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The release of sodium citicoline from enteric coated tablets

Uwalnianie citicoliny sodowej z tabletek dojelitowych

INTRODUCTION

Citicoline is also known as CDP-choline and cytidine diphosphate choline (cytidine 5'-diphosphocholine). CDP-choline belongs to the group of biomolecules in living systems known as "nucleotides" that play important roles in cellular metabolism. [13]. Endogenously, the formation of citicoline is the rate-limiting step in the synthesis of phosphatidylcholine, a key membrane phospholipid, from choline. Exogenous citicoline is hydrolyzed in the small intestine and readily absorbed as cytidine and choline [9,15]. Following absorption, choline and cytidine are dispersed throughout the body, enter systemic circulation for utilization in various biosynthetic pathways, and cross the blood-brain barrier for re-synthesis into citicoline in the brain [12]. Citicoline reduces central nervous system ischemic injury by preventing accumulation of toxic free fatty acids [4,8]. It also improves memory and remembering process in stroke patients [3,5].

The aim of the study was to evaluate the release of drug substance - sodium citicoline from enteric coated tablets based on patented core tablets [6]. Moreover, there were determined their physical properties as well as release kinetics of the drug into dissolution media.

MATERIALS AND METHODS

Sodium citicoline powdered with average 20-50 μm (CDP- choline, Brassel Searle, Italy), gliceryl monostearate (BDH, UK), potato starch (ICN, Polfa Rzeszów, Poland), cellulose acetate (POCH, Gliwice, Poland), castor oil (PPH Galfarm, Kraków, Poland), metanol (Merck, Germany), chloroform (POCH, Gliwice, Poland), 0.1 mol L^{-1} hydrochloric acid (POCH, Poland), phosphate buffer pH 6.8 prepared by Polish Pharmacopoeia 8th edition, purified water, spectrophotometr Spectromom 195 (MON, Hungary), flow-through cell apparatus (Medical University of Lublin, Poland), tablet producing machine EKO Korsh (Germany), coating pan (Erweka, Germany).

Preparation of core tablets. Tablets containing: sodium citicoline (0.5 g), glyceryl monostearate and potato starch (0.075 g) were prepared by wett granulation according to a method previously described in our study [14]. The physical properties of tablets were determined according to Polish Pharmacopoeia 8th edition [11].

CoatIng process. The coating solution was prepared by adding 10 g cellulose acetate and 0.5 g castor oil into 100 g mixture of 7:1 a methanol and chloroform.

The compressed tablets were charged into a coating pan, with rotating speed 35 rpm. A small portion of coating solution (10mL) was sprayed onto tablets and the pan was closed for 2 min. Then, the pan was opened and solvent was slowly evaporated. After that, the next portion of coating dispersion was added up to 50 mL. Exhaust air temperature was maintained at 40 - 45°C. The process of coating with portion of solution coat (50mL) was repeated 10 times with the intervals of 24 h. The tablets were kept at room temperature (21±2°C) for least 24 h before the coated tablets were studied. Experiments were performed in sixplicate.

The average weight, diameter, thickness, hardness and friabilit y. This test was done according to the Polish Pharnacopoeia 8th edition. The test was repeated six times.

Drug content. The tablets coated content was determined with the same equipment used in the quantitative analysis of sodium citicoline according to a method previously described in our study [14] at a detection wavelenght of 274 nm.

In vitro disintegration. Tablets were tested using the method detailed for enteric coated tablets in Polish Pharmacopoeia.

The values of average weight, diameter, hardness, thickness, friability and disintegration time are shown in Table 1.

Table 1. Physical parameters of coated tablets and core tablets

Product	Average weight (mg)	Thickness (mm)	Diameter (mm)	Hardness kG/mm^2	Friablity (%)	Distintegration time (min)
Coated tablets	0.602±5%	4.49 ±0.1	12.55±0.1	-	-	18
Core tablets	0.585±5%	4.1±0.1	12.1 ±0.1	4.8 kG	0.98	10

In vitro dissolution. Dissolution of the enteric coated tablets was determined using the flow-through cell apparatus [7]. A weighed tablet was placed in the chamber and release investigation was carried out at 37°C at a flow rate of 2.0±0.2 mL min^{-1}. Two dissolution media were used: 0.1 mol L^{-1}. hydrochloric acid (HCL) for the first 2 h and of 0.1 mol L^{-1}. phosphate buffer (pH 6.8) for a 90 min. Fractions (10 mL) were collected.

The amount of drug dissolved in each medium, after filtering through Sartorius filter (0.22 μm) and suitably diluted, was determined by ultraviolet spectrophotometry at 272 nm. The same parameters were used for the dissolution test for the core tablets, except that the 0.1 mol L^{-1} HCL portion of the test was deleted.

The study was repeated six times and kinetics parameters are shown in Table 2.

RESULTS AND DISSCUSION

The formulated enteric coated tablets provide faster passage of the drug substance to the small intestine and its metabolism which results in the increase of the efficiency and at the same time may improve or maintain biovailability of this drug [1]. As previously mentioned, citicoline is metabolized in the gut wall and liver. The byproducts of exogenous citicoline formed by hydrolysis in the intestinal wall are choline and cytidine [13].

After manufacturing, the aqueous dispersion enteric coated tablets readily passed the Polish Pharmacopoeia enteric coated tablet disintegration test.

Aquous dispersion enteric coats demonstrated good physical resistance to the acid medium with the tablets where dissolution profiles showed no release in hydrochloric acid of pH 1.2 for first two hours. When the tablets were placed in the pH 6.8 phosphate buffer the coated tablets dissolved faster, being 80% dissolved after 45 min and the total quantity of the substance released from tablets after 90 min was 82.3%.

The results of release tablets are given in Table 2.

Table 2. Release kinetics of sodium citicoline from coated tablets and core tablets

Parameters	Coated tablets n=6	Core tablets n=6
Mt_{45} mean±SD (%)	80.5±2.9	58.1±2.8
Mt_{90} mean±SD (%)	82.7±3.1	90.6±3.7
t_{80} (min)	39.4	73.6
AUCD (mg*min)	2084	2462
K (mg*$min^{-0.5}$)	87.67	61.507

Mt – quantity of released substance (%); K – release rate constant (mg*min-0.5); AUDC – area under the dissolution curve (mg*min); t80 – time for 80% release (min)

To describe the kinetics of the drug release from the enteric coated tablets, mathematical model of Higuchi was used. This Higuchi's square root equation, describes the release from systems where the rate of drug release is related to the rate of drug diffusion [10].

Fig. 1 shows that release of sodium citicoline from the enteric coated tablets proceeds according to the square root of times functions [2],

$$M_t = K_o (\sqrt{t} - \sqrt{T_D}),$$

where: Mt – quantity of released substance (mg), Ko – the release rate constant ($mg.min^{-0.5}$),

The dissolution profiles of sodium citicoline from enteric coated tablets in the 2nd fluid (pH 6.8) were rapidly released, suggesting that the enteric coating layer dissolved rapidly. The dissolution profiles of sodium citicoline compared to core tablets results are shown in Fig. 1.

The substance quality released (m) at succesive 5 – min time intervals, presented in Fig. 2, and Higuchi's equation allowed us to calculate total areas under the release curve (AUCD).

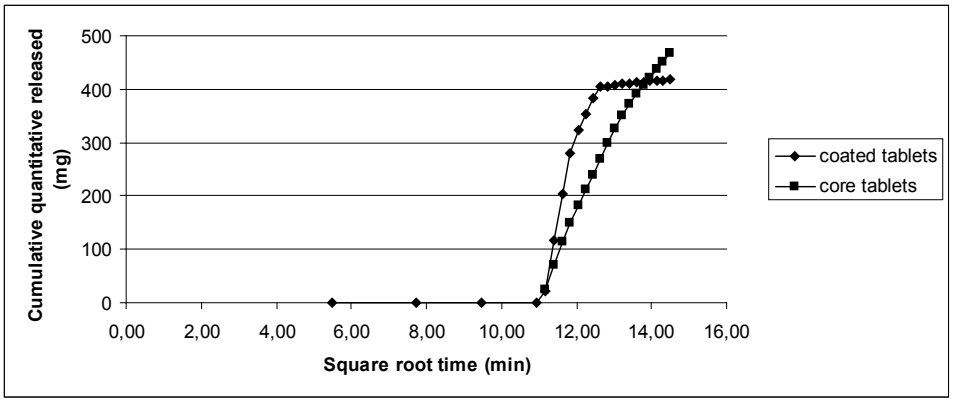

Fig. 1. Release profiles of sodium citicoline versus square root of time for the dissolution data in accordance with the Higuchi's square equation

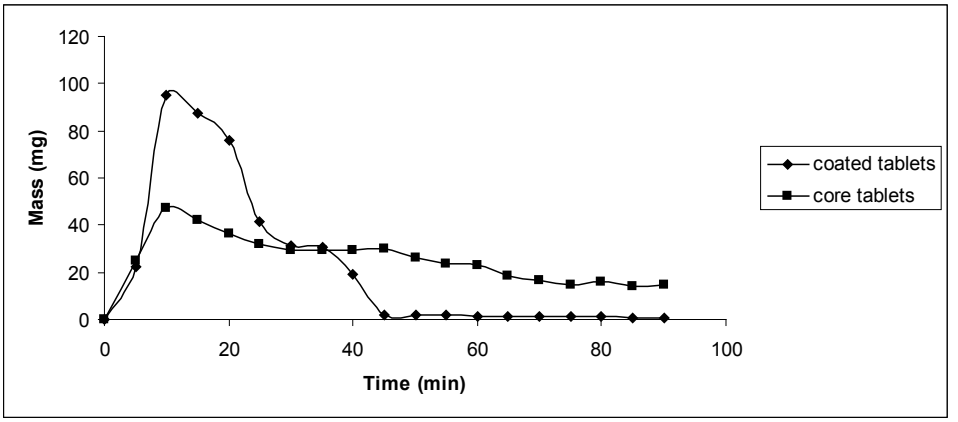

Fig. 2. Dissolution profiles of sodium citicoline from coated tablets and core tablets

Comparative studies using uncoated tablets showed that the dissolution process of coated tablets is quicker than core tablets.

The AUCD values are calculated from the equation:

$$\mathrm{AUCD} = \int_0^t \mathrm{m} \cdot \mathrm{dt} \ ,$$

where: m is quantity of the substance released at time intervals dt = 5 min from the areas under the dissolution curves (Fig. 2).

The calculated values of AUCD were 2084 mg.min

CONCLUSION

Our results indicated that enteric coated tablet, composed of core tablet containing drug and enteric coating layer, showed acid resistance and suggest that the application of an enteric coat could improve drug absorption. The release process may be described using modified Higuchi's equation.

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SUMMARY

By using the method of flow-through cell apparatus, we studied the release of sodium citicoline from enteric coated tablets into hydrochloric acid (0.1 mol L^{-1}) for 2 h and for another 90 min phosphate buffer pH 6.8 at 37 ° C at constant flow rates (2 mL min^{-1}). For comparison, also a release of sodium citicoline from core tablets into phosphate buffer was performed. The release rate of the active substance in buffer solution was 87.67 mg*$min^{-0.5}$ Release process can be described by a modified Higuchi's equation.

Keywords: sodium citicoline, enteric coated tablets, flow-through cell apparatus.

STRESZCZENIE

Przy użyciu metody przepływowej zbadano uwalnianie citikoliny sodowej z tabletek dojelitowych do kwasu solnego (0.1 mol/l) przez 2 godz. a następnie do buforu fosforanowego o pH 6.8 przez 90 min w temp. 37^{o}C przy stałych wartościach przepływu (2ml/min.). Dla porównania przeprowadzono również uwalnianie z rdzeni tabletek do buforu fosforanowego. Szybkość uwalniania substancji aktywnej z tabletek dojelitowych do roztworu buforu wynosiła 87,67 mg*$min^{-0.5}$. Proces uwalniania można opisać zmodyfikowanym równaniem Higuchiego.

Słowa kluczowe: citicolina sodowa, tabletki dojelitowe, aparat przepływowy,