Solution Enhancement of Drug Substances using Soluble Amylose

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INTRODUCTION

Amylose is a rather linear molecule. In aqueous solution it forms easily helical structures having a hydrophobic cavity [1].
This non polar cavity permits the formation of inclusion compounds with various guest molecules, analogue with Cyclodextrins. The interaction of amylose with numerous other molecules is widely described in the literature [2].
Whereas cyclodextrins and its derivatives are extensively used to make inclusion compounds, all attempts to use amylose rich starches for similar applications have failed. This may be caused by analytical, problems but also by the poor solubility of pure amylose having a high molecular weight. A new cold water soluble material with higher amount of amylose is available. It potential to solubilise drugs has been investigated.

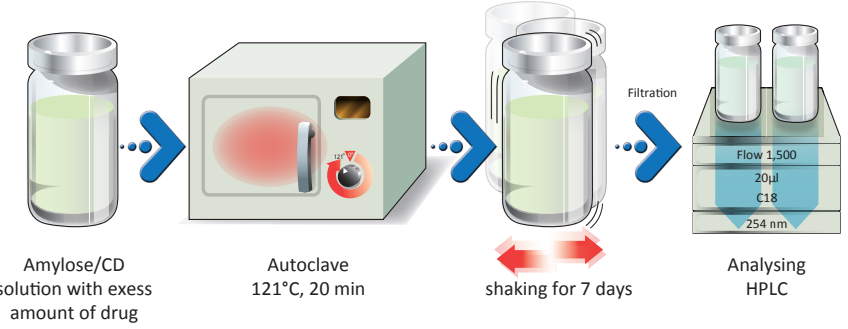
MATERIALS & METHODS

MATERIALS: As soluble amylose has been used KLEPTOSE® Linecaps 17 is a novel excipient from Roquette Frères, Lestrem, France. It is obtained by partial hydrolysis of pea starch (about 40% amylose) and spray drying. It has and DE-value of 17. It is composed of glucose, oligosaccharides and polysaccharides (about 60% of the composition). The mean molecular weight has been found with 12 000. The polysaccharide fraction contains both amylopectin and also a higher amount of linear amylose molecules.
Hydroxypropyl-beta-cyclodextrin KLEPTOSE® HPB from Roquette Frères was from oral excipient quality.
All used API's where of analytical quality and were used without further purification.

MOLECULAR WEIGHT: The sample is dissolved in pure water and analyzed with size exclusion chromato graphy, equipped with refractometric index detection. The calibration is done with pullulane. The Mw – distribution is recorded, the mean value of the complete weight distribution is calculated.

DRUG SOLUBILISATION: The drug dissolution in presence of potentially solubilising agents has been measured according to an established protocol [3]. Briefly, an excess amount of the drug was added to an aqueous linecaps solution; the suspension formed was heated in an autoclave at 121 °C for 20 min in sealed glass vial and then allowed to cool to room temperature. Next, a small amount of drug was added to the suspension and the mixture was allowed to equilibrate in the sealed vial at room temperature (23 ± 1 °C) for 7 days protected from light and under constant agitation at 250 rpm. After equilibrium was attained, the suspension was filtered, the filtrate diluted with the mobile phase and analyzed by HPLC. **Figure 1** summarizes the test protocol for the solubilisation studies. Phase-solubility profiles were determined according to the method of Higuchi and Connors [4].

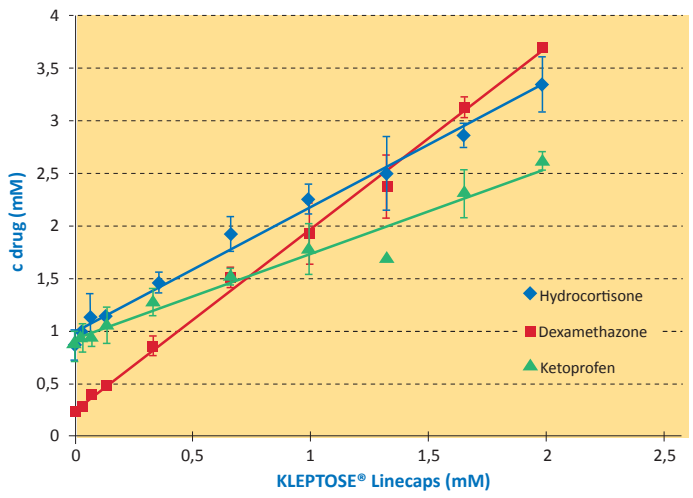
Figure 1. Used test protocol for then solubilisation studies.



RESULTS & DISCUSSION

Phase solubility studies according to Higuchi and Connors [4] demonstrated an interaction of drug substances with this new excipient. A linear relationship between the drug solubility and the excipient concentration was recorded (see **Fig. 2**).
The improved drug dissolution could be either caused by a formation of an inclusion compound, as expected, or by a ternary interaction of the starch polymers with the API's. No additional trials were done to prove the formation of inclusion compounds.

Figure 2. Phase solubility study, using KLEPTOSE® Linecaps 17 as solubilising agent.



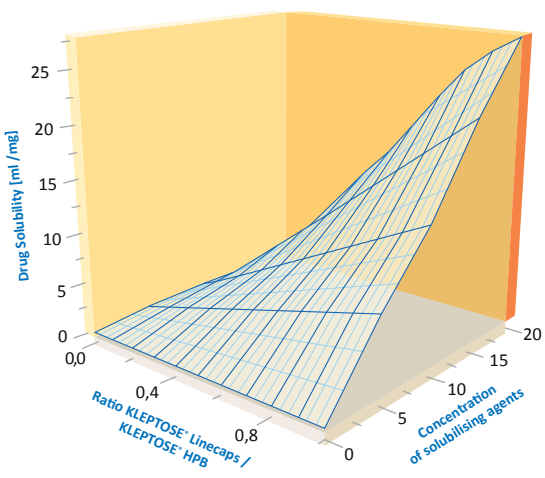
When comparing aliquot quantities of excipients (either soluble amylose or HP-beta-CD), big differences in the drug solubility appear (see **table 1**). The solubilisation potential of linear amylose is significantly lower than that of KLEPTOSE® HPB.
This is mainly caused by a higher molecular weight of the amylose rich excipient with 12 000 versus 1400 for HP-beta-CD; needing more gram to reach the same molarity.

Table 1. Solubility of selected drug substances (mg/ml) in solutions of 100mg/ml of soluble amylose or modified cyclodextrin.

	Pure water	KLEPTOSE® Linecaps 17 100 mg/ ml	HP-beta-CD 100 mg/ ml
Hydrocortisone	0.32 ± 0.05	0.70 ± 0.06	17.85
Dexamethasone	0.09 ± 0.01	0.60 ± 0.04	7.21
Ketoprofen	0.22 ± 0.04	0.39 ± 0.02	10.36
Paracetamol	15.94 ± 1.14	19.13 ± 0.55	-
Lidocaine	4.45 ± 0.23	4.51 ± 0.51	8.5

Blends of linear amylose KLEPTOSE® Linecaps 17 and KLEPTOSE® HBP at different ratios did not show any synergistic effect for the solubilisation potential for Hydrocortisone (see **figure 3**).

Figure 3. Hydrocortisone solubility (mg/ml) in blends of KLEPTOSE® Linecaps 17 and KLEPTOSE® HBP.



CONCLUSION

Soluble amylose can improve the solubility of poorly soluble drugs. Nevertheless only for selected applications it is a realistic alternative for regular cyclodextrins. The high molecular weight of these carbohydrates imposes the use of large quantities in weight to reach the same effect as with cyclodextrins.
Soluble amylose is an interesting alternative for taste masking in oral liquid preparations or in pediatric formulations [5].

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