaction two derivative of azoloazines, namely, sodium salt **2** of 5-methyl-6-nitro-7-oxo-1,2,4-triazolo[1,5-a]pyrimidinide (antiviral drug) and sodium salt **4** of 4-oxo-1,4-dihydropyrazolo[5,1-c]-1,2,4-triazine-3,8-dicarboxylic acid diethyl ester (antidiabetic drug) were utilized aiming to obtain azoloazine drug modified PVCs. As a first approach we had attempted to use the previously described methods [9, 10], namely the reaction between **2,4** and PVC in the solution of DMF or cyclohexanone in the presence of K_2CO_3. However, even after 24 h no modification of PVC was observed (Table S1).

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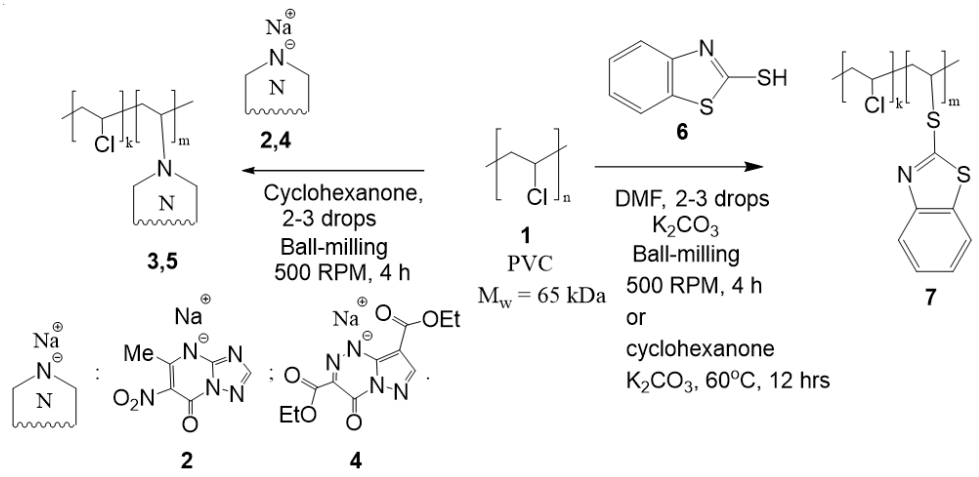

Scheme 1 Preparation of azole-based PVC **3,5,7**.

In all the cases the unchanged PVC was isolated. A possible reason for that is a weak solubility of sodium salts **2,4** in organic solvents. On the other hand, ball milling was found to be an efficient tool for the post-modification of polymers [19, 20], and only a few examples of using ball-milling for the dichlorination/complete destruction of PVC were reported [21, 22]. Therefore, as a next step we attempted to carry out the reaction between PVC and sodium salts **2, 4** of azoloazines in the presence of K_2CO_3 as an both base source and abrasive upon ball stainless-steel milling in 50 mL milling jar with 4 stainless-steel milling balls. At the very beginning, the optimization of the reaction conditions was carried out (Table S1). Thus, no reaction was observed under ball-milling at 100–400 rpm even after 8 h, and only unreacted PVC was isolated. Meanwhile, at 500 rpm in 4 h azoloazine-modified PVCs **3,5** were obtained. In the ^{1}H NMR the presence of azoloazine moieties was observed as one-proton singlets around 8 ppm (protons of CH fragments of azole ring) as well as hydrogen signals of substituents of azine moieties. In addition, for the both polymers **3, 5** the characteristic signals of PVC core were observed as multiplets at 4.42–4.71 ppm (CH_2CHXCH_2 (X = Cl, Het). According to the ^{1}H NMR data (Figures S1–S2) the modification degree was 15% for **3** and 20% for **5**. The modification degree was estimated from the ratio of integral intensities of substituted CHX groups (X = Cl or azoloazine) of main chain of PVC versus integral intensity of peaks of protons of CH group of azoloazine substituents in ^{1}H NMR spectra. To confirm the loading of azoloazine moieties into PVC core in polymers **3,5**, their GPC analysis was carried out. Based on the GPC data (Figures S4–S5), the M_n of polymer **3** was 104.7 kDa (PDI = 1.4) and for polymer **5** M_n = 80.4 kDa (PDI = 1.4), which is higher than M_n starting PVC (M_n ~ 65 kDa). In addition, based on the data of elemental analysis, a decrease in the Cl content as compared to starting PVC along with an increase in the content of *N* in the polymer samples (Tables S3–S6) takes place, and the data of elemental analysis in 3 parallels were very close to each other, which confirms the similarity of polymer composition in the whole polymer volume. In addition to azoloazines salts **2,4**, the possibility for the introduction of *in situ* formed *S*-potassium salt of 2-mercaptobenzothiazole (multi-activity drug component) **6** was studied. Thus, upon heating of PVC and **6** in the solution of DMF in the presence of K_2CO_3 *S*-azole-substituted polymer **7** was obtained. In addition, the reaction was carried out upon ball-milling conditions. Based on the ^{1}H NMR, depending of the time of the ball-milling process, the modification degree has varied from *ca.* 1% to 6.8% (Table S2, Figure S4). It is worth to mention that, according to ^{1}H NMR (Figure S3–S4), the degree of modification was higher in case of mechanochemical approach (4.1% (solution) *vs* 6.8% (ball-milling)), which, possibly, indicates some advantages of mechanochemical approach over solution-based ones.

4. Limitations of solvent-assisted method

The limitations of solvent processes were the following: long reaction time and low solubility of salt forms of azole-based drugs as well as low reactivity of *N*-sodium salts **2,4** of azoloazines. To overcame these limitations, we carried out the reaction under the ball-milling conditions at room temperature with much shortened reaction time.

5. Conclusions

In summary, three examples of azole-based drug modified PVCs were prepared by means of the reaction between PVC and *N*-sodium salts **2,4** of azoloazines under mechanochemical conditions, namely ball-milling at 500 RPM for 4 h, or by means of the reaction of between PVC and *in situ* formed *S*-potassium salts of azole **6** in solution in the presence of K_2CO_3 upon heating or by means of ball milling of PVC and azole **6** in the presence of K_2CO_3 at 500 RPM for 4 h. The molecular weight of newly obtained polymers was confirmed by GPC analysis, and the reduce in the content of Cl was confirmed by elemental analysis. According to the ^{1}H NMR the degree of modification of PVC has varied from 4% to 20%. So, ball-milling can be considered as an efficient tool for the introduction of azole- or azoloazine drug fragments into the commercial polymers, such as PVC. The studies of biological activities of thus obtained PVC-supported azoles/azoloazines are under way.

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• Supplementary materials

This manuscript contains supplementary materials, which are available on the corresponding online page.

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• Conflict of interest

The authors declare no conflict of interest.

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