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ATTEMPTS AT FORMULATION OF SYRUP WITH THEOPHYLLINE

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Abstract: The aim of this study was attempt to formulate syrup with theophylline. This form of drug would enable easy adjustment of individual doses of drug for therapeutic purposes in children. Due to poor solubility of theophylline in water, attempts at increasing of its solubility by adding special adjuvant substances, which could increase solubility and stabilise the obtained solution, were of particular importance.

Keywords: syrup, theophylline, adjuvant substances, stability, solubility.

Theophylline is one of the oldest and most commonly used antiasthmatic drugs. New understanding of asthma as a disease, caused by chronic inflammatory process, has changed the therapeutic approach, making anti–inflammatory drugs the first choice substances.

Current studies disclosed anti–inflammatory, but also immunomodulatory effect of theophyllline and caused renewed interest in this drug, in particular as this effect can be seen at very low doses of theophylline (1, 2). According to the report of NHLBI/WHO (National Heart, Lung and Blood Institute), published in 1995, the importance of theophylline in the controlled treatment of asthma increased. This drug is recommended by world experts in all stages of chronic asthma.

Theophylline have been used together with ethylenediamine; this form of the drug is now controversial. Numerous adverse reactions occurring after the administration of theophylline preparations with ethylenediamine, reported in literature, are ascribed to the latter compound (3). Thus, leading producers of theophylline preparations have recently introduced forms containing only theophylline as the active substance.

Theophylline is poorly soluble in water (8.3 mg/l). Adding substances which increase solubility, make possible to include greater amount of therapeutic substance in the water or oil solution, and thus, to obtain a pharmaceutical form suitable for clinical conditions. Adding non–water solvents which mix with water such as, ethanol, glycerol and other glycols, can additionally improve the absorption of such therapeutic substances as, for example, theophylline (4).

Hydrotrophic substances, so called intermediate solvents, contain powerful hydrophilic polar groups, which cause molecular dispersion of the substance in water. Thus, they create soluble complex bonds. Such properties are seen in some polar organic solvents such as, mono– and polyhydroxide alcohols, glycols, sugars with numerous hydroxide groups (mannitol, sorbitol, glucose, fructose, saccharose) and esters, ethers of polyhydroxide alcohols. Solubility can be improved also by organic acid salts (benzoate sodium, salicylate sodium), mono, di– and trihydroxybenzoates, carboxylic acids (tartaric acid, benzoic acid, citric acid) and compounds with nitrogen atom in their molecules such as, ethylenediamine, polyvinylpirolidone). Solubility in water of non electrolytes can be also changed by the presence of ionogenic substances such as, tartaric, citric and benzoic acids and their salts, and also amino acids (4–8).

Currently, numerous preparations of theophylline are present at the pharmaceutical market, where lot of them are preparations of modified release rate or prolonged activity. They contain amounts of the active substance which are sufficient for adult patients. Large amounts of theophylline in these preparations are not appropriate for the treatment of children, in particular because of these preparations cannot be precisely divided, which is necessary, if the doses are to be individualised, and thus if the therapy is to be effective.

Therefore, an attempt was made to create a form of the drug therapeutically attractive due to high degree of fragmentation and bioavailability – the syrup, containing theophylline as the active substance for small children. Due to poor solubility of theophylline in water, its solubility needed to be increased by adding substances

enhancing solubility, which would also stabilise the obtained solution.

EXPERIMENTAL

Materials and reagents

Theophyllinum anhydricum BP 88 (Margo), Theophylline (Sigma Reference Standard Lot 53H59521), propylene glycol (Sigma), glycerine solution 86% (POCh), methylpropylparaben (Sigma), methanol (Sigma), propanol–2 p.a. (POCh), toluene p.a. (Sigma), ammonia 25% cz.d.a. (POCh), tartaric acid (Sigma), citric acid (Sigma), sodium benzoate solutions (Sigma), hydrochloric acid (Sigma), sodium hydroxide (Sigma), mannitol (Sigma), ethanol (Polmos), gustatory and fragrant substances (Dragocco), sacharose.

Preparation of syrups with theophylline

The first stage concentrated on finding a substance which would increase the solubility of theophylline in water solution to a greatest degree. Thus, we have studied the solutions of compounds such as citric, benzoic and tartaric acids, sodium benzoate, hydrochloric acid, sodium hydroxide, ethanol and mannitol.

In the second stage, the active substance was dissolved in the mixtures of the above mentioned substances with propylene glycol and glycerine.

Then, the composition of syrups containing theophylline in the dose of 100 mg/15 ml was established. The dose of theophylline was chosen to enhance individualisation of treatment for particular partients, i.e. enable administration of higher doses, multiplicity of the standard volume of the solution (15 ml) and smaller doses possible to measure and administer precisely.

Therefore, 0.67 g of theophylline was weighed and dissolved in respective amounts of adjuvant substances solutions used for the preparation of particular types of syrups. Then, preservatives, gustatory and fragrant substances were added. The composition of created syrups is presented in Table 1.

Determination of theophylline content by spectrophotometry

The content of theophylline in created formulations of syrups was done by spectrophotometer Spectrom 195 D by the method described in the British Pharmacopoeia (BP 88) [9]. To determine the content of the active substance in the prepared formulations, calibration curves were drawn separately for theophylline solutions of acidic and alkaline character.

The performed analyses gave calibration curves described by linear equation y=ax+b.

For solution of acidic character the equation was:

y=0.053x+0.0396 at the correlation coefficient r=0.996

For solution of alkaline character the equation was:

y=0.0623x+0.0200 at the correlation coefficient r=0.998

Both equations were used to calculate the content of theophylline in the prepared liquid formulations.

Determinations of the presence of theophylline degradation products by thin layer chromatograpy

Storage of theophylline solutions may create conditions in which theophylline may react with the adjuvant substances or with environmental factors. It may lead to the degradation of theophylline and formation of theophyllidine – product of theophylline degradation – well known in literature [10]. Even though theophyllidine is claimed to form at very high temperature in highly alkaline environment, there is no evidence saying that it cannot form in other conditions, in particular in liquid theophylline solutions of various composition.

Therefore, a standard theophylline solution was made by dissolving 50 mg of the standard active substance in 5 ml of mixture of methyl alcohol and water 4:1.

Chromatography was done on glass plates covered by silica gel 60F 254 from Merck, which were activated for 1 hour at 120°C before the studied and standard solutions were added. As the mobile phase, a mixture of toluene, 2–propanol and 25% solution of ammonia 30:60:10 was used. The developing process was done in a glass chamber saturated with solvent vapours, placed in a dark compartment with the walls protected from light by special paper. The developing was continued for 100 minutes.

The activated chromatographic plate with a marked start and 15 cm of chromatography route was covered with 20 µl of the studied solution and 10 µl of the standard. The plate was placed in the chromatographic chamber saturated with the vapours of solvent. When the chromatograms were developed to 15 cm, the plate was removed from the chamber, dried at 120°C and the chromatograms were evaluated in UV radiation at the wavelength of 254 nm.

The studied solutions were prepared by sampling of 15 ml of syrup and mixing it with 5 ml of methanol. Then, the samples were shaken, cent-

Table 1. The composition of syrups

Composition [g/100 ml]	1	2	3	4	5	6	7	8	9	10
Theophylline	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67
Benzoic acid	0.01	0.02	0.03	0.03						
Sodium benzoate					0.05	0.45	0.015	1.00		
Citric acid	1.00	2.40	1.00	2.40	3.60	0.50				0.84
Tartaric acid	1.00	1.00	1.00	1.00	1.00					
Hydrochloric acid										0.43
Sodium hydroxide							0.08	0.04	0.40	
Ethanol 96°								1.00		
Mannitol									1.50	
Propylene glycol	20.80	20.80	20.80	26.00		20.80	5.20			
Glycerin 86%			8.60							
Methyl-propylparaben (2:1)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Water + gustatory and fragrant substances [ml]	up to 100 ml									

rifuged and placed on chromatographic plates beside theophylline standard. When observed in UV radiation, the stains of standard and studied substances were similar about the shape and position (R_F 0.24).

Determining the stability of liquid theophyllline formulations

In order to choose optimal formulation, the determination of the studied solutions behaviour during storage in standard conditions is important. Thus, stability of theophylline syrups, stored at room temperature for 12 months, was studied. The study included: determination of the content of the active substance, pH, visual evaluation of the solutions and determination of the presence of degradation products.

RESULTS

In the first stage of our study, we attempted to dissolve theophylline in single solutions of adjuvant substances which could increase its solubility. Results were, however, not satisfactory. The second stage concerned the dissolving of the active substance in mixtures of adjuvant substances with propylene glycol and glycerine. From the created compositions we have chosen those, where the smallest amount of adjuvant substance increased the solubility of theophylline in water.

Determined amounts of the active substance directly after the preparation of various formulations were 99.1% to 101.1% of the theoretical value. Specific gravity of the created syrups was from 1.15 to 1.23 g/l, and pH from 2.1 to 8.6.

Stability of theophylline in earlier prepared syrups (content presented in Table 1) was analysed after 1, 2, 3, 6, 15 and 30 days, and after 3, 6 and 12 months from their preparation. The obtained results are presented in Table 2.

The same time intervals were used to control pH changes and make visual evaluation, which may show physical and chemical changes of the solutions.

No visual changes were noted in acidic syrups during the study. In formulations of alkaline pH between 16th and 30th days significant opalescence was noted, which may indicate that strong alkaline environment is not appropriate for theophylline formulations. Thus, these solutions were excluded from further study (composition 7 and 8). In acid syrups changes in theophylline content did not exceed 10%. No products of theophylline degradation were seen.

Table 2. Stability of theophylline in prepared syrups

Composition	Theophylline content [g/100 ml] in syrups in time								
	[days]						[months]		
	1	2	3	6	15	30	3	6	12
1	0.677	0.673	0.677	0.676	0.677	0.676	0.665	0.659	0.620
2	0.671	0.671	0.673	0.672	0.669	0.669	0.660	0.637	0.618
3	0.667	0.668	0.668	0.668	0.668	0.668	0.666	0.634	0.607
4	0.670	0.670	0.669	0.669	0.667	0.668	0.662	0.647	0.615
5	0.669	0.669	0.669	0.668	0.667	0.664	0.664	0.643	0.628
6	0.675	0.672	0.673	0.675	0.674	0.675	0.666	0.639	0.617
7	0.668	0.664	0.654	0.642	0.634				
8	0.669	0.662	0.650	0.642	0.630				
9	0.677	0.677	0.675	0.677	0.676	0.672	0.667	0.665	0.665
10	0.677	0.674	0.672	0.673	0.675	0.673	0.670	0.669	0.668

CONCLUSIONS

1. We have created eight compositions of syrups with theophylline concentration of 100 mg/15 ml, using adjuvant substances which guarantee obtaining of pharmaceutical form with optimal physico–chemical parameters.

2. The adjuvant substances used, significantly increased the solubility of theophylline.

3. The method of theophylline determination used, enabled precise determination of its content in the created form of the drug.

4. The study on the stability of obtained syrups revealed that acidic syrups are stabile during twelve months from preparation when stored at room temperature. In alkaline syrups after several days opalescence occurs.

5. The thin layer chromatography method used, did not show any symptoms of biodegradation in the studied syrups and products of theophylline.

6. The formulations 5, 9, 10 (described in Table 1), with the least contents of the adjuvant substances were chosen for pharmacokinetic tests which constitute the next stage of our study.

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