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Preparation and Characterization of Clopidogrel/DIMEB Complex

I. KOLBE*, M. VIKMON, A. GERLÓCZY and J. SZEJTLI
Cyclolab, Cyclodextrin R&D Laboratory Ltd., Budapest, Illatos u.7. H-1097 Hungary

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Abstract

Surprisingly, it was found that Clopidogrel base (CLP) easily forms a solid complex with DIMEB in cold solution by precipitation. The complex can be isolated by filtration, the stoichiometry of the isolated complex corresponds to 1 : 1 molar ratio. Powder X-ray diffractometry proved the complex formation in solid state. The improved solubility of the complex offers the possibility of an adequate drug release over the whole pH-range of the GI-tract.

Introduction

Clopidogrel bisulfate (PLAVIX) is a thienopyridine derivative, that is a potent inhibitor of ADP-induced platelet aggregation (dosage unit: 75 mg/tbl.). According to a large multicentre clinical trial (CAPRIE), the drug demonstrated clinical efficacy superior to that of Aspirin in the prevention of ischaemic stroke, myocardial infarction and vascular death in patients with atherosclerotic diseases [1].

Clopidogrel bisulfate is freely soluble in water, but its solubility is strongly pH-dependent. The site of absorption of such kind of drugs is restricted to the acidic environment of the stomach and the bioavailability will vary according to the actual pH of the GI-tract. Oral bioavailability of such drugs varies greatly in patients with an increased gastric pH due to achlorohydria or antiulcer treatment.

Aqueous solution of Clopidogrel bisulfate (100 mg/ml) is strongly acidic, the pH of the solution is lower than pH 1.0. Adjusting the pH toward a physiologically acceptable value, the solubility of the salt sharply decreases, above pH 5 the base form of the drug – which has a gummy structure – is precipitated. The base form of the drug is practically insoluble in water, its solubility is lower than 0.02 mg/ml.

These unfavorable physicochemical properties of the drug – especially regarding the pH-solubility profile – cause difficulties in the preparation of parenteral and in extended release oral formulations with appropriate dissolution over the physiological pH-range of the GI-tract. Aim of the present work: to investigate the effect of methylated cyclodextrins on solubility of Clopidogrel base.

Experimental

Materials

Clopidogrel bisulfate [product of Sanofi Res.] heptakis 2,6-di-O-methyl-β-cyclodextrin (DIMEB) [Cyclolab Ltd., Hungary]. All other materials used were of analytical grade.

Preparation of solid complexes

5.6 g (4.2 mmol) DIMEB was dissolved in 15 ml of distilled water and was buffered to 8.6–8.8 pH by adding phosphate buffer to the solution. A solution of 0.84 g (2 mmol) clopidogrel bisulfate in 5 ml distilled water was added dropwise to the buffered DIMEB solution under stirring. A very fine, thick precipitate was formed. After 5 hours stirring the precipitate was filtered and dried under vacuo. Weight: 3.2 g. Clopidogrel content: 18.0 $\pm$ 0.5% (UV-spectrophotometry).

X-ray diffractometry

Powder X-ray diffraction patterns of DIMEB and that of the solid complex were recorded on a Philips diffractometer Typ.PW3710 using Cu-K_α irradiation. In the diffractograms the relative intensity of reflexion peaks were recorded in the function of diffraction angles 2Θ.

Solubility/redissolution study

Solubility of the solid complex was examined by dispersed amount method in distilled water and phosphate buffer of pH 7.6. 100 or 200 mg of the drug was weighed in to 4.0 ml of dissolution medium. Clopidogrel content of the solution was determined after appropriate dilution with 0.2N HCl-ethanol (1 : 1) by UV-spectrophotometry, using λ_{max} at 271 nm.

* Author for correspondence, E-mail: kolbe@cyclolab.hu

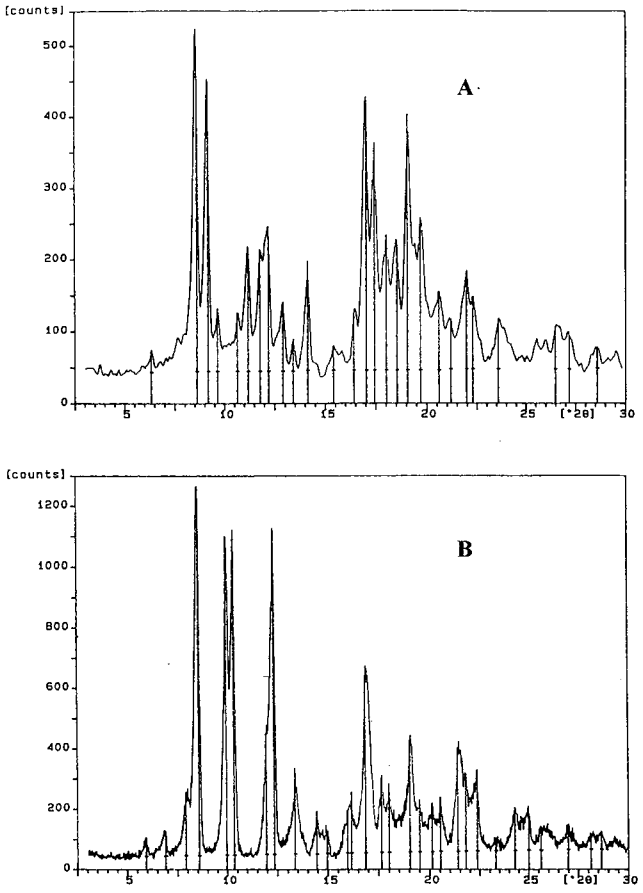

Figure 1. Powder X-ray diffractograms of CLP/DIMEB 1 : 1 complex (A) and DIMEB (B).

Results and discussion

Methylated cyclodextrins, like heptakis 2,6-di-O-methyl-β-cyclodextrin (DIMEB) usually show outstanding solubilizing potency on poorly water soluble drugs. In contrast with parent cyclodextrins, the solubility isotherm with methylated derivatives is usually a linear, A-type solubility curve, due to the formation of highly soluble cyclodextrin complex. Solid DIMEB complexes can be prepared regularly by removing the water content of the homogeneous solution by freeze- or spray-drying. An other way of complex isolation is the heating of the common solution, which results in precipitation of the solid complex due to reversed solubility-temperature dependence of DIMEB [2].

Investigating the effect of DIMEB on the solubility properties of clopidogrel bisulfate and the base form, unusual behaviour of complex formation could be observed. It was found, that clopidogrel base easily forms solid complex with DIMEB in a well defined molar ratio by precipitation even from cold solution. The complex could be isolated by filtration, the stoichiometry of the isolated complex corresponds to 1 : 1 molar ratio, revealed from the analysis by UV-spectrophotometry.

Characterization of the precipitated complex is shown in Figure 1. X-ray diffractogramm of the solid complex (Figure 1A) differs from that of DIMEB (Figure 1B), which indicates that the complex has an own unique crystal structure.

Table 1. Solubility of CLP/DIMEB complex in distilled water and in pH 7.6 buffer solution

Medium/weight in	Solubility of the complex (CLP mg/ml)	Final pH	Solubility of CLP bisulfate (CLP mg/ml)	Dose/solubility ratio for the complex*
Distilled water				
100 mg/4 ml	0.63	5.6	<0.02	90–120
200 mg/4 ml	0.83	5.1		
Phosphate buffer				
100 mg/4 ml	0.50	7.6	<0.01	120–150
200 mg/4 ml	0.64	7.4		

* Dose/solubility ratio is the volume of GI fluid, necessary to dissolve the administered dose (if this volume exceeds 1000 ml, an incomplete bioavailability is likely).

X-ray diffractometry clearly proved the real complex formation of clopidogrel base with DIMEB.

Solubility of clopidogrel/DIMEB complex in distilled water and in pH 7.6 buffer solution is shown in Table 1.

The complex is freely soluble at the pH of the gastric juice, and has an improved solubility profile at the higher pH region of the gastro-intestinal tract, than that of the clopidogrel salt. The solubility of Clopidogrel bisulfate salt at pH 7 is $\approx$0.01 mg/ml, in pH 7.6 buffer solution an approximately 640 fold solubility enhancement was achieved. The dose/solubility ratio of the complexed drug is below 150 ml even in the highest pH-region of the GI-tract, while it is theoretically several litres for CLP itself. Therefore an enhanced and more uniform absorption of orally administered clopidogrel/DIMEB complex is likely.

Conclusions

- The non-soluble base form of the highly water soluble Clopidogrel bisulfate, forms a stoichyometric complex with DIMEB by precipitation in a molar ratio of 1 : 1.
- X-ray diffractometry proves the existence of the complex in solid state.
- The complex is freely soluble at the pH of the gastric juice, and has a significantly improved pH-solubility profile at the higher pH region of the GI-tract than that of the CLP salt.
- An enhanced and more uniform absorption of orally administered DIMEB complexed clopidogrel is likely.
- Precipitation of solid complex from cold DIMEB solution in a well-defined molar ratio is an unusual effect, no similar observation has been published in the literature.

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