ELSEVIER

Il Farmaco 54 (1999) 1–14

IL FARMACO

Review

Quality and functionality of excipients

Giorgio Pifferi [a,*], Paola Santoro [a], Massimo Pedrani [b]

[a] *Istituto di Chimica Farmaceutica e Tossicologica, V.le Abruzzi 42, I-20132 Milan, Italy*
[b] *Emmiepi-Pharma, V.le Arbe 77, I-20125 Milan, Italy*

Accepted 15 September 1998

Abstract

The quality of medicines depends not only on the active principles and production processes, but also the performance of the excipients. The traditional concept of the excipient as any component other than the active substance has undergone a substantial evolution from an 'inert' and cheap vehicle to an essential constituent of the formulation. The rapid evolution of scientific, regulatory and economic factors, the introduction of delivery systems and the advance in biopharmaceutics have led to a new interest in the role and functionality of the excipients. More than one thousand raw materials are available from a multitude of sources and are used today in the pharmaceutical industry. Their chemical structures vary from small molecules to complex natural or synthetic polymeric mixtures. Excipients are now chosen to perform a variety of functions to guarantee the stability and bioavailability of the drug substance from the drug product and its manufacturability on a production scale. Beyond the dosage form necessities, excipients are required to perform important and specific technological functions, particularly in the case of solid dosage forms. As a consequence, their characterisation must go beyond the simple tests for identity, purity and strength as prescribed in general by the Pharmacopoeia monographs. With the exception of the Textbook of Pharmaceutical Excipients, not many reference sources describing the physical mechanical characteristics of the powders for a specific role are available. Full physical characterisation of solid materials is now made possible with the help of high resolution analytical techniques on the molecular, particulate and bulk levels. This systematic approach is necessary to guarantee the behaviour of the excipient during the formulation and production phases. Some examples have been chosen in this mini-review in an effort to highlight the emerging trends in the development of 'tailor-made' materials. Three main approaches are followed by the industry: physical or minor chemical manipulation of materials already known, combination of two or more marketed excipients in order to reduce unwanted defects and, finally, preparation of new chemical entities with huge investments for the toxicity studies. Excipient harmonisation, standardised functionality tests, preformulation data bases and expert systems will contribute to change the conventional trial-and-error formulation approach into a far more scientific and technological development.

Keywords: Excipient performance; Pharmacopoeial standards; Solid material characterisation; Pregelatinised starch; Microcrystalline cellulose; Amorphous lactose

1. Evolution of the concept of the excipient

1.1. Traditional concept of the excipient

The biological and analytical requirements necessary for the registration of an active principle as a medicinal speciality, whether of natural or synthetic origin, have always been at the centre of the pharmaceutical industry's and health authorities' attention [1]. Ever increasing demands and expectations with regard to quality have stimulated the development of new drugs characterised by higher assay and lower content of impurities [2]. However, the quality of a drug does not depend only on the characteristics of the active substances and the production process but also partly on the quality of the excipients. In general, the latter contributes notably

* Corresponding author.

to the performance of the drug and this, contrary to what was believed in the past, is fundamental to guarantee the safety and efficacy of the final pharmaceutical product [3]. Confirmation of this 'historical' under-estimation of the role played by the excipient is already discernible in the definition of the *traditional concept* which saw it simply as a substance that facilitates the administration and preservation of the active principle.

Some factors outside the pharmaceutical sector, such as the supply sources, the quality of the material, the manufacture and marketing of raw materials (Table 1) justify, at least in part, the scant attention paid to the matter of excipients up to a few years ago. This attitude was also engendered by the very low incidence of the cost of the excipients in the global cost of the compound, often lower than 1%. On the other hand, if we take into consideration the composition of a medicinal product from the point of view of its weight, it will be noted that the percentage of the active principle contained in the formula is generally considerably lower than that of the excipients. In the three drugs shown as examples in Table 2, the weight of the active principle varies from a maximum value of 12% in the formulation of sugar-coated tablets, to 0.5% in drops, to the lowest content of 0.0008% in the preparations for ampoules. These percentages become simply infinitesimal if homeopathic preparations are taken into consideration, seeing that they are obtained from successive dilutions of thousandths from the parent tinctures [4].

From the chemical point of view, even the so-called *inertia* of the excipients is to be accepted with reservations. In fact, like active principles, excipients have their own internal thermodynamic energy. This results in a certain reactivity which, though low, may, when influenced by chemical and physical factors in the environment, trigger some reactions leading to degradation, with fortunately usually slow kinetics. In the formulations in Table 2 there are some excipients containing reactive organic functions such as ethyl alcohol and propylene glycol, the terpenic essences in flavourings, iodised colourings, iron oxides and complexing (ex. EDTA) and reducing substances such as lactose. Considerable percentages of chiral excipients (starch, cellulose) are also employed and these may react with racemic active principles due to the law of mass, giving rise to diastereoisomers endowed with different chemical properties and therefore different bioavailability [5].

Another fundamental characteristic of the classical excipient, besides its so-called chemical inertia, is its *pharmacological and toxicological inactivity*. One cannot generalise in this case either when one thinks of the use that has been made of ethanol and boric acid, sulfites and tartrazine with their immunological effects, organic mercury compounds and some mineral oils, not to mention the psychological effects of excipients as *placebos*.

From these preliminary remarks it is clear that the two traditional requirements of an excipient, inertia and pharmacological and toxicological inactivity, are not always met. The supposed inertia of an excipient is often more of an expectation than the result of a real thermodynamic paralysis. Only a thorough study in the

Table 1
The traditional excipient

Source	From a multitude of natural sources, in general as a complex mixture of similar compounds, and from synthetic polymers.
Production	For chemical, food, agricultural and cosmetic industries, partly and not particularly, for the pharmaceutics industry.
Quality	Often not suitable for pharmaceutical use, tested by the consumer, not by the manufacturer, physical properties not qualified as excipient.
Market	Raw materials for commercial scale productions, with limited grade offered, low price and no trademark.

Table 2
Weight ratio between active principle and excipients

Valium®2 guttae		Laroxyl® pills		Turbocalcin® vials	
Diazepam	mg 5	Amitriptyline	mg 11	Carbocalcitonin	μg 8
Colourant E 127	to ml 1	Colourant E 172	mcg 500	Turbocalcin[1]vials	to ml 1
Alcohol	100	Starch	10.6	Sodium chloride	mg 7.5
Propyl glycol	600	Lactose	17.5	Sodium acetate	2
Saccharin	11.4	PVP	0.9	Acetic acid	
Orange ess.	20	Magnesium stearate	4.1	W.F.I	to ml 1
Lemon ess.	10	Gum arabic	1.1		
Colourant E 127	9.2	Ethyl cellulose	0.3		
Water	to ml 1	Colorant E 172	mcg 25		
		Titanium oxide	mcg 500		
		Paraffin	14		
		Sucrose	to 90		
Ratio = 0.5%		Ratio = 12%		Ratio = 0.0008%	

preformulation phase will show which are the most suitable excipients, clarify their reciprocal interactions and evaluate their real contribution to the efficacy of the medicinal product [6].

1.2. The excipient as adjuvant agent

The majority of pharmaceutical dosage forms falls into the category of solid, semi-solid and liquid disperse systems, in which the active principle/s are considerably diluted, as we have seen. The excipients have therefore to carry out the functions of diluent, filler and solvent so as to give the dose of active principle suitable *weight*, *consistency and volume* from the galenic point of view, and make it more convenient to administer [7]. In this case, the excipient assumes the function of *vehicle* suitable for the desired administration route, so as to transport the active principle to the desired place of absorption in the organism. The study and creation of more or less complex disperse systems require a sufficient knowledge of physical chemistry and physics to be able to assess their contribution to the stability and release of the active principle.

Besides the traditional functions of support and vehicle therefore, the excipient is also expected to function as an *adjuvant*, from the Latin verb '*adjuvare*', that is to help the active principle to carry out its activity by conditioning its release from the pharmaceutical dosage form. In the National Formulary Admission Policy of 1994 [8] there is the following definition: ''Excipients are any component other than the active substance(s) intentionally added to the formulation of a dosage form.'' To interpret the adverb 'intentionally' in this definition, we must remember the main administration routes of a medicinal product and the complexity of the roles the excipient must play in their respective formulations [9]. For each of the administration routes indicated in Table 3, the excipient must guarantee the stability of the pharmaceutical dosage form, the precision and accuracy of the dosage, as well as modify, when necessary, its organoleptic characteristics (smell, taste, swallowability and local tolerability) so as to improve the patient's 'compliance'.

Table 3
The excipient in modern formulations

Routes of administration	Rôles to enhance
Oral	Organoleptic properties
Rectal and vaginal	Compliance
Inhalation	Dose precision and accuracy
Topical	Stability
Transdermal	Side-effects
Intraocular	Desaggregation, dissolution
Intranasal	Controlled release
Parenteral	Absorption

To these traditional rôles are added today those of controlling and regulating the rate of disaggregation and dissolution, with possible favourable repercussions on the release profile of the active principle and its bioavailability, understood as the speed and amount of active principle released from the pharmaceutical dosage form and entering the systemic circulation. The pharmaceutical dosage form thus outlined can optimise the therapeutic efficacy of the medicinal product while simultaneously reducing its undesired side effects. The study of the formulation of a medicinal product on an empirical basis is now a thing of the past and Pharmaceutical Technique is gradually and inevitably changing from an Art (witness the italian initials FSA: fai secondo arte) into an Applied Science, which requires multi-disciplinary competence, as we shall see further on.

1.3. The evolution of excipients

From the standpoint of what we have said so far, the excipient is no longer to be considered an inert product but an essential and functional component of a modern pharmaceutical dosage form [10]. What are the external factors that have contributed to this evolution, not only in the concept but also in the regulations governing excipients? In Table 4 certain elements have been summarised so as to facilitate the understanding of the rapid and profound change in the characteristics and quality of excipients which has occurred since the 1970s and 1980s [11].

The globalisation of demand and economies of scale are the consequences of an industrial philosophy that rewards partnerships and mergers between pharmaceutical companies with the formation of important multinational companies enjoying considerable financial reserves. This enables them to support the basic and applied research activities necessary to innovate their range of products in the future. The organisation of work (*just in time*), too, and the size and scattered locations of the production plants are rapidly undergoing transformation and rationalisation so as to reduce as much as possible the time required for development and the number and variability of production batches. As a reflection of this, even the machinery, such as ampoule-fillers, tabletting and encapsulating machines, has to be re-designed so as to work at high speeds.

It follows that it is necessary to have at one's disposal new excipients that are compatible not only with modern processes and production machinery (rotating and not conventional tabletting machines, rotating granulators, compactors, etc.) but also with *innovative active principles* coming, that is, from biotechnologies and modern peptide synthesis [12]. Moreover, the interest in and wide-spread use of new therapeutic systems and modified-release forms is another factor that spurs the demand for more sophisticated excipients that can fulfil

Table 4
Factors impacting on the evolution of excipients

Scientific and regulatory factors	
National Formulary as exclusive Excipient Compendium	(1980)
Over 100 new monographs added to NF	(1975–1990)
NF Panel on Moisture Characterisation	(1985–1990)
USP/NF Special Advisory Panel in Physical Test Methods	(1991)
Int. Pharmac. Excipient Council (IPEC) Foundation	(1991–1994–1998)
Int. Pharmac. Excipient Council European Conference	(1994)
Eur. Pharmacopoeia Group of Experts to Test Functionality	(1995)
The Int. Conference on Harmonisation	ICH (1991), ICH 2 (1993), ICH 3 (1995), ICH 4 (1997)
Handbook of Pharmaceutical Excipients	I ed. (1986) II ed. (1995)
Technological and economic factors	
Higher productive power	(tablet presses with higher compaction speeds, non conventional rotary presses,…)
New excipients	(for novel and potent drugs, for biotechnology products, for controlled release formulations, for new delivery systems,…)
Globalisation demand	(organisational restructuring, merging, just-in-time, automation,…)

specific functions within the formulation. These innovative formulations permit the optimisation of plasmatic concentrations of the active principle, thus increasing efficacy, the patient's compliance and the added value of the medicinal product [13].

The scientific and regulatory events that have contributed to the evolution of the excipients sector over the last twenty years, in concomitance with the economic and technological factors, are not to be neglected. Returning to the situation in the past, excipients were taken from materials of natural origin and in common use in the chemical and agricultural food-stuffs sectors and employed in the pharmaceutical field just as they were, without further purification to improve the assay or their chemical or physical characteristics. Analytical tests were conducted for the most part within the Pharmaceutical Industry and not by the supplier of the raw material. The tests were often limited and not sufficient to characterise the excipients' quality, much less their functionality. To give a few examples, only one type of 'spray-dried' lactose was available for the production of tablets and capsules by direct compression. Magnesium stearate was widely employed as a lubricant, even though there was scant knowledge of its structure and lubricating capacity. Since 1970, the situation has evolved swiftly under the pressure of new knowledge of the solid state of materials and the ever more stringent qualitative requirements demanded by the Regulatory Authorities.

Table 4 lists some scientific events, such as the inclusion of over a hundred monographs on excipients in the US National Formulary and the publication of two editions of the 'Handbook of Pharmaceutical Excipients', which contains monographs that meet pharmaceutical technologists' needs much more closely [14]. Furthermore, at the beginning of 1990, the Secretaries of the three most important Pharmacopoeias, the USP, the Eur. Ph. and the J. Ph., agreed on the importance of harmonising the standards and the testing methods regarding excipients, so as to satisfy the requirements of the industry and their own respective Regulatory Agencies. Considerable progress has been achieved since 1990 (Table 4) as a consequence of a good four Joint Pharmacopoeial Open Conferences on International Harmonisation of Excipient Standards and four ICH (Brussels, November 1991; Orlando, October 1993; Yokohama, November 1995; Brussels, 1997). The monograph on lactose monohydrate has reached the last stage of publication and those on magnesium stearate, saccharose, polyvinylpirrolidone as well as powdered and microcrystallised cellulose are at advanced stages in the procedure [15,16]. Some testing methods on the physical state, such as particle size, specific superficial area, poured and tapped density are also in an advanced phase of joint compilation.

The renewed interest in modified release forms and in new therapeutic systems, as well as new production technologies, has contributed, as already mentioned, to research into new materials endowed with specific technological properties and their development as functional excipients. All these factors and more have changed the traditional concept of an excipient into the more up-to-date one of *functional agent*, that is, one that can fulfil several functions within the pharmaceutical formulation. They have also contributed to focusing the pharmaceutical technologists' attention on the quality of the excipient, which also contributes to the efficacy and safety of use of the medicinal product, together with that of the active principles.

2. Functions and specifications of excipients

2.1. Functions of excipients

On the basis of the preceding considerations, it is clear that excipients are no longer to be considered as

Table 5
Modern excipient functions

Stability	Drug absorption
Antioxidants	Disintegrants
Chelating agents	Plasticisers
Preservatives	Drug release modifiers
Stabilisers	Penetration enhancers
Buffers	Wetting agents, solvents
pH modifiers	Film formers
	Bioadhesives
	Encapsulating agents
	Biodegradable polymers
Manufacturability	
Dosage form necessities	Specific techn. Properties
Ointment bases	Emulsifying, suspending ag.
Semisolid excipients	Gelling agents
Diluents,…	Lubrication enhancers
	Flow, compaction enhancers
	Propellents, bulking agents,…

inert materials but essential components of ever more sophisticated and modern pharmaceutical dosage forms. Excipients are employed to carry out different functions that may be grouped into three categories, according to whether they influence stability, release and absorption of the active principle or manufacturability during the manufacturing process phase [17]. Excipients with this latter function may be subdivided in turn into those that are basic components of a certain pharmaceutical dosage form (dosage-form necessities), such as ointment bases, or into a second sub-group of materials that can fulfil particular technological functions, such as lubricants (Table 5). Thus, by varying the type, quantity and quality of the excipient incorporated, the pharmaceutical technologist can correct and optimise the characteristics of the final formulated product.

In the case of the manufacture of tablets and hard capsules, for instance, modern excipients must be suitable for the preparation of homogeneous and flowable mixtures during the intermediate manufacturing process of the powders and granulates, so that the modern tabletting and encapsulating machines are fed swiftly and smoothly. In order to fulfil the multiple functions shown in Table 5, the specifications of modern-day excipients must add a series of technological functional measures to the normal characterisation of analytical purity [18,19]. The technological tests of physical chemistry and mechanical physics are drawn up schematically in Table 6 and are as important today as the traditional tests that were carried out to ascertain the analytical identification, assay and purity of the active principle.

2.2. Pharmacopoeial monographs and their limitations

Confirmation of the gaps in the analytical specifications of excipients may be gathered from reading the monograph on ***magnesium stearate*** (*magnesium stearicum*) in the Italian Official Pharmacopoeia IX Edition [20], where the following tests are prescribed:

- Composition: mixture of variable and unspecified proportions of magnesium stearate, palmitate and oleate.
- Title: Mg between 3.8 and 5%.
- Organoleptic characters: very fine powder, white, oily…
- Solubility: practically insoluble in water, ethanol and ether.
- Identification: melting point of organic residue, characteristic reactions of magnesium.
- Assays: colorimetric comparison of solution S with a comparable solution, appearance of chloroform solution of fatty acids.
- Acidity or alkalinity: blue indicator of bromothymol.
- Acidity index of fatty acids: between 295 and 210.
- Chlorine, sulfate and heavy metals test: within the limits.
- Loss on drying: equal to or lower than 6% at 100–105°C.

The *quantitative determination* prescribes the complexometric titration of magnesium with zinc sulfate and sodium edetate.

Table 6
Modern excipient specification

The tests on the functionality of the excipients comprehend:	
Control of purity	
Chemical characterisation: identity, purity, strength, composition	
Control of performance	
Physical characterisation:	Physico–mechanical testing:
describes the functional attributes that make the excipient perform (why the excipient does what it does)	relates to a specific application (what the excipient does)
Excipient specifications thus ensure the dosage-form necessities:	
Safety, Stability, Absorption, Manufacturability	

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.