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Feasibility study of theophylline solution in water and sodium carboxy-methylcellulose

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Abstract: *Solution is a liquid dosage form that ensures better bioavailability of drug upon oral administration. In this study an attempt was taken to prepare theophylline solution (20mg/ml) using sodium carboxy-methylcellulose as a vehicle. Feasibility of Na-CMC as drug vehicle was tested and compared with widely used vehicle water. Effect of different storage conditions on organoleptic and physicochemical properties was tested for a period of three months. Drug potency was found 9-13 mg/ml and 14-16 mg/ml in water and Na-CMC respectively and was consistent with time. Viscosity of the solution was good with easy pourability for both of the vehicles used. Theophylline solution in water showed changes in color after two months. However, no changes in organoleptic properties with CMC-Na as vehicle within the experimental time period irrespective of storage condition. Moreover, good stability of the theophylline solution was seen with Na-CMC at 1% (w/v) concentration.*

Keywords: Solution; carboxymethylcellulose sodium; asthma; theophylline.

1. Introduction

Solution is one of the most common dosage forms for oral administration. It is a clear homogenous system where the solid substances remain dissolved in a liquid phase [1]. It has several advantages like rapid onset of action, faster absorption rate, simple method of preparation and so on compared to solid dosage form. Along with this liquid dosage forms are best choice for children and elderly patients for ease of swelling [2]. Use of sweeteners, flavoring agents, coloring agents make this dosage form palatable and results in increased patient compliance [3]. Syrup, suspension, elixir, emulsion are other forms of oral liquid dosage forms. In spite of these liquid dosage forms, solution has some additional advantages. Solution is free from sedimentation and ensures uniform dose than suspension or emulsion which requires shaking [4]. Besides this gastric irritation caused by some drugs can be avoided when administered as solution because of immediate dilution by gastric contents. However this dosage form is not denied of problems. Major disadvantages of solution are poor stability, prone to microbial growth, difficulties in storage and transportation and not suitable for poorly soluble drugs [5]. Although solution has some problems, it is one of the widely used dosage form still now. Depending on drug solubility, both aqueous and organic solvents are used as vehicle or drug carrier in solution. Water is widely used vehicle for solution due to its easy availability and better biocompatibility [6].

Sodium carboxymethylcellulose (Na-CMC) is sodium salt form of a cellulose derivative having carboxymethyl group. It is widely used in both food and pharmaceutical industry. Na-CMC is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Varying on its concentration Na-CMC can be used as emulsifying agent, gelling agent in oral and topical solutions. Usually in oral solution Na-CMC is used at a concentration of 0.1-1% (w/v) [7]. Its higher aqueous solubility, good swelling properties and erosion characteristics make it a good candidate for use as a carrier in solution [6]. Na-CMC is easily dispersible that ensures better solubility of drug and uniform distribution in a preparation. At the same time use of Na-CMC may retard drug release that helps to improve patient compliance by reducing dosing frequency [8].

Asthma is inflammation of airways that causes bronchoconstriction and one of the leading causes of death in Bangladesh [9]. Regrettably asthma is only manageable, not curable. Different types of bronchodilators are mainly used in the treatment of asthma. One of them is theophylline which is a second line drug used in addition with steroids in chronic asthma. This drug has been using over the last 50 years or so [10]. It acts by phosphodiesterase inhibition followed by increased cAMP level that causes airways relaxation [11]. Most of the commercially available theophylline preparations in Bangladesh are solid dosage forms. A few of the manufacturers prepare theophylline as syrup and injection [12]. Unfortunately all the available preparations of theophylline are not suitable for all kinds of patients. The solid and liquid forms contain glycogenic materials like sorbitol, glycerol, sugar etc. which make it unsuitable for asthma patients with diabetes [13]. Similarly high content of sugar in syrup causes dental carries and sometimes gastrointestinal problems in children due to their underdeveloped digestive system [14]. Therefore it will be useful if theophylline is formulated in liquid form without glycogenic materials and high sugar content.

In this study we are focusing on formulation and preparation of theophylline solution using water and Na-CMC (1% w/v). Different quality tests were performed along within stability study in different storage conditions to determine the feasibility of theophylline solution. If the results found good and acceptable, it will be a new hope for both pediatric and geriatric patients with chronic asthma.

2. Materials and methods

2.1 Materials

Theophylline anhydrous was gift from Square Pharmaceuticals Ltd., Bangladesh. Citric acid, ascorbic acid (antioxidants), aspartame (sweetener), methyl paraben (preservative) and sodium carboxymethylcellulose (Na-CMC) were gift from Department of Pharmacy, Jahangirnagar University, Bangladesh.

2.2 Methods

2.2.1 Theophylline solution preparation: All the excipients were added to water gradually and mixed well by magnetic stirring. After that theophylline was added in a concentration of 20mg/ml and stirred until a clear solution was formed. The same was followed when using 1% Na-CMC as a vehicle. All the prepared solutions were filled in glass container and stored in two different conditions- a) at room temperature, b) dark and cool place (20ºC).

2.2.2 Quality control tests

i) Aesthetic properties: Aesthetic properties of prepared solutions namely color, odor, transparency were observed visually during the experimental time period of three months. Quality of solution based on aesthetic properties was evaluated according to the typical thermometer scale of consumer acceptability.

ii) Assay: For assay of theophylline solution, 0.1ml of solution was withdrawn and diluted 1000 times with water. Then absorbance of diluted solution was determined using UV-visible spectrophotometer (Shimadzu 1601 PC, Japan) at 214nm wavelength. The concentration of theophylline in solution was determined by using standard calibration curve from 1µg/ml to 32µg/ml. This test was done for all solutions and from all storage condition.

iii) Viscosity: Viscosity of prepared theophylline solution at different storage conditions was tested using Ostwald viscometer. Viscosity of prepared solutions was compared with viscosity of water at room temperature.

3. Results

i) Aesthetic properties: Physical stability of solutions was usually determined by its changes on organoleptic properties with time and environmental conditions i.e. light, temperature, humidity etc. [15]. Results of aesthetic properties for theophylline solution in water and Na-CMC are given on Table 1 and Table 2 respectively.

Table 1: Stability of theophylline solution in water

Day	Solution in water					
	Room temperature			Dark and cool place		
	Color	Odor	Ppt↓	Color	Odor	Ppt↓
1	○	√	×	○	√	×
7	○	√	×	○	√	×
15	○	√	×	○	√	×
30	○	√	×	○	√	×
60	🟡	√	×	○	√	×
90	🟡	√	×	🟡	√	×

Note: Ppt↓- Precipitation, ○- Colorless, 🟡-Yellowish color, √-Good, × - Absent.

Table 2: Stability of theophylline solution in 1% Na-CMC

Day	Solution in water					
	Room temperature			Dark and cool place		
	Color	Odor	Ppt↓	Color	Odor	Ppt↓
1	○	√	×	○	√	×
7	○	√	×	○	√	×
15	○	√	×	○	√	×
30	○	√	×	○	√	×
60	○	√	×	○	√	×
90	○	√	×	○	√	×

Note: Ppt↓- Precipitation, ○ - Colorless, √-Good, ×- Absent

ii) Assay: Assay of the prepared solutions was done to determine quality, efficacy and safety of drug therapy [16]. Result of assay for prepared solution is given in figure 1.

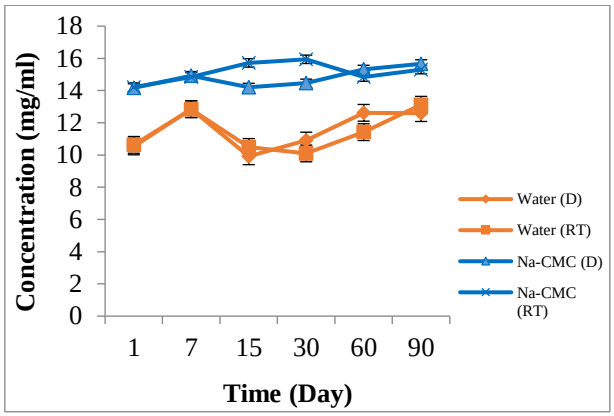

Figure 1: Theophylline concentration in different vehicle with time. D = Dark and cool place, RT= Room temperature.

iii) Viscosity: Viscosity of solution changes with temperature and also depends on excipients used [15]. Effect of storage condition on theophylline solution during experimental time period is shown in figure 2.

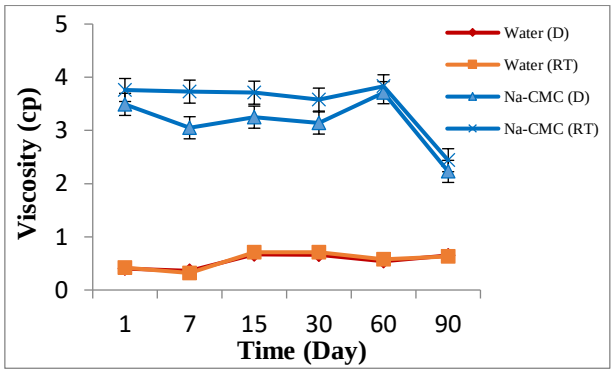

Figure 2: Viscosity of theophylline solution with time. D = Dark and cool place, RT= Room temperature.

4. Discussion

As we make an effort to prepare theophylline solution with a better carrier, therefore theophylline solution was prepared using both water and Na-CMC as carrier. At the same time effect of light and temperature was also tested for the prepared solutions for a time span of three months. Results of different quality tests show the possibility of theophylline solution.

In case of aesthetic properties, changes in color, odor was observed. No changes took place for theophylline

solution in 1% Na-CMC (w/v) regardless of storage condition. But in case of solution in water, preparation turns slight yellowish after second and third month at room temperature and dark and cool place respectively (table 1 and 2). This may be due to photolytic reaction which affects the structural conformation of any component used in the solution. In case of Na-CMC its viscosity imparting property protects the components from such conformation change. No sedimentation as well as precipitation of drug particles took place for all the solutions during the stability period. Assay of theophylline solution gives useful information for how much drug will be dispensed on unit dose. For solution in water drug concentration was found 9-13 mg/ml and 14-16 mg/ml for solution in Na-CMC during experimental time period (figure 1). Drug concentration was not affected by storage condition and showed a consistency with time mainly for 1% Na-CMC. In case of water as a solvent, drug concentration showed a discrepancy with time which may be a result of poor solubility of theophylline in water. Theophylline was used at a concentration of 20 mg/ml of concentration and our assay results are very close to this amount for 1% Na-CMC. Therefore dosage uniformity can be maintained if theophylline is administered as solution. Further study is needed in this regard. On the other hand viscosity of theophylline solution was same regardless of light and temperature. Viscosity of solution in water was lower (0.5 on average) than solution in Na-CMC (3.0 on average) because of viscosity imparting nature of Na-CMC (figure 2). But no problem was found during dispensing of solution from bottle for its viscous nature. This property can be used to get sustained drug release from theophylline solution. Usually viscosity decreases with temperature. In our study we stored solutions in both dark and cool condition and room temperature. As the temperature difference was not so high between the two storage conditions, viscosity of the solution remain almost same for both of the carriers. Although in case of Na-CMC, a fall in viscosity was found after 3 months for all storage conditions. Further study is needed to determine the reason behind this. As our results are found good for assay, viscosity and organoleptic properties, it is possible to formulate theophylline as solution for oral administration. Depending on the results of assay and stability study at different storage conditions we can assume that Na-CMC at a concentration of 1% w/v is a good vehicle for theophylline solution compared to water. Such preparation will be better for both pediatric and geriatric patients and also for diabetic patients as our solution devoid of any sugar or glycogenic substances.

5. Conclusion

This study has shown promising data for potency and viscosity of theophylline solution. At the same time data showing effect of light and temperature on solution quality is also encouraging. Therefore it can be concluded that it is possible to formulate and prepare theophylline solution and data can be simulated to in-vivo study for further progression of research.

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