CHAPTER 5

Soluble Polymers as Targetable Drug Carriers*

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A. Introduction

The efficiency of drugs would increase considerably if we were able to direct them selectively to their cellular targets. The need for targetable drug carriers was realized a long time ago. It was P. Ehrlich, in 1906, who coined the phrase “the magic bullet” describing drugs which might be selectively directed to their specific site of action. But it is only in the last 20 years that natural science has developed to such a level that several laboratories have started to try to translate this dream to reality.

It was RINGSDORF (1975) who described a new theoretical model for the development of synthetic polymers which could serve as targetable drug carriers. The consequence of attachment of low molecular weight drugs to macromolecular carriers alters their rate of excretion from the body, changes their toxicity and immunogenicity, and limits their uptake by cells via endocytosis, thus providing the opportunity to direct the drug to the particular cell type where its activity is needed.

This chapter concentrates on the rationale of using water soluble macromolecules as targetable lysosomotropic drug carriers. Rational design of lysosomotropic macromolecular drug carriers must take into account biological processes which take place when these drugs are administered into the living organism. The main objective, however, is to deliver the polymer bound drug to the particular cell type where its action is desirable. To achieve this a suitable targeting moiety-receptor (antigen) system must be known and the former has to be attached to the carrier. The polymer bound drug may interact with the cellular membrane or act intracellularly. However, there are intrinsic difficulties in targeting membrane-directed drugs. This review is therefore mainly concerned with polymeric carriers directing drugs which normally act via an intracellular site.

The bond between the drug and the carrier must be stable in the bloodstream and in the interstitial space. Upon arrival in the lysosomal compartment of the target cell the drug must be either released from the carrier by lysosomal enzymes or activated by other means, for instance by

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irradiation. The carrier itself should be totally digested in the lysosomal compartment. If a nondegradable carrier is used, its whole molecular weight distribution (MWD) must be under the renal threshold. In this case, however, not only the MWD but also the chemical structure of the carrier is of utmost importance. Its structure should be designed in such a way that, after being released from the dead cell into the bloodstream, it should be taken up by nontarget cells by fluid phase pinocytosis which is a slow process indeed. Only in this case can the capture (by receptor-mediated pinocytosis) -recapture (by adsorptive pinocytosis) cycle be broken and the carrier eliminated from the body.

All these questions will be discussed in the following sections. The interaction of water soluble macromolecules with the living organism is discussed on the cellular and subcellular levels. Factors which are important to the rational design of macromolecular carriers are described and examples of conjugates suitable to combat diseases (with the emphasis on cancer) are discussed.

B. Consequences of Drug Binding to Macromolecular Carriers: Cellular Level

Binding low MW drugs to macromolecular carriers restricts their access to the cell interior by the uptake process known as endocytosis. Endocytosis encompasses two processes: phagocytosis and pinocytosis (Table 1). In both cases, a macromolecule associates at a site on the cell surface and the membrane invaginates and pinches off inside of the cell forming an intracellular vesicle containing the macromolecule. Phagocytosis represents the process by which large particulate material enters the cell and is usually carried out by specialized phagocytic cells. Pinocytosis, on the other hand, is carried out virtually by all cells in which the cell takes in liquid or liquid containing solutes from the extracellular space.

I. Pinocytosis

There are basically three forms of pinocytosis: fluid phase, adsorptive, and receptor-mediated. The basic difference between fluid phase and adsorptive pinocytosis is found in Fig. 1. Fluid phase pinocytosis is the most general form in which soluble macromolecules and solutes enter the cell in liquid droplets. Many, if not all, nucleated cells use fluid phase pinocytosis to internalize material from the extracellular space. It is known as a “constitutive” process because it is continuous (as opposed to triggered as is phagocytosis); thus the cell is always ingesting pieces of its plasma membrane. Pinocytic vesicles are on the average of 0.1–0.3 μm, and in a typical cultured cell more than 100 are internalized per minute (TARTAKOFF 1987).