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Novel excipients – from concept to launch



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ABSTRACT

New excipients can improve the quality of drug products and are needed for the development of innovative drug delivery systems. Even though in recent years, a number of new modified or co-processed excipients have been introduced in the market, almost all manufacturers refrain from the development of novel excipients, since it takes time, requires resources and is associated with a certain risk of failure. This article gives an overview of the types of new excipients and explains why the development of a novel excipient is particularly challenging. In addition, the regulatory framework for the approval of new excipients creates a dilemma for the manufacturers and users of novel ingredients.

INTRODUCTION

Pharmaceutical excipients are the inactive ingredients of a drug product. They are a very heterogeneous group of materials and differ in their origin, chemistry, physicochemical properties and functionality. Most commonly used excipients are sugars, starches or modified starches, minerals, cellulose and its derivatives, fats and oils or solvents. All these materials have a long history of use in pharmaceuticals, food and cosmetic applications. With the transition from simple formulations to drug delivery systems the demand for synthetic or semi-synthetic functional polymers (acrylates, ethoxylated compounds or polyvinylpyrrolidone grades) has increased tremendously (1). Today, as the pharmaceutical industry has to deal with the patent cliff, reduced health care spending and more stringent regulations, drug development has become more difficult (2). New excipients offer opportunities and could make a difference, e.g. new solubilizers are needed to overcome drug delivery challenges of poorly water-soluble actives. New excipients can help to re-formulate approved drugs in order to improve quality and safety of the medicine or to reduce its manufacturing costs. However, even though in recent years a number of modified and co-processed excipients came to the market almost all manufacturers

refrain from the development of novel excipients (3). The development of a new excipient takes time, requires resources and is associated with high failure risks.

TYPES OF NEW EXCIPIENTS

In general, there are three types of new excipients and the development process of these varies significantly:

Modified excipients

Well known excipients with established quality standards can be modified with regard to their impurity profile or their physical properties. A certain particle size or particle structure can be advantageous for the manufacture of a dosage form or may be required for a new application. High purity grades of excipients that have a reduced level of reactive impurities are desired to increase the stability of sensitive active ingredients (4, 5). Modified excipients therefore do not require safety assessment as they meet the requirements of pharmacopoeia monographs (with stability indicating methods in place) and often have stricter limits or differ in their functionality related characteristics. Examples of modified excipients include: Kollidon[®] VA 64 Fine from BASF, a copovidone grade of modified particles with improved compressibility and Tween[™] 80 HP, a high purity grade of polysorbate 80 offered by Croda for sensitive actives and parenteral applications.

Co-processed excipients

Two or more excipients are formulated without chemical changes in order to achieve new performance characteristics which cannot be achieved by simple physical mixing. Typical manufacturing processes are granulation, spray formulation or encapsulation technologies (6). Co-processed excipients are typically designed to improve the efficiency of drug product manufacturing (7). Combinations for direct compression of tablets or certain ready to use film coating formulations are frequently used. In most cases, the safety profile of a co-processed excipient will match that of the corresponding physical mixture. Examples for co-processed excipients are the Aquarius[®] product line for film coating from Ashland or BASF's Ludiflash[®], an excipient for direct compression of orally dispersible tablets.

Novel excipients

The ICH Guideline M4Q defines an excipient to be novel if it is used for the first time in a drug product or a new route of administration. The guideline applies to all excipients with a new

Excipient type	Examples
Modified excipients	Tween™ 80 HP (Croda) Kollidon® VA 64 Fine (BASF) Swelstar™ Mx1 (Asahi Kasei) GalenIQ™ 721 (Palatinit) Specrablend™ HS (Sensient)
Co-processed excipients	Prosolv® ODT (JRS) Ludiflash® (BASF) Aquarius® (Ashland) Captisol® (Cydex)
Novel excipients	Recombunin® (Novozymes) Soluplus® (BASF) Kollicoat® Smartseal 30 D (BASF)

Figure 1. Overview of new excipients.

chemical structure or established excipients that are chemically modified. It requires a thorough characterization of the physico-chemical properties, functionality and safety of the excipient (8). Biotechnologically or biologically derived substances such as albumin are also considered as novel excipients, even though they are well known. Examples of novel excipients are Soluplus® a polymeric solubilizer or Kollicoat® Smartseal 30 D both from BASF or Recombunin® from Novozyme.

Novel excipients – a rare species

Figure 1 gives an overview of new excipients and Figure 2 compares the development of the three types of new excipients.

Product development of new excipients has three main goals: First, to demonstrate the advantage over existing materials for the target application, secondly to establish a reliable manufacturing process that leads to the desired product characteristics and – last but not least – thirdly, to demonstrate the appropriate stability of the new grade. The development for modified excipients time is relatively short with a low R&D investment and a low associated risk (see Figure 2).

The development of a co-processed excipient is more complex. Scale-up and transfer to production are more demanding and it is usually required to demonstrate the integrity of the chemical structure. In addition it is necessary to develop analytical methods, to define a specification and to investigate the stability of the product. Thus, the development time is usually longer (2-5 years), with an increased R&D investment and a higher risk.

The development of a novel excipient – and in particular that of a new chemical entity with no structural analogy to established excipients – is substantially similar to the non-clinical development of a new active ingredient: A high R&D investment and a long development time of 6-7 years associated with a high risk of failure make such projects less attractive. As a consequence, only very few manufacturers are willing to invest in the development of a novel excipient.

DEVELOPMENT OF A NOVEL EXCIPIENT

The development of a novel excipient is a rather complex task and many different aspects have to be considered.

Specialists with expertise in chemical synthesis, chemical engineering analytics, toxicology and safety evaluation, production and quality assurance, performance testing and marketing should be part of the project team. Figure 3 illustrates the general topics that the project team must address.

Some of the product development goals may overlap with others. For example, it might be difficult to manufacture materials with the best performance in a particular application at a commercial scale or at a reasonable cost. Very often it is necessary to find a compromise. Furthermore, it is important to define a precise target profile for the new excipient with “go” and “kill” criteria that have to be revisited at predefined milestones.

Ideas for new excipients usually originate in unmet needs of the users. The fact that approximately 80% of new actives in drug discovery are poorly soluble combined with trend to establish melt extrusion in pharmaceutical manufacturing initiated the development of a new polymeric solubilizer at BASF (9).

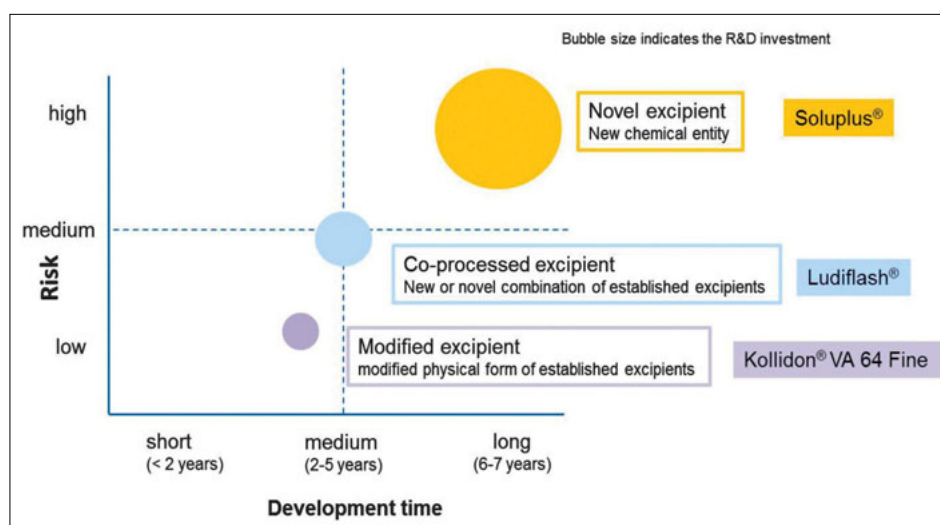


Figure 2. Development of new excipients

Figure 3 gives a brief overview about the development of a novel polymeric excipient. The two different colors indicate that not all steps are under direct control of the excipient manufacturer.

A close cooperation with users in the pharmaceutical industry is a prerequisite for the successful completion of the project.

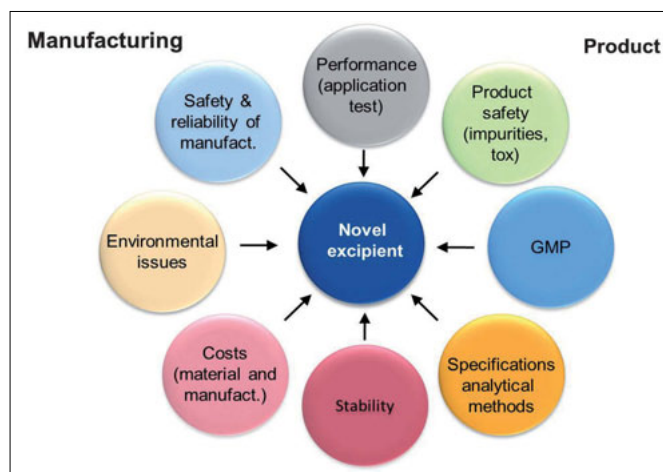


Figure 3. Important aspects of excipient development.

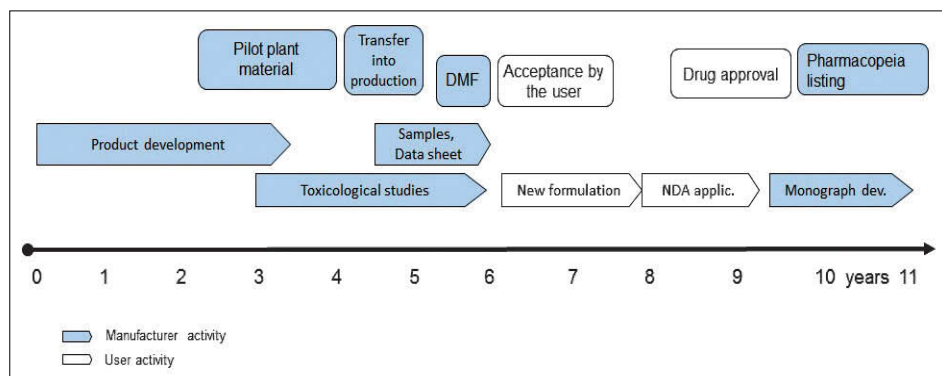


Figure 4. Project overview of the development of a novel excipient.

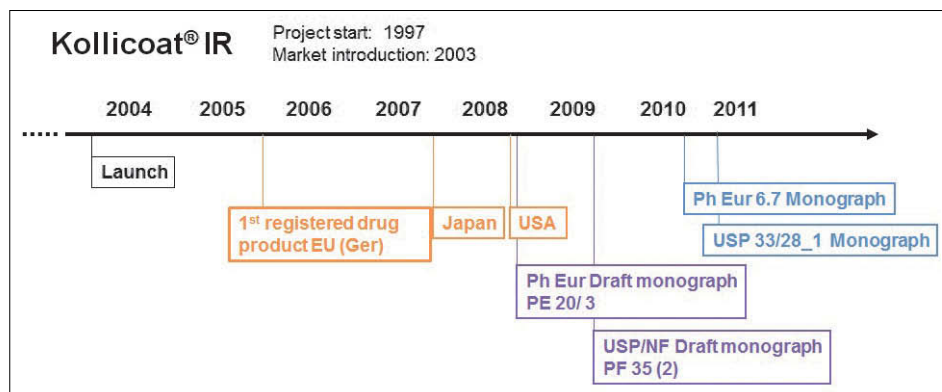


Figure 5. Launch phase of a novel excipient.

The target of the initial project phase (so called "product development") is to define a chemical structure and to identify a suitable route of synthesis that leads to a polymer with desired properties. In this phase, a high number of different polymers is screened. Once the lead structure is identified, the polymer is optimized with regard to composition, chain architecture and molecular weight. It is very important that these substances are evaluated against the target profile. In addition, it is also necessary to identify impurities that may potentially affect the performance or safety of the excipient and to define preliminary limits for a specification.

After the completion of the laboratory phase, a scale-up is initiated. When the process is successfully transferred to a pilot plant (typically in the range of 4 m³) and the material is of desired quality, a toxicological characterization of the excipient is initiated. The study program should follow the FDA-Guidance for the Industry "Guidance for the Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients" and should include numerous tests to assess acute, sub-chronical and chronic, developmental and reproductive toxicity, toxicity to the environment as well as mutagenicity and carcinogenicity tests (10). In parallel, the structure, composition, impurities and degradation products of the new excipient must be identified and characterized. Specification limits are defined based on safety, compendial requirements, process capability and relevance for the application. The analytical methods should be close to pharmacopeia procedures and have to be fit for purpose (11).

The final project phase focuses on the transfer to commercial production and the preparation of the market launch.

Even though a process validation is not explicitly required for the manufacture of excipients, it is highly recommended for a new excipient. This is even more important, if the route

of synthesis is new, and experience with the process is limited. Packaging materials have to be chosen carefully and their suitability should be demonstrated. A stability study with a study design incorporating long term and accelerated conditions as it is mandatory for drug substances, and should be applicable for a novel excipient too. ICH-Guidelines that apply for new drug substances and publications of the International Pharmaceutical Excipients Council (IPEC) offer guidance on how to implement GMPs, how to conduct stability studies or how to issue certificates of analysis (12, 13). The marketing team then develops a launch strategy, prepares samples and product information (including application data to demonstrate the performance of the new excipient) for the users. Since there is no independent approval process for excipients, information on chemistry, manufacturing and control as well as the toxicological information has to be compiled in

a suitable form that can be made available for registration purposes. Some countries like the US, Canada and Japan allow quality and safety information about an excipient to be submitted by the manufacturer in the form of a drug master file (DMF). In Europe and other regions, where excipients are excluded from this process, it is a good practice to disclose scientific information in the form of a regulatory information file to the user. The content of such a document could be similar to the so called "open part" of an Active Substance Master File (ASFM) as it is used for active ingredients in Europe (14). The IPEC-Americas Excipient Master File Guide also follows this structure and emphasizes aspects that are specific to excipients (15).

THE REGULATORY DILEMMA

Introducing a new excipient to the marketplace without necessary regulatory approval process can be a huge setback to the excipient manufacturer. Formulation scientists would like to incorporate excipients that achieve the best performance in the drug delivery system. However, at the same time, they prefer excipients that have a preapproved functional role in drug products and a pharmacopeial monograph in order to avoid additional risks in the approval process. The launch phase of a novel excipient signifies the time range from the market introduction until the publication of pharmacopeial monographs. The example of Kollicoat® IR, a polyethylene glycol-polyvinyl alcohol graft copolymer for instant release film coating applications, shows that the transition from a "novel excipient" to a commonly accepted excipient can easily take between seven and ten years (Figure 5). The lack of an independent approval process for excipients and the fact that information about the quality and safety is reviewed by health authorities only in the

context of a new drug application causes a dilemma for both manufacturers and users of excipients. Manufacturers of novel excipients would like to disclose sensitive information in confidentiality. Direct communication with health authorities is desirable and an excipient master file system in Europe would already tremendously improve the situation (16).

In the end, only a direct approval process for pharmaceutical excipients could solve the regulatory dilemma. The pharmaceutical industry would greatly benefit from a reduced risk when using innovative excipients. The shorter launch period would help manufacturers to compensate for the high R&D investment for development of novel materials.

CONCLUSION

New excipients can improve drug product quality and are the basis for development of new drug delivery systems. In recent years mainly modified excipients or co-processed excipients have been introduced to the market. These two categories aim at improving the performance in existing applications or manufacturing processes. Novel materials are desired to overcome formulation challenges that cannot be addressed with standard excipients, but the development of a novel excipient has similarity to a new drug development and presents a real challenge. A registration process for novel excipients that is independent of drug product registration would be desirable for the industry. This could mitigate the risk of a delayed drug product registration for first time users and open the door for more innovative excipients.

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