

# Hydroxyethyl Starch

A Current Overview

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P. Lawin, J. Zander and B. Weidler

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## Hydroxyethyl Starch: A Current Overview



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## Preface

The present discussion of current approaches to the use of plasma expanders and to the questions that remain as yet unanswered in this field is a stimulating one. The focal point of the discussion is hydroxyethyl starch, but it also embraces the various other plasma substitutes. There are a number of questions: why are three different groups of substances still in clinical use? Does any single one of them really have advantages over the others? The fundamental question is actually whether we need plasma expanders at all, and if so, what the indications are for using them.

In addition to the question of indications, there are also questions concerning contraindications. Is using crystalline solutions not actually more physiological? Can better results in terms of macrohemodynamics and microcirculation be achieved using crystalline solutions than with colloid solutions?

The answers to these questions are bound to derive from considerations of physiology and pharmacology. The former can provide information on changes in microcirculation, and the latter supplies information on the pharmacokinetics of various substances, above all on their metabolism.

From a clinical viewpoint, the efficacy of the various substrates need to be assessed in relation to various indications, e.g., in vascular disease, in plasma substitution in cases of acute blood loss during surgery or after trauma, or in central nervous system disease resulting from perfusion disturbances. In addition, hemodilution is assuming an increasingly important role in reducing the number of homologous blood donations that are required, and both the quality and the quantity of plasma expanders are under discussion.

It is therefore to be welcomed that respected contributors from the theoretical and clinical spheres have provided here a survey of the current state of knowledge, offering fresh stimulation for future research and clinical applications.

Our special thanks are due to Fresenius Ltd. for their support, and especially to Dr. Weidler, whose input played a decisive role in the preparation of this workshop.

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# New developments in the physicochemical characterization of hydroxyethyl starch

K. Sommermeyer

## Introduction

If one were to compile a list of the specific physicochemical properties of hydroxyethyl starch (HES) that are essential to give a clear and complete picture of the molecule, they would be as follows:

1. Molecular weight distribution or average molecular weights.
2. Chain length distribution / degree of branching or average chain length.
3. Substitution pattern or degree of substitution.
4. Substitution sequence.

On the one hand, these values determine how easily the molecule is eliminated by the kidneys, by providing information on the average shape and size of the molecules and their solvation state, i.e., how many water molecules are bound to hydroxyethyl starch in different ways (Fig. 1). On the other hand, susceptibility to degradation by  $\alpha$ -amylase will also vary with the above characteristics.

Renal elimination and degradation are the main parameters which have an influence on the pharmacokinetics of HES. In addition, it is possible that one of the above-mentioned

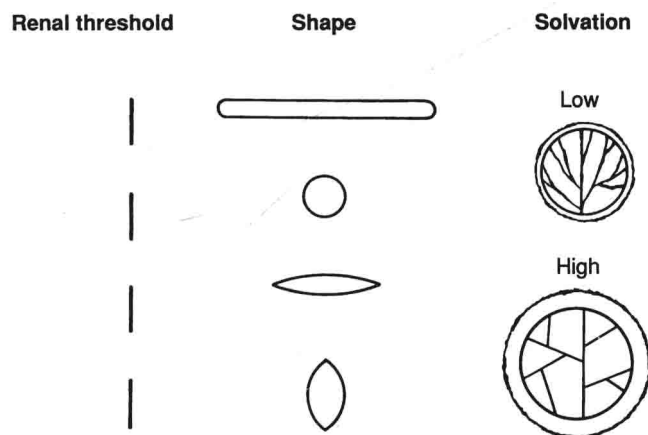


Fig. 1 Renal elimination as a function of the shape and solvation of the molecule

Where molecules are of the **same molecular weight**, renal elimination will depend on the **shape and solvation state** of the molecule.

characteristics plays a decisive role in the interim storage of HES in tissue [1]. These characteristics therefore need to be studied and turned into measured and known parameters for clinical applications of hydroxyethyl starch.

I shall report here on the current state of methodology in achieving these aims.

## Structure of amylopectin, degree of substitution, and substitution pattern for hydroxyethyl starch species

Hydroxyethyl starch is the hydroxyethyl derivative of degraded amylopectin. Although the branched structure of amylopectin has long been known, the exact architecture is still the subject of research. Figure 2 shows three different models that were proposed during the 1940s. They differ from each other in the branching order of the linear chains, consisting of glucose groups connected by  $\alpha$ -1,4-glycosidic bonds. There are  $\alpha$ -1,6-glycosidic bonds at the sites of branching. The chains that bear the sole reducing end group of the entire molecule are classed as C-chains [2]. A-chains do not carry any further branching sites. All other chains are described as B-chains.

Model 3 is currently considered the most likely model. Details of the structure have been elucidated by applying enzymatic degradation methods and chromatographic separation

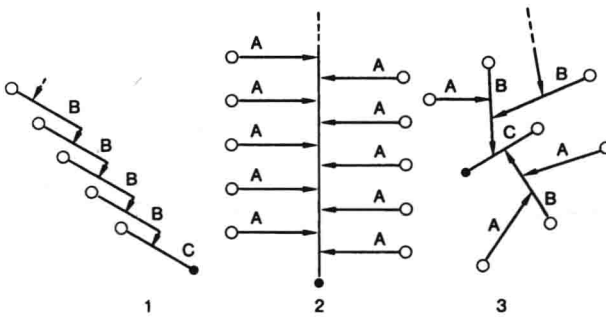


Fig. 2 Three different proposed structures for amylopectin

○ = Terminal, non-reducing end group

● = Reducing end group

→ =  $\alpha$ -D-(1→6) bond

— = A chain of 20 to 25  $\alpha$ -D-(1→4) bonded D-glucose molecules

methods to maize starch, which consists of 99% amylopectin and therefore forms the starting-point for the production of hydroxyethyl starch.

Figure 3 shows a more refined model, published in 1987, showing the average chain length, broken down into inner and outer, short and long A and B chains [3].

The scope of the present chapter does not permit any more detailed analysis of these results. The average chain length of 18.5 anhydroglucose units, 10.0 for the outer chain length



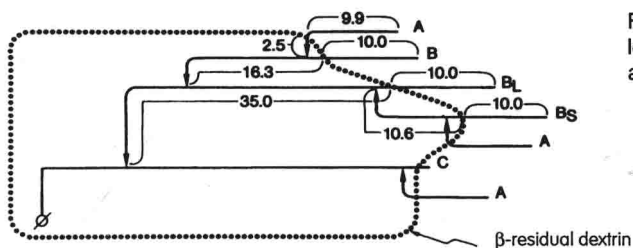


Fig. 3 Outer and inner chain length distribution of amylopectin

and 8.5 for the inner chain length, should be noted. More recent work has shown that the amylopectin molecule has regions with a very high degree of branching alongside almost linear chains (i.e., heterogeneous branching) [6].

The hydroxyethyl groups are more or less randomly distributed over the partially degraded amylopectin molecule. They may occupy positions 2, 3 and 6 of the anhydroglucose units (Fig. 4).

Substituting hydroxyethyl groups already introduced is equally possible. One relatively

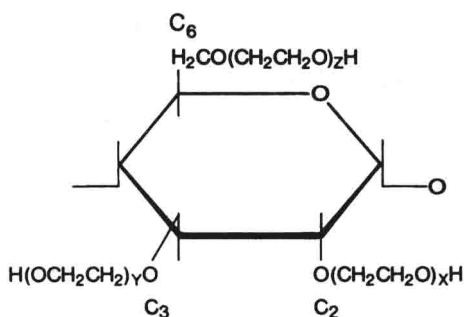


Fig. 4 An anhydroglucose unit with  $\alpha$ -1,4-glycosidic bonding

simple way of recording and describing substitution by hydroxyethyl groups is to use the degrees of substitution DS and MS, while neglecting the recording and quantifying of individual substitution positions. MS (molar substitution) is defined as the average number of hydroxyethyl groups per anhydroglucose unit. It is therefore a statistical value, determined by the total number of hydroxyethyl groups in a sample, which is then applied to all anhydroglucose units present. By contrast, DS (degree of substitution) is defined as the ratio of substituted anhydroglucose units to the total number of anhydroglucose units, regardless of whether these are single or multiple substitutions. From these definitions it may be seen that  $MS > DS$  for polysubstitution. Where there is only monosubstitution, i.e., each substituted anhydroglucose unit carries only one hydroxyethyl group, then  $MS = DS$ .

Far more informative than the MS and DS data is the substitution pattern, i.e., the recording of individual, variously substituted anhydroglucoses, randomly distributed over individual polymer molecules.

These include the monosubstituted units 2-0- or 3-0- and 6-0-hydroxyethyl