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# New and efficient technique for the synthesis of Urapidil using β-cyclodextrin as an inverse phase-transfer catalyst

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ABSTRACT

A novel and efficient procedure has been developed for the preparation of Urapidil, (6-({3-4-(2-methoxyphenyl) piperazin-1-yl] propyl} amino)-1,3-dimethyl pyrimidine-2,4-(1H, 3H)-dione), from 6-[(3-chloropropyl) amino]-1, 3-dimethyluracil and 1-(2-methoxyphenyl) piperazine hydrochloride under inverse phase-transfer catalysis (IPTC) conditions. To optimize the reaction conditions, the alkylation reaction was carried out with a range of inverse phase-transfer catalysts, agitation speeds, reaction times, reaction temperatures, mole ratios and catalyst loadings. In addition, the factors affecting the rate of reaction were studied and the rate constant obtained is consistent with the pseudo-first order rate equation. When β-cyclodextrin was used as a catalyst, Urapidil was obtained as a white crystalline powder in 82.6% isolated yield with 99.6% purity after 2–3 h reaction in alkaline aqueous media at 95 °C with an agitation rate of 1500 rpm.



## 1. Introduction

Urapidil, 6-({3-4-(2-methoxyphenyl) piperazin-1-yl] propyl} amino)-1,3-dimethyl pyrimidine-2,4-(1H, 3H)-dione (**8**), is a sympatholytic antihypertensive drug [1–7]. It acts as both an $\alpha_1$-adrenoceptor antagonist and an 5-$HT_1$A receptor agonist. Urapidil was initially introduced to the pharmaceutical market in 1981 in German and has subsequently been applied in more than 30 countries around the world. Its efficacy and safety are well established, but a "green" synthesis process optimization is yet to be established.

Urapidil is prepared by a four-step synthetic process (Scheme 1) [3]. In the first step, N,N′-dimethyl urea (**1**) is condensed with cyanoacetic acid (**2**) in hot acetic anhydride to afford the intermediate 6-amino-1, 3-dimethyl-2, 4(1H, 3H)-pyrimidinedione (**3**) in 92.1% yield. The following two steps, the deamination of 3-with 3-amino-1-propanol, and the hydroxyl group chlorination, also proceeded well to provide **6**. The final step, Urapidil is produced by the N-alkylation of 6-[(3-chloropropyl) amino]-1,3-dimethyluracil (**6**) with 1-(2-methoxy phenyl) piperazine (**7**). The N-alkylation step has been carried out in aqueous media with no catalyst. The heterogeneity of the reaction mixture, in which both **6** and **8** were almost insoluble, led to large variations in product purity (85–90%) and poor yields (29–40%).

Inverse phase-transfer catalysis (IPTC) is an efficient method to solve the heterogeneity problem. The inverse phase-transfer catalysts can transfer the organic substrate into the aqueous phase and, therefore, improve the mass transfer between two immiscible reactants. The advantages of IPTC over PTC are: (a) easier catalyst separation and reuse, and (b) no other organic solvents are necessary if substrates are liquid at the reaction temperature. Nowadays, inverse phase-transfer catalysis has received increasing attention due to its applicability to various reactions [8–16]. Moreover, the application of IPTC in industry has been extended to pollution and environmental control processes.

The main purpose of this study is to synthesize Urapidil from the N-alkylation reaction of compounds **6** and **7** in an alkaline aqueous solution under IPTC conditions. Until now, no report on the use of IPTC for the N-alkylation of 1-(2-methoxy phenyl) piperazine (**7**) has been presented. In the present work, the IPTC reaction conditions for the production of Urapidil with consistent yields and purity were investigated. The effects of the reaction parameters, including the type of inverse phase-transfer catalyst, the agitation speed, the reaction time, the reaction temperature, the mole ratios of the raw materials and the catalyst loading were examined in detail. In addition, the factors affecting the rate of reaction were studied.

## 2. Experimental

### 2.1. Materials

All the inverse phase-transfer catalysts used in the present study were commercially available materials. β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin were obtained from Tianjin Kermel chemical reagent Co. Ltd. Hexadecy ltrimethyl ammonium bromide

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