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# CHOICE OF EXCIPIENTS FOR INTERNATIONAL USE *)

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## Abstract

Excipients must meet the physico-chemical requirements for the dosage form, but additional factors must also be considered. These include freedom from any adverse reactions, approval by regulatory agencies, defined chemical and physical properties, analytical and microbiological purity, supply and international availability. A rational approach for the formulation of tablets and capsules with first and second choice excipients is discussed.

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In the last few years there has been a growing realization that the performance of many dosage forms is determined to a large degree by the proper choice of excipients. In addition, the relative benefits and risks of certain additives such as colorants, flavoring agents and preservatives have been discussed more and more frequently. Finally, growing concern about the ecological future of our planet has led to a reap-

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praisal of the use of certain solvents. It is therefore timely to review the questions raised by these developments in a meeting such as this.

Switzerland is a very small country. The home market of the larger Swiss companies is therefore relatively small and all decisions taken by these companies must be made in consideration to the implications to the main markets in Europe and overseas. Exports from Switzerland are mainly to smaller countries. The larger countries have production sites of their own. Given this situation, questions relating to the acceptability, properties and performance of excipients in different countries and under different conditions are not new to us. Before starting with a review of the different items to be considered it should be mentioned that the large Swiss companies have Pharmacy Research and Development groups in several countries. The cooperation which exists between these groups enable our company in countries such as India or Japan to make local adjustments to formulations developed in Switzerland, the United States or elsewhere. In principle, however, the same formulations should be used by all group companies. Choosing excipients for dosage forms will therefore usually be some sort of a compromise, taking local regulations, availability and technical performance into consideration.

The influence of compatibility studies on the choice of excipients for tablets and capsules will first be reviewed.

The most inert filler and disintegrant is starch. Lactose is also inert except for its reaction with primary amines. However, it is still a first choice material due to its worldwide availability and good

TABLE I

**Compatibility of Excipients in Tablets and Capsules**

**FILLERS, DISINTEGRANTS**

| | | |
|---|---|---|
| Corn starch: | ok (formaldehyde!) | I |
| Lactose: | ok (except primary amines) | I |
| Mannitol: | ok (technical problems) | II |
| Sucrose: | ok (hygroscopic point at 77.4% r.h.) | II |
| Avicel®: / Primojel®: | somewhat less satisfactory than starch | II |
| Emcompress®: | may lose water | II |
| Tricalcium phosphate: | may accelerate hydrolytic degradations | II |

I, II: Priorities for use (includes all aspects)

technical properties. The inert Mannitol is a second choice material mainly because of its unsatisfactory technical properties. Sucrose is quite inert and has similar compression properties as Lactose but has a rather low hygroscopic point. Avicel$^{R}$ and Primogel$^{R}$ or Explotab$^{R}$, brand names for Microcrystalline cellulose and Sodium carboxymethyl starch, are less inert than starch. Encompress$^{R}$ a brand of granular Dicalcium phosphate dihydrate may lose water and cause problems with sensitive ingredients. Tricalcium phosphate, which is available as a fine powder, may also accelerate hydrolytic degradations. The preferred binder is Starch paste. The other binders, Polyvinylpyrrolidone, Hydroxypropylmethyl cellulose and Gelatin are not inert. In addition, Gelatin tends to promote microbial spoilage. Colloidal silica which has the properties of a glidant but also that of a binder and a wicking agent may turn out to be quite reactive. It is nevertheless a first choice material because its interesting properties give tablets good hard-

ness and fast disintegration at the same time. Due to the low concentrations employed its reactivity is prohibitive only with very sensitive active ingredients. Talc is not reactive, however it is difficult to obtain it in good and constant quality. Moreover, its role in tablets (except for coating) is often without foundation. Among the lubricants, Magnesium stearate is first choice because of its availability. Compatibility of the different lubricants has to be evaluated individually. No general clear-cut advantage for any of the compounds can be stated.

Even if a certain excipient meets the physicochemical requirements for the dosage form we must ask whether, according to existing knowledge, it is free from any adverse reactions and whether it is approved or will be approved by regulatory agencies worldwide. I hope to make it clear that the second point does not necessarily follow from the first.

While most excipients do not give rise to any adverse reactions in the quantities normally used, certain preservatives and dyestuffs are known to have an allergenic potential (Ref. 1-5). In the case of phenolic preservatives (which include the parabens) this potential appears to be related to their antimicrobial activity.

Paragraph 10 of the 1976 Drug Law of the Federal Republic of Germany states that all active ingredients must be publicly declared. This requirement includes preservatives because of their antimicrobial activity. Whether dyestuffs with a weak allergenic potential should be included in this category is still debated. However, in countries such as Sweden lists of drug preparations containing Tartrazine and other azo dyestuffs have already been published. This obviously

leads to a certain marketing disadvantage for these products. According to new regulations, issued in November 1976, the azo dystuffs Tartrazine, Sunset Yellow FCF, Ponceau 4R, and Amaranth will not be permitted any more for foodstuffs in Sweden after 1978/1979. For these reasons we try to avoid the use of such preservatives and synthetic dyestuffs in new preparations.

For topical and injectable preparations only excipients are chosen which are devoid of local tissue irritation and hemolytic activity in the concentrations used. These compounds are sufficiently well known that it is not necessary to discuss them any further.

It should also be mentioned that we try to avoid Sucrose in syrups because of its cariogenic potential. In any case this excipient would face serious registration difficulties in Scandinavia.

The choice of excipients which do not give rise to adverse reactions is a relatively straightforward pbolem compared with their approval by regulatory agencies. Here again, the basic problem is to demonstrate absence of toxicity and freedom from adverse reactions. At present the only clear recommendations for the type of toxicological data required on a new excipient are to be found in the German regulations (1971) and the European Economic Community Directives (EEC75/318).

> Council Directive 75/318/EEC, May 20, 1975 (Guidelines)
>
> "An excipient used for the first time in the pharmaceutical field shall be treated like an active ingredient"

This requirement is already is already being incorporated into the national regulations of EEC member

states. The following toxicological data on a new excipient should therefore be on file. (Acute toxicity usually includes 3 species, observed for 14 days after a single dose. If possible, the $LD_{50}$ by parenteral route should also be established in one species.)

Toxicological Data on a New Excipient (75/318/EEC)
(long term oral administration)

Acute toxicity
to standard international protocols

Repetitive administration
6 months, 2 species (one non-rodent)

Carcinogenicity
1 species (18 months mouse or 2 years rat)

Reproduction studies
Segments I, II and III (fertility, teratogenicity, effects on lactation)
I, II and III: rat
II: at least one further species non-rodent (e.g. rabbit)

These studies are demanded in Europe for products intended for long-term administration. For FDA oriented countries, e.g. Australia and Canada, 2 year repetitive-dose studies in rats and 1 year studies in dogs may be required instead of the 6 months studies described above. In certain countries it may also be required to carry out mutagenicity studies. It can be anticipated that for certain substances pharmacokinetic evaluation will also be necessary. In cases where it can be clearly demonstrated that the substance is not absorbed in man the need for long-term repetititive administration and carcinogenicity studies could be discussed with the authorities. In the case of polymers this might be shown with radioactively labelled material.

I do not wish to comment here on the need to document say, a new cellulose derivative, according to this directive.

In any case, these new requirements make it very unlikely that too many new excipients will be used in in the future. Suppliers of raw materials have generally not been willing to generate the toxicological data outlined above and even large companies have more than enough to do with characterizing their existing and new active ingredients.

Excipients already used in the pharmaceutical industry can be broadly classified into four categories:

1. Excipients described in Pharmacopoeias.
2. Excipients used for foodstuffs.
3. Excipients used for cosmetics (topical preparations)
4. Newer excipients with no official status but already registered with certain health authorities.

Generally a substance listed in any of the major Pharmacopoeias such as the USP or the European Pharmacopoeia can be used worldwide. A notable exception to this rule is Japan where only excipients mentioned in one of the official compendia are permitted.

Excipients for Pharmaceutical Use in Japan must be contained in
- Japan Pharmacopoeia VIII (J.P.) or in
- Japanese Standards of Food Additives III (J.S.F.A.), or in
- Special Koseisho Regulations

These compendia list some excipients not regularly used in Europe, e.g. Calcium carboxymethyl cellulose, but do not list such common ones as the free acid of Saccharin (the sodium salt is listed) and Diethyl phthalate (the Dibutyl phthalate is listed). Worse yet, the use of Polyvinylpyrrolidone, which was formerly acceptable, has now become restricted. Of the iron

TABLE II

**Compatibility of Excipients in Tablets and Capsules**

**BINDERS, GLIDANTS, LUBRICANTS**

| | | |
|---|---|---|
| Starch paste: | ok | I |
| PVP: | frequently accelerates degradation | II |
| HPMC: | better than PVP | II |
| Gelatin: | rather worse than HPMC or starch | II |
| Colloidal silica: | quite reactive | I |
| Talc: | mostly ok | II |
| Magnesium stearate | individual incompatibilities, no general rules | I |
| Calcium stearate | | II |
| Stearic acid | | II |
| Neutral fats: | usually non-reactive | II |

I, II: Priorities for use (includes all aspects)

oxides only the red variety ($Fe_2O_3$) is permitted while the use of the yellow ($Fe_2O_3$ monohydrate) and especially the black oxides ($FeO.Fe_2O_3$) seems doubtful. Koseisho, the Japanese health authority, also restricts the use of excipients with a pharmacological effect, e.g. Citric and Ascorbic acid, to one fifth of the minimum daily dose. In Taiwan's newly promulgated Guidelines Methyl paraben is not approved while the other parabens may still be used. Mercurial preservatives such as Thiomersal and Phenylmercuric compounds, while not yet banned, have been severely restricted in Japan. They have been banned in Italy.

Generally, excipients listed in Pharmacopoeias must conform to the relevant pharmacopoeial specifications. In critical countries, this may restrict the use of very similar, but not identical, compounds, e.g. cellulose ethers with different degrees of substitution.

In the last few years some powerful new disintegrants for tablets and capsules have appeared. They are of great assistance where long disintegration times or slow dissolution rates are a problem. The compounds have been grouped below according to their acceptability; it appears that Sodium carboxymethyl starch creates the least problem worldwide even though it is not listed yet in any Pharmacopoeia.

New disintegrants

PRIMOJEL$^{R}$, Scholten (NL)
Sodium carboxymethyl starch
Legal status o.k. (incl. Japan)

NYMCEL, ZSB-10$^{R}$ mod., Nyma (NL)
Sodium carboxymethyl cellulose, low degree of substitution
Legal status o.k. (Europe, South America)

PLASDONE XL, GAF (USA)
Cross linked polyvinylpyrrolidone
Legal status o.k. (Europe)

LHPC, Shinetsu (J)
Hydroxypropyl cellulose, low substitution, not yet commercial

Another group of excipients not mentioned in Pharmacopoeias are semi-synthetic and hydrogenated oils. These are sold as specialties with controlled particle size. They are particularly useful as tablet lubricants when stearates are incompatible or as retarding agents for slow release forms. One would not think that any glyceride derived from vegetable oils would present difficulties with the authorities. Moreover, such glycerides are mentioned in the GRAS list, the list of the Council of Europe and in the WHO Technical Reports where acceptable daily intake (ADI) values are also given. In spite of this we had certain registration problems with one such compound. To make such non-Pharmacopoeial products better known was one of the

reasons that the three Basle companies jointly published a catalog of excipients (Ref. 7). This task is now pursued on a larger scale by the Industrial Pharmaceutical Technology Section with the support of the British Pharmaceutical Society (Ref. 8).

I would now like to discuss the color problem as we see it from Europe. Even before the ban of FD & C Red No. 2 in the United States (which was followed by only Taiwan and Venezuela) we could work with only five synthetic dyestuffs accepted worldwide.

Use of Dyes and Pigments by Ciba-Geigy (except Japan and USA)

Prior to 1975
Amaranth (FD & C Red No. 2)
Erythrosine (FD & C Red No. 3)
Indigo Carmine (FD & C Blue No. 2)
Sunset Yellow FCF (FD & C Yellow No. 6)
Tartrazine (FD & C Yellow No. 5)
(Ponceau 4 R: older products only)
Titanium dioxide

Present policy
iron oxides ) if colors are needed
Titanium dioxide )
β-Carotene (mainly reformulations of sugar coated tablets)

We have recently adopted a new policy for development preparations. Iron oxides are used for identification if more than one dosage of an active ingredient is to be marketed. Clapsules are also colored with iron oxides. In using synthetic colors the benefits and risks have to be weighed carefully. A tablet or a capsule is still identified most easily by its color. We are therefore hesitant to change colors of existing pro-

TABLE III

**Legal Status of Carotenoid Food Colors, June 1976**

| Country | β-Carotene | β-Apocarotenal | Canthaxanthin |
|---|---|---|---|
| EEC Countries | x | x | x |
| Switzerland | x | x | x |
| South American Countries | x | x | x |
| USA | x | x | x |
| Philippines | x | x | |
| Japan | x | | |
| New Zealand | x | | |
| South Korea | x | | |
| Turkey | x | | |
| USSR and Eastern European Countries | x | | |

ducts. When reformulations become inevitable, for examples when Tartrazine is to be eliminated, we try to stay as close as possible to the old color. This is sometimes impossible, but for dark yellow to orange shades β-Carotene preparations are now available (Ref. 9). This natural colorant is relatively stable in sugar coated tablets. It is also acceptable worldwide. The dark red Canthaxanthin may also be used for sugar coated tablets.

The stable and non-allergenic (Ref. 2-4) blue dyestuff Patent Blue V, a non-azo dye (C.I.42051), is unfortunately permitted only in Europe. It is interesting to note that the dyestuff problem varies from country to country; our present policy applies mainly to Europe and especially to the Scandinavian and central European countries. I am convinced, however, that the number of tablets and capsules brightly colored with synthetic dyestuffs will also decline elsewhere.

Similar, though sometimes less severe, restrictions are to be expected for other pharmaceutical adjuvants or necessities such as flavoring agents and antioxidants. Except for the artificial sweeteners Cyclamate and Saccharin flavoring agents are either natural products or imitations of them. The Cyclamate case is too well known to be discussed here. For oral liquid preparations Sorbitol and the sweeter Xylitol are useful alternatives. Antioxidants such as Propyl gallate or Butylated hydroxy anisol and toluol may cause allergic reactions and should be avoided (Ref. 1, 10).

Many countries presently have regulations or laws in preparation which will define the concentrations of chlorinated hydrocarbon solvents spilled into the atmosphere or water. In our company Methylene chloride has been used together with alcohol for both water soluble and enteric film coats. With the advent of low viscosity, water soluble Hydroxypropyl methyl cellulose (Ref. 7) the newly developed preparations are now coated on a purely aqueous basis. An aqueous acrylate dispersion is also commercially available for this purpose (Ref. 7), especially for tablets with coats for controlled release hitherto based on ethyl cellulose.It is to be hoped that such dispersions will not face too many difficulties before being accepted worldwide. Unfortunately, organic solvents are still needed for enteric film coats.

The use of Methylene chloride for granualtion purposes is going to be sharply reduced in our company. The same is true for alcohol because this solvent greatly increases the risk of dust explosions in fluid bed dryers. It has been possible to largely avoid organic solvents by means of fluid bed granulation and by proper choice of water soluble or water dispersible granulating agents.

TABLE IV

**'Microcrystalline' Cellulose**
(Hüttenrauch and Keiner, Pharmazie 31, 183 [1976])

| | Molecular weight | Degree of polymerisation |
|---|---|---|
| Native Cellulose (Cotton) | 300,000–500,000 | 2000–3000 |
| 'Microcrystalline' Cellulose | 30,000–50,000 | 200–300 |

| | Crystallinity |
|---|---|
| Native Cellulose | 90–94% |
| Avicel® | 31–37% |
| Elcema® (Rehocel®) | 12–24% |

All the questions discussed so far have been dealing in one way or the other with safety. I would now like to briefly mention some other aspects.

Defined chemical composition and physical properties are of course essential prerequisites for excipients. The same is true with regard to analytical and microbiological purity. For all these factors, excipients must conform to the same stringent requirements as active ingredients. In our experience, problems with excipients occur almost daily and include not only such things as presence of undesired impurities but also changes in technological performance. Careful choice of the suppliers of our raw materials as well as constant contact with their agents is essential. Suppliers who concentrate on the pharmaceutical or maybe the food industry are in most cases better qualified to guarantee high quality products. It pays to check this point from an international viewpoint before deciding whether to use an excipient or not.

This leads us to the problem of regular supply and international availability of excipients. Since quality and performance are of utmost importance it has been inevitable that more and more brand-named excipients have invaded or even flooded the market. These include Microcrystalline cellulose, most of the new disintegrants, directly compressible excipients composed of Lactose, various sugars, Dicalcium phosphate, special types of starches and also many excipients for topical preparations. In most cases one product cannot be easily replaced by another. For example, there are several brands of so-called Microcrystalline cellulose. One type, represented by Avicel$^{R}$, is obtained by mechanical as well as acid treatment; another type (Elcema$^{R}$) by mechanical treatment only. This leads to different degrees of crystallinity which might well have an influence on theproperties of the dosage form.

When our Purchasing Department asked us whether Avicel$^{R}$ could not replaced by the cheaper Elcema$^{R}$ we answered that it possibly could be, but not without first performing tests on the properties and stability of some critical preparations prepared hitherto with Avicel$^{R}$.

In our company, brand-named or specialty excpients are used only if they lead to a better product, usually one with better controlled bioavailability or one with superior mechanical or analytical properties. This justifies a higher price but creates some problems for import of the substance into countries with high import duties. For India, such imports are not possible at all. Therefore in some cases our local development group must formulate with locally available excipients.

In consideration of what has been discussed so far we have grouped the excipients for tablets and capsules into two categories:

Excipients of first choice include Corn starch, Lactose (milled or unmilled), Colloidal silica, Magnesium stearate and water as solvent. For coating, aqueous film coating with low viscosity Hydroxypropyl methylcellulose plus Talc and Inorganic pigments, where necessary, is now the first choice.

Second choice materials for tablets and capsules include Microcrystalline cellulose, Polyvinylpyrrolidone K 30, Talc, Stearic acid, Calcium stearate, hydrogenated and semi-synthetic oils, Di- and Tricalcium phosphates, Mannitol, Sucrose, Gelatin, and Carboxymethyl starch. The choice of these excipients usually becomes necessary for compatibility, technical or bioavailability reasons. For sustained release products still other excipients may be needed. Sugar coating is also second choice when compared to aqueous film coating. Inorganic pigments are preferred but in future β-Carotene preparations will also be tried.

In summary, there are many difficult decisions to make when choosing excipients to make when choosing excipients in a company which operates worldwide. The world is still too diverse for any one solution to be equally acceptable to everybody. However, some sort of compromise along the lines I have outlined seems to offer a workable solution. Closer cooperation between industry, the universities and regulatory agencies in defining the scope and use of pharmaceutical excipients is certainly very much needed.

Let us hope that some day there will be a catalog of all the useful excipients and adjuvants and that this catalog will be accepted by regulatory agencies all over the world.

References:

(1) A. Grnholt and P.O. Thune, T. norske laegeforen 95, 20 (1975)

(2) G. Michaelsson, L. Petterson and L. Juhlin, Arch. Dermatol. 109, 49 (1974)

(3) L. Rosenhall and O. Zetterstrom, Lakartidningen 70, 1417 (1973)

(4) L. Juhlin and G. Michaelsson, Brit. J. Dermatol. 88, 525 (1972)

(5) L. Juhlin, G. Michaelsson and O. Zetterstrom, J. Allergy. 50, 92 (1972)

(6) Eurofood, No. 101, October 1976

(7) Katalog pharmazeutischer Hilfsstoffe, Basel 1974. Distributed by APV, Hafenstrasse 23, D-6500 Mainz (Germany)

(8) APhA Academy Reporter 12 (4), September 1976

(9) H. Klaui and O. Raunhardt, Alimenta 15, 37-45 (1976)

(10) G. Kahn, P. Phanuphak and H.N. Claman, Arch. Dermatol. 109, 506 (1974)