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Preliminary communication

Polyamidoamine dendrimers used as solubility enhancers of ketoprofen

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Abstract

Ketoprofen is a non-steroidal anti-inflammatory drug which is not freely soluble in water and creates gastrointestinal problems. In the present study we investigated the potential of polyamidoamine (PAMAM) dendrimers to increase the solubility of ketoprofen. The effect of variables, such as pH condition, concentration and generation of dendrimer, has been investigated. The experimental results showed that the solubility of ketoprofen in the dendrimer solutions was proportional to dendrimer concentration. Under suitable conditions PAMAM dendrimers can be highly effective used to enhance the solubility of ketoprofen.

Keywords: Polyamidoamine dendrimers; PAMAM; Solubility enhancer; Ketoprofen

1. Introduction

Ketoprofen, 2-(3-benzoylphenyl)-propionic acid, an aryl propionic acid derivative, is an anti-rheumatic drug with well-known anti-inflammatory, antipyretic and analgesic properties [1], as well as mild to moderate pain and dysmenorrhea [2]. Also it is an inhibitor of prostaglandin synthetase [3]. However, it is not freely soluble in water and causes local or systemic disturbance in the gastrointestinal tract [4]. Ketoprofen was found to cause gastrointestinal side effects requiring withdrawal of treatment. Its poor solubility of 0.01% (w/w) in distilled water (pH 7) restricts its use in topical and parenteral applications [5,6]. As poor solubility is generally related to a low bioavailability, this presents a major challenge during drug formulation [7]. In order to improve the solubility of the drug in water, addition of surface active agents and formation of water-soluble salts were carried out and to enhance dissolution and absorption rate, increasing the wettability and micronization of drug particles has often been used to increase the bioavailability of poorly water-soluble drug molecules [8–10], However methods mentioned above have not always been sufficient to achieve this goal.

It is well-known that dendrimers have well-defined tree-like structures with extraordinary symmetry, high branching and maximized terminal functionality density [11–14]. Polyamidoamine (PAMAM) with an ellipsoidal or spheroidal shape (Fig. 1) is one of the most-studied starburst macromolecules. PAMAM has a much higher amino group density comparing with conventional macromolecules, e.g. a third generation PAMAM prepared from ammonia core has 1.24×10^{-4} amine moieties per unit volume (cubic Angstrom units) in contrast to the 1.58×10^{-6} amine moieties per unit volume of a conventional star polymer [14]. The special structure and high density of amino groups in PAMAM may be expected to have

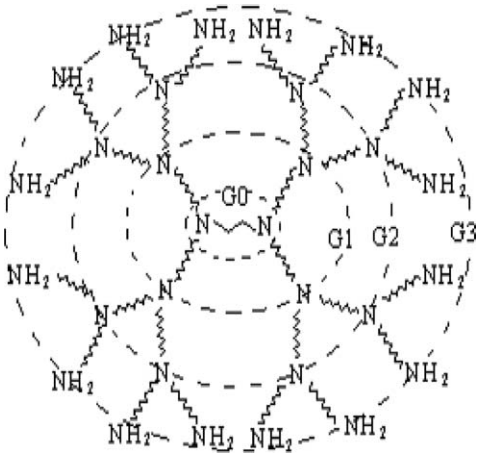

Fig. 1. Schematically molecular structure of the G3 PAMAM dendrimer.

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potential applications in enhancing the solubility of the low aqueous solubility drugs and as delivery systems for bioactive materials [15]. This study uses different generations of PAMAM dendrimers (G2-G5) to investigate the potential of PAMAM dendrimers to increase the solubility of hydrophobic drugs as exemplified by the non-steroidal anti-inflammatory drug ketoprofen.

2. Experiments

2.1. Materials

Ketoprofen was purchased from Hubei Wuxue Xunda Pharmaceutical Co. (Hubei, China). Ethylenediamine, methyl acrylate, methanol (HPLC grade) were obtained from Shanghai Chemical Co. (Shanghai, China). For both solubility studies, distilled water was used.

2.2. Synthesis of PAMAM dendrimers

PAMAM dendrimers were synthesized by the following method [12]. Ethylenediamine (10.0 g, 0.166 mol) was dissolved in 100 ml methanol in a 1-l round-bottomed flask. Methyl acrylate (94.6 g, 0.751 mol) was added at 40 °C and the system stirred for 24 h under nitrogen. Excess methyl acrylate was removed under vacuum at room temperature. A Michael addition between the amine and the acrylate yielded a product bearing four terminal methyl ester groups, defined as the G0.5 PAMAM. Subsequently, ethylenediamine (120 g, 2.00 mol) was dissolved in methanol and added to the G0.5 PAMAM and, after stirring for 48 h under nitrogen and removing excess reactants by vacuum distillation, a product bearing four terminal amino groups were obtained, defined as the G1 PAMAM. By repeating the above cycle, higher generation PAMAM dendrimers (up to G5) were synthesized. The characteristic data of different generations of PAMAM are listed in Table 1.

2.3. Solubility testing experiments

The solubility of ketoprofen in PAMAM dendrimer solutions in the range 0–10 mg/ml was determined at pH 3, 4 and 6 in phosphate buffers (0.05 M NaH_2PO_4). The method used for sample preparation was similar for each system, i.e. excess ketoprofen was added to 5 ml vials containing 4 ml of each test solution. The vials were then incubated in a shaking water bath at 37 °C for 24 h. Then the solutions were centrifuged at 5000 rpm for a minute and the absorbance of the ketoprofen test solutions at the characteristic wavelength 260 nm were tested using the Varian Cary VIII spectrophotometer.

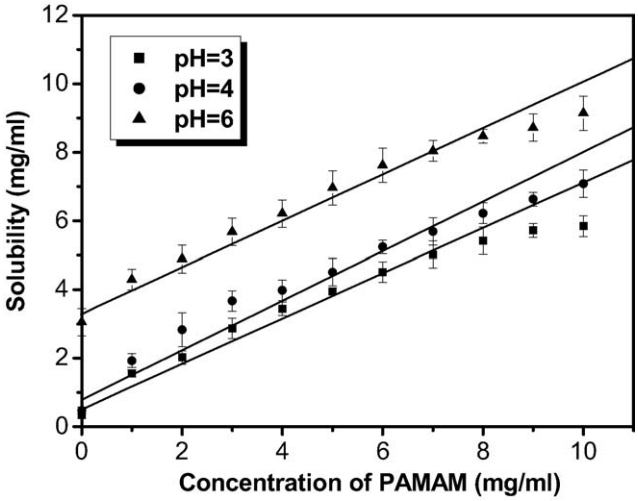

Fig. 2. Solubility of ketoprofen in the presence of increasing concentration of G4 PAMAM dendrimer.

3. Results and discussion

3.1. Effect of PAMAM concentration on solubility of ketoprofen

A series of solubility experiments of ketoprofen were carried out using G4 PAMAM dendrimer of molecular weight 6900 Da and 32 amine groups in the outer shell, and the results were shown in Fig. 2. It was observed that the solubility of ketoprofen increased significantly with PAMAM concentrations. In the presence of G4 PAMAM dendrimer at a fixed pH condition, the solubility of ketoprofen in the dendrimer solutions increased in an approximately linear manner with an increase in dendrimer concentration. This was presumably due to the increase in the number of surface amines that are available to interact with ketoprofen molecules.

3.2. Effect of pH condition on solubility of ketoprofen

To ascertain the most effective pH condition on solubility of ketoprofen using PAMAM dendrimers, samples of ketoprofen solution were produced at a range of pH values, the

Table 1
The characteristic data of PAMAM dendrimers

Generation	Molecular formula	Molecular weight	Number of terminal amino groups	Number of total amino groups	Radius from SAXS (Å)
G1	$C_{22}H_{48}O_4N_{10}$	516	4	10	–
G2	$C_{62}H_{128}O_{12}N_{26}$	1428	8	26	–
G3	$C_{142}H_{288}O_{28}N_{58}$	3252	16	58	15.8
G4	$C_{302}H_{608}O_{60}N_{122}$	6900	32	122	17.1
G5	$C_{622}H_{1248}O_{124}N_{250}$	14196	64	250	24.1

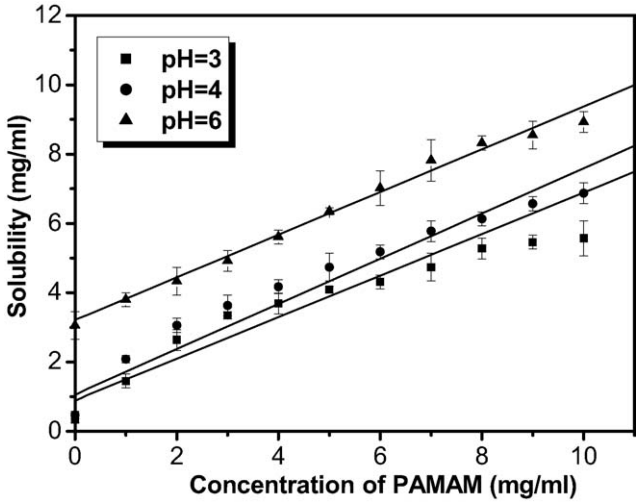

Fig. 3. Solubility of ketoprofen in the presence of increasing concentration of G2 PAMAM dendrimer.

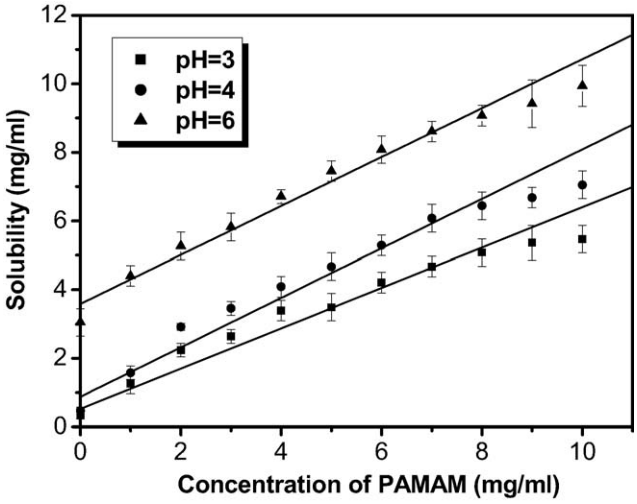

Fig. 4. Solubility of ketoprofen in the presence of increasing concentration of G3 PAMAM dendrimer.

concentration of G4 PAMAM dendrimer being constant. The results are also shown in Fig. 2 and, as can be seen, the process was pH-dependent. The solubility of ketoprofen in PAMAM dendrimer solutions was highest at pH 6, less at pH 4, and least at pH 3. It is proposed therefore, that the solubility enhancement is due to an electrostatically interaction between the surface amine groups of dendrimer molecule and the carboxyl group of ketoprofen. Evidence for this is seen from the solubility of ketoprofen over a range of pH value (Fig. 2). At low pH there is lower significant increase of solubility of ketoprofen in dendrimer solution compared to that at high pH. This is because the weakly acidic ketoprofen molecule is not fully ionized at low pH conditions and hence cannot freely interact electrostatically with the dendrimer molecule.

3.3. Effect of different generations of PAMAM on solubility of ketoprofen

The effect of various generations of PAMAM dendrimers (G2-G5) on the process was investigated at pH 3, 4, 6, respectively. The results are shown in Figs. 3–5, from which it is clear that the solubility of ketoprofen was affected by the generation of PAMAM dendrimer. The solubility of ketoprofen in higher generation PAMAM solution was in fact higher that those in lower ones. The solubility of ketoprofen in PAMAM solutions depend on the surface area and amino groups of PAMAM particles, thus a molecule of higher generation PAMAM particle has a higher ability to absorb and interact with the ketoprofen molecule than that of lower one.

4. Conclusion

Different generation (G2-G5) PAMAM dendrimers have the potential to significantly enhance the solubility of poorly water-soluble drugs such as ketoprofen. The drug solubility

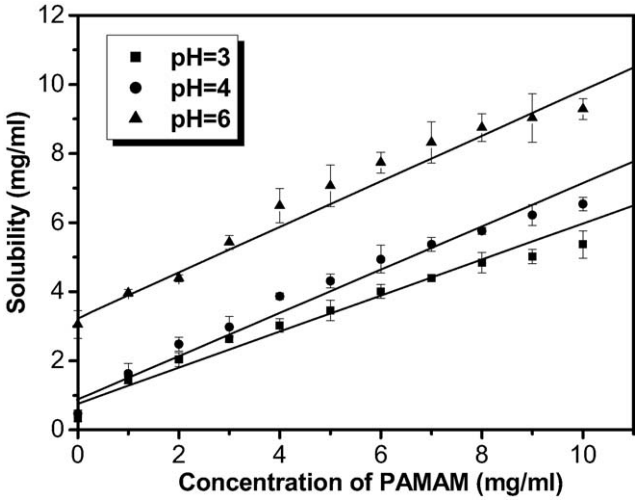

Fig. 5. Solubility of ketoprofen in the presence of increasing concentration of G5 PAMAM dendrimer.

depends on the concentration of the dendrimer, the pH value of the solution, and the generation of the dendrimer. Both observations are evidence of interactions between the surface amine groups of dendrimer molecule and the carboxyl group of ketoprofen.

Acknowledgements

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