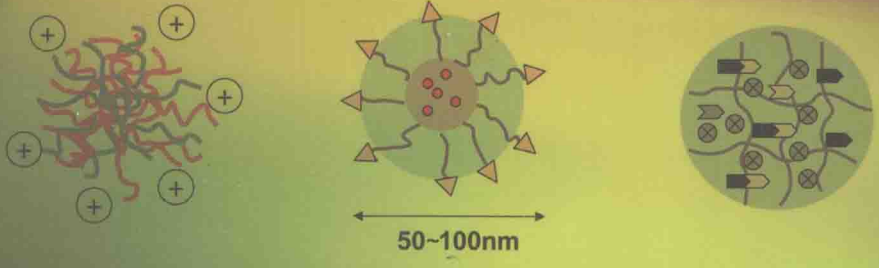
Polymers for Pharmaceutical Application

药用高分子材料

（中文导读版）

刘 黎　郭圣荣　主编



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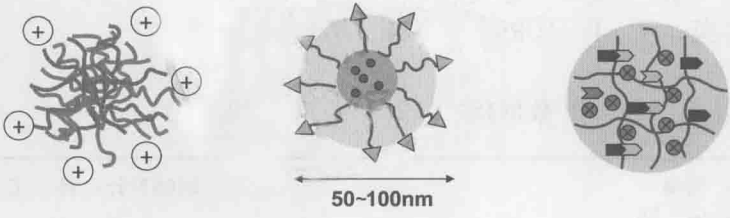

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·北京·

药用高分子材料是药物制剂不可缺少的物质基础，系统学习了解药用高分子材料相关知识，是现代药学科技工作者，尤其是药剂学专业学生的迫切需要。

本书是编者总结十余年的教学经验，参考大量英文原版文献和书籍并选取适合教学大纲要求的内容编写而成，主要内容以英文编写，并对关键知识点配以中文导读，便于学生阅读和理解。全书共分 6 章，内容包括：药用辅料概述；高分子材料概述；常用天然高分子辅料和合成高分子辅料的结构、性质及其在药剂学中的应用；新型生物可降解的合成药用高分子材料；最后介绍了新型药物输送体系中的药用水凝胶材料、纳米制剂与自组装高分子、高分子-药物轭合物和高分子基因载体。

本书可作为药学专业本科生教材和药剂学专业研究生参考教材，也可供药学、医学和高分子材料学等方面的科技工作者参考。

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前言
Foreword

近年来，许多高校开展了采用汉语和英语的双语教学实践，这对办学国际化和国际化办学很重要，也是培养具有国际竞争力的高素质人才的需要。

随着药用新材料的发展对药物输送系统和技术的不断促进，国际上对药用高分子材料的研究也越来越受到人们的关注。系统学习了解药用高分子材料相关知识，是现代药学科技工作者、尤其是药剂学专业学生的迫切需要。但目前，还没有一本适合药用高分子材料课程的双语教材。国际上，这一领域符合教学要求的英文原版书籍也很匮乏，国外第一本作为教材使用的《Polymers in Drug Delivery》于2006年才由CRC出版社出版。若在教学中直接采用英文原版教材，价格不菲，学生对于大量专业名词术语的理解也有困难。本教材《Polymers for Pharmaceutical Application——药用高分子材料（中文导读版）》就是为了适应双语教学的新形势和课程要求而编写的。希望本书的出版可以填补药用高分子材料双语教学教材的空白，有助于双语教学过程的规范。学生阅读英文版内容并对照关键知识点的中文导读，可以接触和掌握大量专业词汇，对药学专业本科生的专业英文水平提高一定有所裨益。

编者先后在复旦大学和上海交通大学药学院讲授药用高分子材料课程10余年。本教材以编者多年的教学经验为基础，参考大量英文原版文献和书籍，根据我国教学大纲的要求编写而成。全书共分6章，主要内容如下：第1章为药用辅料概述；第2章为高分子材料概述；第3章、第4章分别介绍选材于《Handbook of Pharmaceutical Excipients》（6th Edition, edited by Raymond C Rowe, Paul J Sheskey and Paul J Weller）中的天然高分子辅料和合成高分子辅料，包括它们的结构、性质及其在药剂学中的应用；第5章介绍现代药物输送系统研发中涉及的合成类生物可降解高分子材料；第6章介绍功能高分子材料在新型药物输送体系中应用进展的几个热点方向，包括：药用水凝胶材料、纳米制剂与自组装高分子、高分子-药物轭合物、高分子基因载体。每章/节的重点内容均有中文导读，便于学生阅读和理解。

在本书编写过程中，上海交通大学药学院药物控释技术与医药用高分子课题组的

沈园园老师，研究生蒋金均、吴可沁、李敏、汪芸，参与了资料收集和整理等工作。英文部分内容得到了上海交通大学外国语学院刘兴华老师的帮助和润色。在此一并表示衷心感谢。

本书可作为药学专业本科生教材和药剂学专业研究生参考教材，也可供药学、医学和高分子材料学等方面的科技工作者参考。

由于药用高分子材料是一个涉及化学、材料、生物、药学和医学的交叉领域，资料的收集整理未必全面，若有疏漏和不完善之处，衷心希望广大读者批评指正。

编者

2014 年 6 月

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Chapter 1.

Introduction to Pharmaceutical Excipients
药用辅料概述

1.1 Definition of pharmaceutical excipients

Medicines are available in many dosage forms including tablets, capsules, oral liquids, topical creams and gels, transdermal patches, injectable products, implants, inhalers, suppositories and so on. These medicinal products contain not only active drugs but also other ingredients collectively known as excipients. The word *excipient* is derived from the Latin word *excipere*, meaning "to receive, to gather, to take out", which can be simply explained as "other than". Therefore, the United States National Formulary of 1994 states that an excipient is any component other than the active principle added intentionally to the medicinal formulation, or "everything in the formulation except the active drug"[1].

Excipients have been used in drug delivery for centuries. Historically, for example, medicines were often mixed with honey or syrup to mask the flavor so that patients especially children would take them. Other excipients may be added to drugs as diluents to ensure that a medicinal product has the weight, consistency and volume necessary for the correct administration of the active principle to the patient. These usages of excipients are simply to make the product taste and look better and to improve patient compliance. Therefore, prescribers initially overlook excipients as inert substances used as vehicles and diluents for drugs on the assumption that they are inactive.

Ideally, excipients should be inert. However, recent studies in pharmaceutics have suggested otherwise. In reality, these inactive ingredients may facilitate the absorption of a drug into the body, or slow the absorption rate of a drug, or facilitate the breakdown of the drug once it reaches the right area of the body. For example, the drug would dissolve slowly with some excipients in the form of a time release coating. In addition to affecting the biopharmaceutical profile of a drug, excipients also play an important part in the manufacturing process.

Today, pharmaceutical excipients refer to substances that are usually included in a pharmaceutical dosage form not to direct the therapeutic action, but to aid the manufacturing process, to protect, support or enhance stability, or for bioavailability or

patient acceptability, to assist in product identification and to enhance the overall safety or function of the product during storage or use. Although technically "inactive" from the therapeutic sense, pharmaceutical excipients are critical and essential components of a modern drug product. It is reported that pharmaceutical excipients represent a market value of about $4 billion accounting for 0.5% of the total pharmaceutical market in 2009[2].

1.2 What are excipients doing in medicines?

Though the active ingredient in a medicine is only part of the arsenal against disease, they are almost never administered alone but in dosage forms that generally include excipients. A drug is desirable to take therapeutic action when it gets to the right place at the right time. That's where drug delivery comes in. Drug delivery is often approached via a drug's chemical formulation, in which pharmaceutical excipients make up the bulk of the total dosage form in many products and exert functions.

Taking the solid form of a tablet as an example, a tablet product must be stable during storage, transport and handling, yet will release its active pharmaceutical ingredient as required once ingested. To achieve the goal, the manufacture of tablets might be a complex process which demands considerable ingenuity involving various excipients, such as diluents or fillers, binders, disintegrants, glidants, lubricants, coloring agents and so on. Table 1-1 presents common excipients used in tablets and their functions.

Dr. Rutesh H. Dave has examined the top 200 prescription tablets and capsules products of 2003, and found out that except coating and coloring agents, the total number of inactive excipients used was ONLY 94 [3]. This finding indicates that an excipient may have more than one use in practice. Moreover, a blend of two or more materials may be necessary as excipients in a product in order to meet the practical requirements. However, it is advisable to reduce the number of excipients needed, so that the risk of interactions among various excipients may be minimized.

In general, excipients are added to formulations in order to improve the bioavailability and the acceptance of the drug on patients. Excipients influence the speed and efficiency of drug absorption, and hence affect drug bioavailability.

Recently, there has been much research on drug delivery systems which aims for greater pharmacological response and minimal side effects. The availability of new drug delivery systems mostly depends on the development of pharmaceutical excipients, which may also allow an extension of patent protection for an active pharmaceutical ingredient.

Table 1-1. Common excipients used in tablets and their functions[2].

Excipient	Function	Examples
Diluents	Provide bulk and enable accurate dosing of potent ingredients	Sugar compounds e.g. lactose, dextrin, glucose, sucrose, sorbitol. Inorganic compounds e.g. silicates, calcium and magnesium salts, sodium or potassium chloride
Binders, compression aids, granulating agents	Bind the tablet ingredients together giving form and mechanical strength	Mainly natural or synthetic polymers e.g. starches and cellulose derivatives
Disintegrants	Aid dispersion of the tablet in the gastrointestinal tract, releasing the active ingredient and increasing the surface area for dissolution	Compounds which swell or dissolve in water e.g. starch, cellulose derivatives and alginates, crospovidone
Glidants	Improve the flow of powders during tablet manufacturing by reducing friction and adhesion between particles. Also used as anti-caking agents.	Colloidal anhydrous silicon and other silica compounds
Lubricants	Similar action to glidants, however, they may slow disintegration and dissolution. The properties of glidants and lubricants differ, although some compounds, such as starch and talc, have both actions.	Stearic acid and its salts (e.g. magnesium stearate)
Tablet coatings and films	Protect tablet from the environment (air, light and moisture), increase the mechanical strength, mask taste and smell, aid swallowing, assist in product identification. Can be used to modify release of the active ingredient. May contain flavours and colorings.	Sugar (sucrose) has now been replaced by film coating using natural or synthetic polymers. Polymers that are insoluble in acid, e.g. cellulose acetate phthalate, are used for enteric coatings to delay release of the active ingredient.
Coloring agents	Improve acceptability to patients, aid identification and prevent counterfeiting. Increase stability of lightsensitive drugs.	Mainly synthetic dyes and natural colours. Compounds that are themselves natural pigments of food may also be used.

1.3 Quality and safty of excipients

A list of excipients included in the medicine is available online in the Consumer Medicine Information leaflet (www.nps.org.au/search_by_medicine_name). Related information can be found under 'Product description' and may be entitled differently as 'Other ingredients' or 'This product also contains ⋯'. Ideally, an excipient is pharmacologically inactive, non-toxic, and does not interact with the active ingredients or other excipients. However, in practice adverse effects may be caused by excipients. Toxicity may relate to compounds used as excipients in the final dosage form, or to residues of compounds (such as solvents) used during the manufacturing process.

Components employed as excipients shall not only contain the characteristics required by their technological function as mentioned above, but also meet the suitable safety requirements. However, the importance of evaluating the possible adverse effects of excipients was underestimated in the past, because their inertia and innocuity

were taken for granted. The toxicological aspect of these substances has been more deeply studied only when they are also employed in the food industry (as anti-oxidants, sweeteners, coloring agents, etc.). Changes do not come till some excipients were reported to have potential risks. Indeed, the International Toxicological Committees (among which the Joint Expert Committee on Food Additives, a mixed committee of the WHO❶/FAO) has demanded thorough investigations of excipients in laboratory animals, with the intent of protecting the consumers' safety. Tackling the issue of excipients toxicity thoroughly is not easy for several reasons: the large number of substances on the market and the diversity of their chemical profiles, their sources, their technological functions, and the presence of secondary products and/or contaminants which may otherwise be the true cause for adverse effects[1].

Hence, any material used in pharmaceutical drug product (e.g., excipient, active pharmaceutical ingredient, packaging, etc.) should observe specific standard and shall be manufactured under appropriate Good Manufacturing Practices (GMP) and supplied under Good Distribution Practices (GDP). The exact definition of GMP or GDP will depend on the material in question and legislation where the excipient is supplied or sold.

It is necessary for pharmacists to be familiar with the properties of pharmaceutical excipients. *Handbook of Pharmaceutical Excipients* contains monographs for 340 excipients, with each monograph including a 'Safety' section that introduces adverse reactions reviewed from the literature. This handbook is in the 7th edition updated in 2012[4]. What's more, the Pharmacopoeias (US Pharmacopoeia, British Pharmacopoeia) also contain monographs for many excipients.

International Pharmaceutical Excipients Council (IPEC), an international industry association founded in 1991 by manufacturers and users of excipients, consists of three regional pharmaceutical excipient industry associations covering the United States, Europe, and Japan (which are known respectively as IPEC-Americas, IPEC Europe, and JPEC). IPEC's objective is to contribute to the development and harmonization of international excipient standards, the introduction of useful new excipients to the marketplace and the development of best practice and guidance concerning excipients. *Qualification of Excipients for Use in Pharmaceuticals*, a document published by IPEC in 2008 introduces the three phases of the excipient qualification process. Although excipient qualification does not directly involve regulatory authorities, many conditions need to be satisfied if an excipient is employed in medicine. On the other hand, excipients are diverse and often have uses in areas other than pharmaceutical applications. Thus, this document is especially valuable for suppliers, as many of the issues described on the material are new to them. This document serves as guidelines offering advice and best practice to both excipient suppliers and users. It is not meant

❶ Abbr. of World Health Organization.

to be proscriptive, but is intended to be comprehensive covering some essential aspects of the supplier-user relationship.

1.4 Relationship between polymers and pharmaceutical excipients

Many polymers, mainly including cellulose derivatives, poly(ethylene glycol) (PEG), and poly(*N*-vinyl pyrrolidone) (PVP), have been widely used in drug delivery system as excipients for more than half a century. They are incorporated with bioactive agents in the pharmaceutical industry usually by the techniques such as compression, spray and dip coating, and encapsulation. Recently, some other polymers, such as nano- and micro-particles, nano- and micro-capsules, dendrimers and micelles, have also been tested as potential drug delivery systems, in which the drug is embedded or covalently conjugated in polymer matrices.

From a practical perspective, the use of polymers in pharmaceutical domain falls into two areas: drug polymer and drug carrier polymers for controlled release. Controlled release methods offer an appropriate tool for site-specific and time-controlled delivery of drugs. From a drug delivery perspective, polymer devices can be categorized as diffusion-controlled (monolithic devices), solvent-activated (swelling- or osmotically-controlled devices), chemically controlled (biodegradable), or externally-triggered systems (e.g., pH, temperature) [5]. Mechanisms involved in controlled release require polymers with a variety of physicochemical properties.

At the early beginning, polymers used as pharmaceutical excipients are commonly off-the-shelf materials. Nevertheless, much research effort has been devoted to designing new formulations to achieve a higher desired pharmacological response, where particular attention are paid to the polymeric systems of drug carriers. In fact, the tremendous growth in this field is driven in part by innovations in polymer science and chemical engineering. Particularly, the advanced research in polymer science has provides the clinician with a large number of new materials, new medical device and new formulations[6].

For example, hydrogels and other polymer-based carriers have been developed to provide safe passage for pharmaceuticals through inhospitable physiological regions. Polymers of controlled molecular architecture can be engineered to give a well-defined response to external conditions as a result of a solid understanding of the underlying mechanisms and the nature of behavioral transitions. Polymers incorporated with therapeutics can be bioactive to provide their own therapeutic benefit or can be biodegradable to improve release kinetics and prevent carrier accumulation. Pharmaceutical agents have been conjugated to polymers to modify transport or circulation half-life characteristics as well as to allow for passive and active targeting.

In addition, the latest drug delivery research using polymeric materials has produced recognitive systems that facilitate cytoplasmic delivery of novel therapeutics.

In a word, Modern advances in drug delivery rely on the rational design of polymers tailored for specific cargo and engineered to exert distinct biological functions. Today, drug delivery research has developed into a major interdisciplinary effort involving chemists, biologists, engineers and physicians.

1.5 Specific notes for polymers used in drug delivery system

A crucial feature of polymers used in drug delivery is the mechanism by which they are removed from the body. They may be excreted directly via kidneys (renal clearance) or biodegraded (metabolic clearance) into smaller molecules, which are then excreted. Passage through the renal glomerular membrane is limited to substances with a molecular weight under 50000, although this value varies depending on the chemical structure of the molecule[7]. Molecular weight is especially relevant for substances that are not biodegradable, and macromolecules with a molecular weight lower than the glomerular limit can be safely removed from the body by preventing their accumulation and therefore their potential toxicity.

Another feature of polymers fit in drug delivery is the asepsis. Prior to use, materials must also be sterilized. Agents used to reduce the chances of clinical infection include steam, dry heat, chemicals, and irradiation. Exposing polymers to heat or ionizing radiation may affect the polymer properties, by chain scission or creating cross-links. Chemical agents such as ethylene oxide may also be absorbed by a material and later could be released into the body. Hence, devices sterilized with ethylene oxide require a period of time following sterilization for any residues to be released before use.

本章中文导读

一、药用辅料的定义

任何一种药物在供给临床应用时，不可能以原料药形式直接供病人使用，必须制成适合于病人应用的给药形式，如片剂、胶囊剂、注射剂、栓剂、软膏剂等，这种为适应治疗、预防或诊断的需要而制备的不同给药形式通称为药物剂型，简称剂型。药物制剂一般由活性成分的原料和辅料所组成。从药品生产的角度看，药用辅料（pharmaceutical excipients）指除了主要药物活性成分以外一切物料的总称，即为生产药品和调配处方时所用的赋形剂和附加剂。

人类使用药用辅料的历史虽然悠久，但传统意义上的辅料被认为是惰性的，是能将药理活性物质制备成药物制剂的非药理活性成分。近来，随着人们对药物由制剂中释放和被吸收过程的深入了解，已经普遍地认识到：辅料有可能改变药物从制剂中释放的速率和稳定性，从而影响其生物利用度和质量。因此，国际药用辅料协会将辅料定义为：药物制剂中经过合理的安全评价的不包括有效成分或前体的组分。它的作用包括：在药物制剂制备过程中有利于成品的加工；提高药物制剂的稳定性、生物利用度和病人的顺应性；有助于从外观上鉴别药物制剂；改善药物制剂在贮藏或应用时的安全性和有效性。

二、药用辅料的作用

虽然剂型中活性药物是实质性主体部分，决定着作用的整个方向，辅料则保证药物以一定的程序选择性地运送到组织部位，防止药物从制剂释出以前失活，并使药物在体内按一定的速率和时间、在一定的部位释放。以医疗中应用最为广泛的口服固体剂型如片剂、胶囊剂等为例，辅料在制剂中可作为填充材料、黏合性和黏附性材料、崩解性材料、包衣膜材料、保湿性材料、缓控释材料等，同时辅料的加入可改善制剂过程。可见，辅料是制剂生产中必不可少的重要组成部分，在药物制剂的生产中发挥着不可或缺的作用，可以说“没有辅料就没有制剂”。

三、药物辅料的质量和安全性

药物的疗效不仅依赖于其中活性成分的作用，而且与辅料的质量密切相关。从药品安全的角度说，用作药用辅料的材料应该是对人体无毒性、无致敏性、无刺激性、无遗传毒性和无致癌性，对人体组织、血液、免疫等系统不产生不良作用的。实际上完全没有不良作用的材料很难找到，但必须尽量降低材料的不良作用，并使其在人体的忍受范围内。药用辅料的安全性包括：①辅料本身可能的毒

性和对人体的不良反应；②材料在合成或加工过程中污染；③辅料和药物或者辅料之间的相互作用导致的不良反应。因此，药用辅料的使用必须经过严格的安全性评价，药用辅料的生产需要进行严格的质量控制。

1991 年成立的国际药用辅料协会 (International Pharmaceutical Excipients Council, IPEC) 致力于药用辅料及其药典标准一体化，管理辅料质量，提出辅料应用的建议，在世界范围内对辅料规范化进行协调，以便于各国之间有关药用辅料的技术交流与合作。在其 2008 版的药用辅料标准中提出了较为详细地对新辅料进行安全性评价的指南。

四、高分子材料与药物辅料的关系

在药剂中发挥重要作用的药用辅料大多是高分子材料。所选用高分子材料的性质及其与药物相互间的作用，决定了药物制剂的性质和质量，控制药物从制剂中的释放行为（释放速率、释放部位、释放的方式如脉冲释放等）。设计和研究新型药物制剂或给药系统取决于新型药用高分子材料的开发。正是许多新的具有特殊性能的高分子材料的出现，诸如口服缓释控释片剂、微球剂、皮下埋植剂以及注射用靶向纳米制剂等现代药物传输系统才得以问世。因此，高分子材料是药物制剂重要的物质基础。

高分子材料作为药用辅料用于药物输送，必须要考虑它如何从体内清除以及无菌化的问题。分子量小于 50000 的材料可以通过肾小球的过滤作用清除体外，或者降解成为小分子被清除[7]。对于在化学性质和物理性质上能够耐受干热或湿热灭菌的高分子材料，采用洁净及无污染的生产条件，在制剂生产过程中加强 GMP 管理以及产品的最终灭菌过程，能满足无菌要求。但对于很多受热不稳定或容易变形的高分子材料，无菌方法的选择直接影响制剂的生物相容性及实际应用。