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From the carrier of active substance to drug delivery systems

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ABSTRACT

Development and innovation all the time are in interests of pharmaceutical science and evaluation of different dosage forms. They are concerned with the aim of compliance of patients. All the time different research groups try to develop and improve form of drugs to receive better bioavailability or strict control of dose, place and time of action of active substances. This is possible by using different excipients, biodegradable, biocompatible polymers that work like carriers, developing simple drug delivery systems, which in time became more and more complicated, nanotechnology that control size, shape and multi-functionality of particulate drug delivery systems. This review shows the main directions in the evaluation of pharmaceutical researches from simple carriers of active substances to drug delivery systems.

Keywords: carrier, drug delivery system, sustained release, zero-order kinetic, nanoparticle.

Introduction

Modern pharmaceutical technology is focused on reaching the target therapeutic effect while minimizing adverse side effects of medicinal substances called API (Active Pharmaceutical Ingredient). Hence, for many years, research centers and research and development departments deal with the development of new APIs, but also the search for novel carriers that could improve bioavailability of APIs. Research and development on the use of different carriers are closely related to the development of drug delivery systems (DDSs) and controlling the active substance release from such systems (controlled drug delivery systems CDDs) [1–4]. They provide drug delivery in the right dose, at a specific location of the body, and its release for a defined period of time.

The dosage form is a mixture of the active substance with excipients which has been given for the required form of drug. After administration of the dosage form the drug release appears at the place of administration, as for example, oral administration of a tablet involves the dissolution of the active substance in the stomach, and thus the passage of substances from the solid form to the solution. The next steps are the absorption, distribution, biotransformation, elimination. During the absorption of the drug substance passes (penetrates) into the blood, crossing biological membranes. Prolonged drug delivery is obtained by special processes, which provides a single dose to quickly reach the minimum concentration of acting substances in the body and maintaining it for a longer time than with a conventional form with immediate release of API (unmodified) [4]. Most of the new APIs are poorly soluble in water and thus have a low bioavailability. That is why, researchers work not only with sustained release but also with increasing the solubility of APIs.

Main directions of research and development in pharmaceutical technology

Reviewing trends in the development of drug delivery systems can be noticed few periods [1–4] that are described in **Table 1**.

All activities in the development of pharmaceutical dosage forms are associated with the need to search for excipients which allow to control the rate of release of active substance. They will provide an improvement in bioavailability or localize action of the active substance in a specific place [3].

Table 1. Trends in the development of pharmaceutical technology

Period of time	Area of research	References
40 and 50-ies of 20th century	– the study on the sustained release of the drug substance, the aim to extend the duration of action of drugs	5–9
60 and 70-ies of 20th century	– first reports of the use of implant with zero-order kinetics of the drug release in vivo; – intensive development of delivery systems with zero-order kinetics and controlled release; – therapeutic systems Ocusert® and Progestesert® were introduced into the treatment	10–23
80-ies of 20th century	– theoretical analysis of the kinetics of release of drugs; – nasal, oral and mucoadhesive adhesion systems for the application 1 or 2 times per day, based on the release of the drug substance by dissolution, diffusion, osmosis or ion exchange; – OROS (Osmotic Release Oral System) was introduced into the treatment	24–25
90-ies of 20th century	– intelligent polymers and hydrogels activated by changes in pH or temperature; – development of nanotechnology: nanoparticles obtained using biodegradable polymers, micelles, dendrimers	27–29
since 2000	– modular systems for the targeted activity, a long-term action with little initial burst effect; – developing a correlation of in vitro – in vivo (prediction of drug release in the body on the basis of the dissolution studies in vitro); – intensive development of nanotechnology	30–38

Dosage forms with prolonged release

The first attempts to use the form of drug with slow release were conducted in the years 1932 to 1937, when the implantation of sterile pellet containing hormones were used. These pellets were invented in 1861 by Lafage [4].

Introduction to the treatment the first antibiotic penicillin resulted in the need to control its concentration in the blood. Penicillin has a short half-life ($t_{0.5}$ = 0.5 h), and therefore for effective therapy it should be administered by injection every 3 h. Romansky and Rittmann [5] used in 1944 the suspension of sodium salt of penicillin in oil with some wax instead of the aqueous solution. The dose of penicillin 200 000 IU in the form of suspension provided suitable concentration in the blood for 12 h after administration [5]. The next step was to use in 1945 calcium salt of penicillin (sparingly soluble salt), with increasing amount of wax in the formulation. After administration of 300,000 IU in such dosage form the concentration of penicillin was maintained in the blood for 12–24h [6]. In 1948 E. Lilly Laboratory introduced the preparation Duracilin, including the composition of the suspension of procaine penicillin in oil, which provided further extension of the action.

Another way of achieving a depot effect was the investigation prepared by H. and A. Choay in 1947 who increased the size of the molecule of insulin by forming an adduct with polyvinylpyrrolidone. Thus prolonged the duration of action of insulin [8].

In the same time in United States Smith, Kline and French Laboratories (SK&F) ran research concerned with enteric coatings. The results were the starting point for Blythe's concept, based on involving the use of many small coated beads to release the drug substance independently of environmental pH. The technique of their manufacture was developed by MacDonnell [4]. On sugar pellets various lipid coating was applied to give different release. The first oral formulation of prolonged action were Dexedrine® Spansule introduced into medical practice in the United States in 1952. This product was based on gelatin capsules filled with pellets coated with various waxes.

In 1950s in Europe Saunders and Srivastava put forward the concept of placement of the therapeutic substances to ion exchange resins in order to obtain a prolonged action [8] and this idea was patented by Keating or Hays at the beginning of 1960s [10–12]. Ion exchange resins become "carriers" for acting substances and started to be used for the formulation of the dosage form.

Ion exchange resins produced from polymers containing functional groups capable of ion exchange

have been known since 1938. The cation exchange resins contain acid groups and form the connection with basic drug substances, while anion exchangers contain basic groups and combine with acidic substances to form salts. The resulting connection drug-ion exchange resin is insoluble in water but after oral administration in the digestive tract they release the active drug, thereby providing sustained release [4, 29, 40]. Initially the use of ion exchange resins emphasized their advantages for extending the release of acting substances, but over time it was observed, that long-term use may cause disturbances in electrolyte in the body due to the reverse ion exchange [4].

The 1950s were a period of intensive research on the development of solid dosage forms of prolonged action. Two-layer tablets occurred during that time, for example SK&F Company introduced a tablet with theophylline consisting of two layers, from one layer acting substance is released immediately and the other layer release theophylline slower. Ciba firm introduced to the market product Lontab® containing a prolonged core surrounded on all sides by the layer immediately release the drug substance [4]. The same ideas are used by other pharmaceutical companies all the time.

The next stage of the development of oral sustained-release tablets was the preparation of tablets that contain insoluble in gastric juice coat between the tablet core and the immediate release coat (Duplex). Also compressing the mixture of granulates with different release rates or the introduction of matrix tablets of plastic or polymers developed modified release products [4]. Such formulation was patented in 1959 by Fryklöf, Sandwell and Ostholm (Duretter®). In the same year the first oral liquid dosage form of the sustained release was also developed [9], using for the first time hydrogenated castor oil and ethylcellulose as excipients.

Dosage forms that release drug with zero-order kinetic

Further development of oral forms of drugs was based primarily on the search of formulations that release the acting substance according to zero-order kinetics, that is, the speed of release is independent of the amount of the substance remaining in the form. The consequence of this was the development of technologies of therapeutic systems. Between 1964 and 1966 Folkman and co-workers [13, 15] proposed a drug delivery system in the form of implant of Silastic® material (rubber silica). They used the term "carrier" as first with respect to the excipient regulating the release rate of the drug.

Chemist A. Zaffaroni, who in the late 60s of 20th century founded the company ALZA, was inspired with Folkman's work. ALZA intensively took up the idea of controlled drug delivery systems. Zaffaroni cooperated with J. Folkman and also with T. Higuchi, who was a pioneer in the study of mechanisms of release of therapeutic substances with controlled systems [1]. Higuchi gave the basis of studies of the kinetics of release of acting substances from dosage forms that are used to this day.

Folkman's suggestions caused also that Zaffaroni introduce in 1971 the term "Therapeutic system". It was identified as a device or dosage form comprising the drug substance (or mixture of substances) that is released continuously at a predetermined rate for a predetermined time and at a particular site of administration [4, 17]. The company ALZA introduced therapeutic systems: Ocusert® (eye system) and Progestesert® (intraurethral), developed therapeutic systems in the form of skin patches [1, 18], and in 1974 patented oral therapeutic system OROS®.

Micro- and nanoparticles as carriers and drug delivery systems

In the 60s of the 20th century, the research on drug delivery systems, are beginning to include not only systems in the "macro", there is also interest in scale "micro" and "nano" [1]. For the first time at the University of Cambridge A.D. Bangham discovered liposomes [14] and Schmitt and Polistina from Davis & Geck Company, Cyanamid Co. synthesized and patented polymer of glycolic acid (PGA), which has been used as biodegradable carrier [16].

Liposomes are small structure in which is possible to place both hydrophilic and lipophilic drugs. They are constructed with one or more phospholipid bilayers closing the interior aqueous phase. The interest in liposomes as carriers of therapeutic substances developed primarily G. Gregoriadis [20, 21]. Number of publications have appeared describing possible use of liposomes as carriers for anticancer drugs [39,41].

Polymers are macromolecular structure capable of forming a micro-/nanocapsules or micro-/nanospheres. Polymer of glycolic acid (PGA), polymer of lactic acid (PLA) and copolymer of lactic acid and glycolic acid (PLGA) were the first to be used. In the late 60s in the Du Pont company Boswel and Scriber used PLA to connect it with protein drugs. They produced microparticles that worked like depot drug delivery system. Technology of preparation of microparticle

has been patented by Boswel and Scribner in 1973 [19]. Boswel in U.S. patent used the term "carrier or matrix" to the PLGA used in order to obtain sustained release of the drug [1, 19]. At the same time Speiser and Kreuter [22] also use methacrylic acid polymer (polymethacrylate methyl) to obtain polymer nanoparticles.

The 70s of the 20th century was a period when polymeric nanoparticles with a diameter of 100 nm were used for the first time and polymers become the basis for the "carriers" of acting substances [2]. Polymers have been used in the preparation of sustained release drugs, and their main task is to ensure a therapeutic level of the acting substance in the body of the patient for a defined period of time without taking next dose during the day [25, 33]. The idea of using micro or nanoparticles in drug delivery began over five decades ago, and the unique skills of small particle size in drug delivery have been appreciated by scientists. From now term "carriers" refers not only to the additives, but also for systems with small size like: liposomes, polymeric micro- and nanoparticles. The terms "carrier" and "drug delivery system" are combined or used interchangeably. In the following years, new reports on the use of biodegradable or non-biodegradable polymers and the development of new micro and nanoparticle methods are emerging.

The most popular nanosystems include hydrogels, cyclodextrins, liquid crystalline phase and nanoparticles: liposomes, polymeric nanoparticles, polymeric micelles, nanoparticles of silica, gold, silver or other metals, carbon nanotubes, solid lipid particles, niosomes, dendrimers and hybrid particles with a porous core [32,34–39].

In the 80s, it is launched a new line of research. In 1984, Hiroshi Maeda of the University of Kumamoto discovered enhanced penetration and retention of nanoparticles (EPR). At this point, the idea of developing a drug form with targeted action. Maeda used in studies styrene-maleic anhydride (SMA) conjugated to the anti-cancer peptide drug, neocarcinostatin (NCS), which he called "SMANCS" and he had labeled the conjugate with a dye [26]. He noted that the dye accumulated in tumor tissue, on this basis concluded that the vascular system created around the growing tumor is leaky, so that allows to collect the drug in the tissue [1, 26].

In the 1980–90s, from drug delivery systems in scale "nano" were developed especially PEGylated polymeric micelles and liposomes. In Japan, K. Kataoka, T. Okano, and M. Yokoyama synthesized poly(ethylene glycol)-poly(aspartic acid) a block copolymer [27].

The new compound showed the ability to form the PEGylated micelles. It was possible to load small drug molecules in micelles on the basis of the physical load or connection with free amino or carboxyl groups. The free hydroxyl groups of the polyethylene glycol were ligands that allowed the micelles reach the tumor cells [1, 27]. At the same time, in the US, A. Kabanov worked out PEGylated micelles produced with Pluronic, nonionic triblock copolymers of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) (PEO-PPO-PEO) [1].

Since the 90s there is a lot of reports about the use of polymeric micelles or liposomes as carriers of acting substances that are able to achieve the targeted action [1]. Gregoriadis and Torchilini developed many liposome formulations, both for imaging and drug delivery systems where the hydrophilic medicinal substances may be placed inside the liposomes and hydrophobic materials in the lipid bilayer. PEGylated liposomes containing doxorubicin have been introduced into medical practice as Doxil ® in 1995 [1].

The "nano" DDS systems are constantly being developed, including dendrimers or other branched polymer systems [1]. Dendrimers were synthesized for the first time in the period 1970–1990 by two different groups: Buhleier and co-workers and Tomali and co-workers [23, 24]. In contrast to the polymers with linear structure dendrimers developed by these two groups have precisely controlled spatial structure [38, 42].

These materials have a uniform and well-defined size and shape, and therefore are of great interest in the biomedical sciences. They have the ability to penetrate cell membranes, and are not rapidly eliminated. The high degree of order of the spatial structure causes that seem to be the ideal carriers [38, 42, 43]. They may be used in controlled release systems applied intravenously or orally, directly into the lungs, as a system on the eye or on the skin. After joining the respective ligand they can also be used for targeted therapy [31, 42, 40].

As already mentioned, most of the emerging medical substance is poorly soluble in water and therefore has low bioavailability. Hence, there is a desire to improve the solubility of such APIs thus improving the availability of drug and later bioavailability.

There are many methods to improve the availability of pharmaceutical drugs sparingly soluble in water. The appropriate "carriers" that influence the improvement of API solubility can be found here. Among the methods which used carriers can be distinguished: the formation of complexes, eg. with cyclodextrins, modification of the crystalline form by loading to mesoporous silica materials or the use of lipid carriers.

The first cyclodextrins were discovered in 1891 by Villiers [44]. The following years were the precise characteristics of the structure and the development of the theory of their use. The formation of complexes of cyclodextrins and drugs was first used in the 70s of 20th century [45]. Cyclodextrins are characterized by the presence of hydroxyl groups at the surface, making them soluble in water. Its interior forms a hydrophobic microenvironment suitable for encapsulating drugs that dissolve better in lipids [46].

Mesoporous silica materials were synthesized in the late 90s of the last century. Due to its characteristics: high surface area and the pore volume became of interest as carriers of drugs and such a use for the first time proposed Valet-Regi and co-workers [47]. From that time these materials are used for loading drug substances which can improve the solubility of the API by changing and/or prevent the formation of crystalline form of API.

In recent years, there is a great interest in self-emulsifying drug delivery systems (SEDDS) forming spontaneously microemulsions (SMEDDS) or nanoemulsions (SNEDDS).

SEDDS formulations are simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. A lipid component prevents sudden precipitation of API and surfactant present in the system improve the wetting and the penetration of the dissolution fluid [36]. In such a type of dosage form micro-/nanoemulsion place role of "carrier" and "delivery system" at the same type. Lipid carriers are used since 1996 when Müller and Lucks introduced solid lipid particles (SLN) and patented the method of their production towards the high-pressure homogenization [28, 37].

Conclusion

All the time continuous improvement of controlled drug delivery systems is observed. The development of knowledge of molecular biology and medicine enable the manufacture and use of carriers apply to the "nano", which will be able to be taken up by specific cells/receptors so that activity of the drug will be directed at specific places and routes inside cells. Increased ability to control the efficiency and specificity of the delivery process will minimize side effects. Knowledge of the processes and DNA sequence encoding the disease could be used to create personalized medicines. The development of controlled drug delivery systems has evolved from macro-, micro- and nano- by using polymers at each stage.

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Conflict of interest statement
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