TOWARDS BETTER SAFETY OF DRUGS AND PHARMACEUTICAL PRODUCTS

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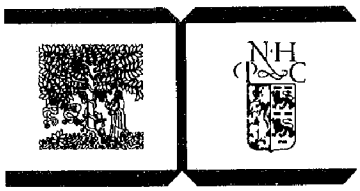

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THE PROBLEMS OF DRUG INTERACTIONS WITH EXCIPIENTS

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INTRODUCTION

Drug substances are molecules with a variety of functional groups, polar and non-polar, exhibiting hydrophilic and hydrophobic properties. The specific structure of a drug determines its actions and reactions within the biophase where the interactions with target receptors result in the desired therapeutic effects. Between a drug and its respective environment many interactions are possible. A series of interactions is summarized in Figure 1.

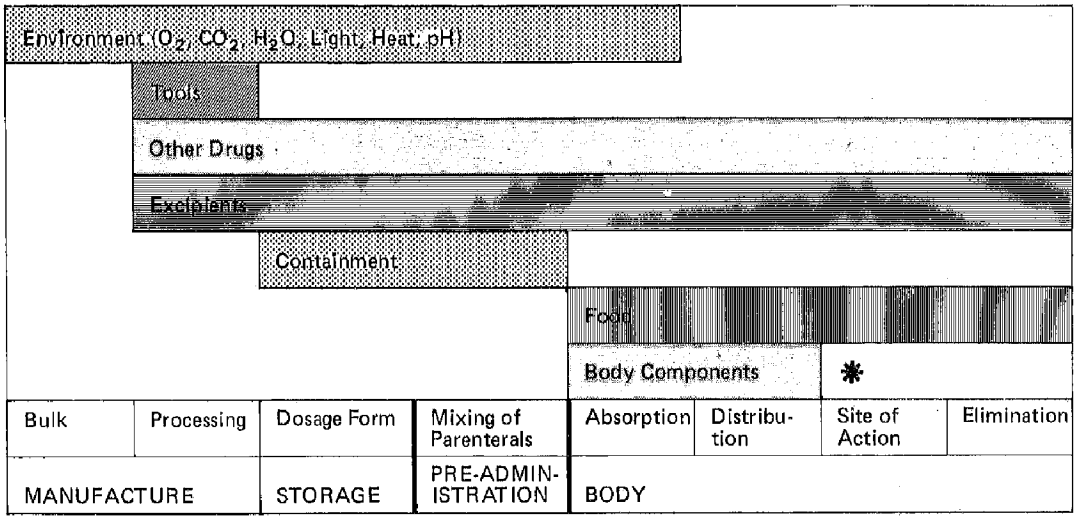

Fig. 1. Possible interactions of a drug substance with various factors during manufacture, storage, and use.

Here we also find the group of interactions we have to deal with now. It would be surprising indeed if drugs were not to interact with non-biological materials as well, including pharmacodynamically inert materials which are indispensable for making dosage forms.

During the past 25 years or so, knowledge about drug-excipient interactions has increased tremendously. In the following, I shall try to give a systematic view of this area spiced with some personal experiences. We shall also have to give answers regarding the question about the importance of these interactions.

TYPES OF INTERACTIONS

According to their nature, the interactions between drugs and excipients may be classified into

physical and physicochemical
chemical
biological

interactions. Table 1 gives a synoptic view over these classes and their distinguishing features.

TABLE 1
CLASSES AND FEATURES OF DRUG - EXCIPIENT INTERACTIONS

		Interaction *in vitro*	found by method	Drug Action *in vivo*	
Normal drug action	Drug A			n	normal
No excipient action	Excipient E			∅	no activity
Weak physicochemical interaction	A + E	+	physicochemical	n	normal
Physicochemical interaction	A + E	+	physicochemical	↓ ↑ ∅	decreased increased no action
Chemical interaction	A + E	+	analytical	↓	decreased side effects toxic effects
Biological interaction	A + E	−	−	↑ ↓	side effects toxic effects

PHYSICAL AND PHYSICOCHEMICAL INTERACTIONS

To begin with, physical and physicochemial interactions to a large extent not only constitute the basis of development and manufacture of dosage forms but also of absorption. Some typical

TABLE 2

SOME PHYSICAL AND PHYSICOCHEMICAL INTERACTIONS

Absorption	Deliquescence	Salt Formation
Adhesion	Dissolution	Segregation
Adsorption	Emulsification	Solubilization
Binding	Inclusion	Solvatization
Coagulation	Ionisation	Spreading
Complexation	Precipitation	Swelling

interactions are listed in Table 2. It is almost commonplace to mention the dissolution of a drug in water or in another solvent as an example of a desired interaction. On the other hand, there are interactions which delay the rate and reduce the extent of release and absorption. Here it is of minor importance where to draw the border-line between physical and physicochemical interactions. Hydrophobization of solid sulfadiazine by admixture of magnesium stearate[1] is regarded as a physical process whereas formation of a sparingly soluble salt of chloroquine with carboxymethylcellulose[2] is a physicochemical process because ionic interactions take place. Both these interactions reduce the release rate *in vitro*, and possibily the rate and extent of absorption.

Two other examples illustrate the many faces of physical and physicochemical interactions. They demonstrate that by the same interactive principle the bioavailability is reduced in one case but is improved in the other.

Boman et al.[3] encountered an interference of a preparation with p-aminosalicylic acid (PAS) with another drug preparation containing rifampicin (RMP) as the active principle, by monitoring the blood levels of the latter in humans. The reduced blood levels of RMP in patients treated with both these drugs simultaneously could be traced back to the adsorption of RMP onto bentonite which served as an excipient in the PAS granules. This adsorption process takes place in the stomach. The figures of Table 3 show a reduction of the available RMP by 1/3. No RMP could be recovered from RMP-loaded bentonite when desorption was attempted with 0.1 N HCl *in vitro*.

This is also an example of a cross-interaction between the active substance of a product A with an excipient in product B; such a situation could not have been foreseen by the manufacturers of the

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