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Effect of Molar Mass of Hydroxypropyl β-cyclodextrin on the Aqueous Solubility of Dimenhydrinate

LAMIJA HINDIJA[1]; JASMINA HADŽIABDIĆ[1]; OGNJENKA RAHIĆ[1]; AMINA TUCAK-SMAJIĆ[1]; MERIMA SIRBUBALO[1]; IMRE KLEBOVICH[2]; EDINA VRANIĆ[1]

[1] *University of Sarajevo, Faculty of Pharmacy, Department of Pharmaceutical Technology, Zmaja od Bosne 8, 71 000, Sarajevo, Bosnia and Herzegovina*
[2] *Department of Pharmaceutics, Semmelweis University, Hőgyes Endre Str. 7., H-1092 Budapest, Hungary*

Correspondence: lamija.hindija@ffsa.unsa.ba

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1. Introduction

Dimenhydrinate (DMH) is used for the prevention and treatment of nausea, vomiting, dizziness and vertigo associated with motion sickness in a dose of 50 mg [1]. It's made of two drugs in a form of salt, diphenhydramine and 8-chlorotheophylline which synergically decrease motion caused neural excitation [2]. DMH is classified as a slightly soluble drug and it belongs to class II of BCS classification as a drug with low solubility and high permeability [3].

Cyclodextrins (CDs) are cyclic oligosaccharides formed by α-1,4-linked glucose units with a hydrophilic outer surface and a lipophilic central cavity. Formation of inclusion complex by incorporating a drug in the central CD cavity provides improvement of physicochemical properties without molecular modifications. Solubility and dissolution rate of poorly water-soluble drugs can be increased [4]. Aqueous solubility of natural CDs is limited due to their tendency to form H-bonded associations. However, due to multiple reactive hydroxyl groups, their functionality can be greatly increased by chemical modification [5]. CDs' substituted derivates can overcome poor solubility issues and enhance bioavailability. Hydroxypropyl-β-CD (HP-β-CD) has good inclusion ability, high water solubility and it's safe for intravenous and oral administration [6].

Stability constant (K_s) and complexation efficacy (CE) are important for assessing the binding characteristics of the drug and CD. They can be determined by the phase solubility studies where the change of the drug solubility is corresponding to the concentration of CD [7]. Linear (A_L) type of the curve implies that one molecule of the drug forms inclusion complex with one molecule of the CD. Apparent stability constant $K_{1:1}$ can be calculated from the following equation:

$$K_{1:1} = \frac{\text{Slope}}{S_0 \cdot (1 - \text{Slope})}$$

S_0 represents the intrinsic solubility of the drug.

To avoid inaccurate and misinterpreted results due to dependence of $K_{1:1}$ on small changes in S_0 and possible self-association of lipophilic drug molecules in aqueous media, CE can be determined [8].

$$CE = K_{1:1} \cdot S_0 = \frac{\text{Slope}}{(1 - \text{Slope})}$$

Efficacy of CD as a complexing agent can also be determined by calculating the utility number (U_{CD}).

$$U_{CD} = \frac{K_{1:1} S_o}{1 + K_{1:1} S_o} \frac{m_{CD}}{m_D} \frac{M_{\gamma D}}{M_{\gamma CD}}$$

m_{CD} represents workable amount of cyclodextrin, m_D is the drug dose while $M_{\gamma D}$ and $M_{\gamma CD}$ stand for molecular weight of drug and CD [9].

The present work aimed to examine the effect of 2-HP-β-CD with various molar masses (M) on the aqueous solubility of DMH.

2. Materials and methods

Phase solubility studies were carried out to determine $K_{1:1}$ and CE of formed complexes. Aqueous solutions of different 2-HP-β-CDs (Kleptose® HPB oral grade M=1387g/mol, Kleptose® HP oral grade M=1501g/mol - Roquette, France and Cavasol W7® HP Pharma M=1410g/mol - Ashland™, Netherlands) were prepared at concentration range from

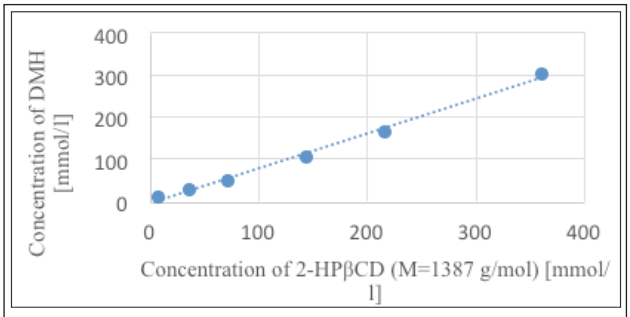

Figure 1 *Phase solubility diagram of DMH and 2-HP-β-CD (M=1387 g/mol) in distilled water*

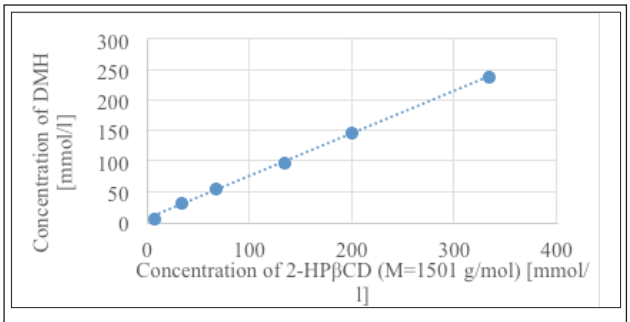

Figure 2 *Phase solubility diagram of DMH and 2-HP-β-CD (M=1501 g/mol) in distilled water*

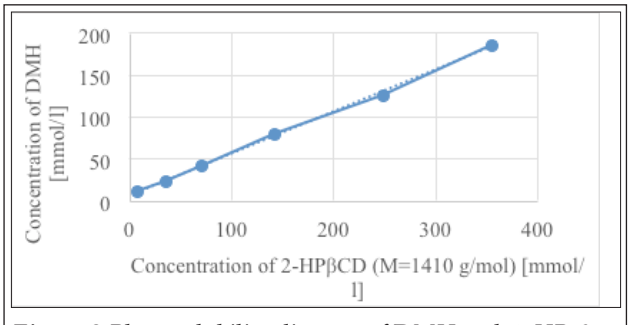

Figure 3 *Phase solubility diagram of DMH and 2-HP-β-CD (M=1410 g/mol) in distilled water*

1% to 50% (w/w). The excess amount of the drug (dimenhydrinate - Bosnalijek, Bosnia and Herzegovina) was added into conical flasks and the mixture was stirred continuously (Magnetic stirrer Witeg, WiseStir MSH-20D) for 24h at 25°C ± 0,1°C to reach equilibrium. Then the aliquot was filtered through a 0,2 pore size membrane filter (Cellulose acetate filter, Sartorius, Germany), diluted with 0,1 M hydrochloric acid and DMH concentration was determined spectrophotometrically at 277 nm (Shimadzu UV spectrophotometer-1601). Each measurement was run in triplicate.

3. Results

The solubility of DMH in 2-HP-β-CD aqueous solutions increased linearly as a function of 2-HP-β-CD concentration showing A_L-type isotherms.

The slope was less than unity thus a 1:1 complex was formed.

Table 1 *Values of $K_{1:1}$, CE, solubility increase (SI) and concentration of 2-HP-β-CD solution when $U_{CD} \geq 1$*

Molar mass of 2-HP-β-CD	$K_{1:1}$ [M^{-1}]	CE	SI	$U_{CD} \geq 1$
1387	259,39	5,22	2,51	10%
1501	116,09	2,339	2,81	10%
1410	49,94	1,006	2,16	10%

SI was calculated as a ratio of solubility of DMH in 10% (w/w) 2-HP-β-CD solution and S_0. Complete solubilization of 50 mg of DMH by complexation with CDs where U_{CD} value is equal or greater than 1 was achieved in 10% solutions of 2-HP-β-CD for all the three CDs.

$K_{1:1}$ of 2-HP-β-CD (M=1410) was below 100 M^{-1} so the premature release of the drug and insignificant improvement in solubility may occur. None of the $K_{1:1}$ values were above 5000 M^{-1} so the incomplete or obstructed release of the drug from CD cavity due to excessive stability of complex shouldn't be expected.

4. Conclusions

The results showed that 2-HP-β-CD enhances the solubility of DMH and forms a 1:1 inclusion complex. The order of solubilizing power is 2-HP-β-CD (M=1387 g/mol) > 2-HP-β-CD (M=1501 g/mol) > 2-HP-β-CD (M=1410 g/mol). 2-HP-β-CD (M=1387 g/mol) forms the most stable inclusion complexes with DMH due to the highest value of $K_{1:1}$ and CE. This 2-HP-β-CD can be considered for usage in different formulations to improve the solubility and stability of DMH.

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