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Pharmaceutically Used Plasticizers

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1. Introduction

The extensive use of polymers in medical and pharmaceutical applications including particularly packaging, medical devices, drug carriers and coatings has caused a substantial demand for the proper plasticizers. Although there are many plasticizers used in the chemical industry, only a few of them have been approved for pharmaceutical applications. The natural-based plasticizers characterized by low toxicity and low migration are required nowadays not only for pharmaceutical and medical applications. In this respect, most of traditional plasticizers are not applicable in this area.

External plasticizers added to pharmaceutically used polymers interact with their chains, but are not chemically attached to them by primary bonds therefore their loss by evaporation, migration or extraction is possible. The benefit of using external plasticizers is the chance to select the right plasticizer type and concentration depending on the desired therapeutic system properties particularly drug release. Low volatile substances with average molecular weights between 200 and 400 such as diesters derived from dicarboxylic acids (e.g. sebacic acid, azelaic acid) or from ethylene glycol and propylene glycol, citric acid (tributylcitrate, triethylcitrate) or glycerol (triacetin, tributyrin) are used. Plasticizer as minor component of polymeric drug delivery systems has not been strictly defined. Even liquid drugs or liquids with a potential pharmacodynamic effect can serve as plasticizers.

As well structural water in the hydrophilic polymer seems to be an internal plasticizer of the polymeric drug delivery systems. In case of contact with body fluids after application the hydrophilic plasticizer can be released from polymer and thus conditions for the incorporated drug release are changed. The hydrophobic plasticizer remains in the system and ensures standard conditions during the process of drug release. On the other hand, hydrophilic plasticizer added to the polymeric drug carrier in high concentration can lead to an increase in water diffusion into the polymer, thus diffusivity parameters of the system are changed. As a consequence the kinetics of drug release is changed by elimination of lag time of drug release process. Plasticizers decrease viscosity and thus can enable or facilitate the application of some preparations; e.g. sufficient low viscosity at temperature below 50 °C is necessary for easy manipulation and simple and harmless application of implants in situ via an injection needle or trocar device.

2. Pharmaceutically used plasticizers

The primary role of all plasticizers as low molecular weight non-volatile additives is to improve the flexibility and processability of polymers by lowering the second order transition temperature (glass transition temperature, T_g) (Rosen, 1993). The extent of T_g reduction in the presence of a plasticizer can be used as a parameter to assess the plasticization efficiency (Senichev & Tereshatov, 2004).

When incorporated into a polymeric material, a plasticizer improves the workability and flexibility of the polymer by increasing the intermolecular separation of the polymer molecules. This results in a reduction in elastic modulus, tensile strength, polymer melt viscosity and T_g . The polymer toughness and flexibility is improved and lower thermal processing temperatures can be employed. (Zhu et al., 2002).

The attributes of an ideal plasticizer are changed with each application. When selecting an appropriate plasticizer, the compatibility with the polymer and plasticization efficiency are the pivotal criteria. Incompatibility is commonly evidenced by phase separation between the biopolymer and plasticizer, presented in the form of exudated drops on the surface of the product immediately after its blending or during final application (Wilson, 1995).

Historically the first plasticized polymer used as a medicinal preparation since the 19th century has been cellulose nitrate. Its solution in a mixture of ethanol and diethyl ether is called collodion and used to cover wounds. After administration, the solvents quickly evaporate and cause unpleasant tension. That is why its plasticizing with 5% castor oil was introduced (Murray, 1867). The composition after incorporation of an antimicrobial substance functions as a protective barrier.

2.1 Criteria of the plasticizer selection in medicine and pharmacy

Different requirements are important for the choice of a plasticizer for polymeric dosage forms in comparison with these for the technical plasticization. Pharmaceutically used plasticizers are selected according these criteria in the following order of importance (Rahman & Brazel, 2004):

- biocompatibility
- compatibility of a plasticizer with a given polymer
- effect of plasticizer on drug release
- effect of plasticizer on mechanical properties
- processing characteristics
- cost-benefit analysis.

2.1.1 Toxicity

In the selection of a plasticizer suitable for the formulation of dosage forms a great emphasis is laid on the criterion of toxicity. This problem is solved with regard to the mode of administration, dosing frequency and dosage size. For example, the tablet coating contains a plasticizer in the order of milligrams, whereas the implants *in situ* may contain hundreds of milligrams of plasticizers.

In the EU there exists the obligatory document ICH Topic Q3C titled Impurities: Guideline for Residual Solvents, which distinguishes three classes of solvents. Class 1 must not be used, Class 2 has a limited daily dose and concentration, and Class 3 includes solvents accepted in usual amounts in pharmaceutical products. The Class 3 residual solvents are accepted without marked restrictions in daily doses of up to 50 mg or in concentrations up to 0.5 %. Class 3 solvents are listed in Table 1 (European Medicines Agency, 2010). Many of the above mentioned solvents can be used as plasticizers of polymers which should be limited by GMP or pharmacopoeial requirements. The selection of plasticizers appropriate for dosage forms formulation is shown in their list in the 35th edition of the United States Pharmacopoeia (USP 35, 2011) (Table 2).

Acids	Acetic acid, Formic acid
Alcohols	1-Butanol, 2-Butanol, Ethanol, 2-Methyl-1-butanol, 2-Methyl-1-propanol, 1-Pentanol, 1-Propanol, 2-Propanol
Esters	Ethyl acetate, Ethyl formate, Isopropyl acetate, Methyl acetate, Propyl acetate
Ethers	Anisole, tert-Butylmethyl ether, Ethyl ether
Hydrocarbons	Cumene, Heptane, Pentane
Ketones	Acetone, Methyl ethyl ketone, Methylisobutyl ketone
Others	Dimethyl sulfoxide

Table 1. Class 3 solvents with low toxic potential.

Hydrophilic	Hydrophobic
Glycerin	Acetyl Tributyl Citrate
Polyethylene Glycols	Acetyl Triethyl Citrate
Polyethylene Glycol Monomethyl Ether	Castor Oil
Propylene Glycol	Diacetylated Monoglycerides
Sorbitol Sorbitan Solution	Dibutyl Sebacate
	Diethyl Phthalate
	Triacetin
	Tributyl Citrate
	Triethyl Citrate

Table 2. List of plasticizers declared in USP 35-NF 30.

As there is no single universal mechanism of polymer plasticization, there is no universal criterion for its selection and for the evaluation of its efficacy. The use of internal plasticizers based on modifications of monomer units by decreasing the polarity of the groups, or modification with large side groups is problematic in pharmacy. The main cause is the fact that an introduction of new compounds into pharmacopoeias as the principal pharmaceutical standards is as complicated as an introduction of a new active substance. It is a process that lasts several years and is considerably costly.

On the rule, external plasticizers are used, which are less heterogeneously miscible, more frequently molecularly miscible with an amorphous phase of polymers. They are the solvents or thinners used in a minority concentration in a mixture with a polymer. The range of the concentrations of the plasticizer in the polymer is due to, besides other things,

the crystallinity of the polymer, usually 5 % to 30 %, but there exist also deviations from this range.

When plasticizers are present in low concentrations, their effect is often the exact opposite of what is typically expected. Low concentrations of plasticizer often result in an increase in the rigidity of the polymer instead of the expected softening effect. This effect is known as antiplasticization, or effect of low plasticizer concentrations (Chamarthy & Pinal, 2008).

It is of advantage when plasticizers are low volatile. The size of the molecule of plasticizers includes a wide range from a water molecule to the molecules of low-molecular oligomers and polymers. Schematically, hydrophilic and hydrophobic plasticizers are distinguished; the border between them is not officially declared, the classification is subjective.

Because of the prevalence of fully biodegradable polymers, particularly for parenteral controlled-release systems as they do not require surgical retrieval from the body after completion of the drug release, recent research has focused on developing compatible plasticizers that also biodegrade.

2.1.2 Biocompatibility of pharmaceutically used plasticizers

The use of any material in the formulation of biomedical and medicinal devices and preparations must comply with three requirements (Zeus Industrial Products, 2005):

- It must be biocompatible from the standpoint of specific use.
- It must comply with the complex legislative and regulatory rules.
- It must comply with environmental requirements.

Biocompatibility is a general term which describes the suitability of the material in the exposure to body fluids. The material in a specific application is considered to be biocompatible if it makes it possible for the organism to function without complications, such as allergic reactions or other side effects. The complications may include chronic inflammations in contact or due to the effect of eluted components interacting with the organism, then the formation of substances which are cytotoxic, substances inducing skin irritation, restenosis, thrombosis, etc. Biocompatibility concerns medical devices and pharmaceutical products.

Various tests are used in dependence on the type of the medical device and the mode of its administration. Medical devices sold in the EU must comply with the EU Medical Device Directive 93/42/EEC, in the implemented form as 2007/47/EC, which harmonizes the legislation in the EU. At present, ISO 10993 comprises a series of 20 parts for various aspects of biocompatibility testing prior to the clinical study. ISO 14155:2011 concerns good clinical practice for the performance of safe clinical studies on human subjects. Three categories of medical device products are differentiated according to the contact with the human tissue. Limited contact is shorter than 24 hours, the prolonged one is between 24 hours and 30 days, and the permanent contact lasts for more than 30 days. Many plasticized medicated implanted systems are in the concordance with category of medical devices for permanent contact with very demanding testing.

Pharmaceutical products containing a pharmaceutical drug have as their standard for the biocompatibility check international or national pharmacopoeias, American Pharmacopoeia

in the study of biocompatibility has been superseded from a major part by the standard ISO 10993. Tests following the USP are carried out on animals in three versions:

- Systemic injection test (intravenous and intraperitoneal)
- Intracutaneous test
- Implantation test

The tests called in the USP as Biological Reactivity Tests are carried out with the pharmaceutical dosage form or the medical device or the extracts obtained from them at different temperatures for different periods of action of the extraction reagent.

2.1.3 Plasticizer uptake by polymer

The rate of plasticizer uptake is depended on the type and concentration of the plasticizer and the type of polymer dispersion, and also on the water solubility of the plasticizer. The plasticization time had a minimal effect on the rate of uptake of water-soluble plasticizers, while it had a strong effect on the uptake of water-insoluble plasticizers. Depending on plasticizer water-solubility and the added amount, when a plasticizer is added to an aqueous polymer dispersion, it is first dissolved and/or dispersed within the outer water phase. Subsequently, the plasticizer diffuses into the polymer particles. A sufficient amount of time for plasticizer uptake by the polymer particles is necessary to avoid forming an inhomogeneous plasticized system (Bodmeier & Paeratakul, 1997).

2.1.4 Plasticizer leaching out of polymer and methods of reduction

Plasticizer migration refers to any method by which a plasticizer leaves a polymer to a solid, liquid or gas phase, which includes solid-solid migration, evaporation of plasticizer, and liquid leaching. These mentioned processes signify the loss of plasticizers from the plasticized polymeric system. The most important way of plasticizer migration within the polymer drug delivery system represents its leaching by physiological fluids after application of the dosage form. Leaching is the major trouble encountered during the plasticizing of polymeric drug delivery systems, as it can eventually result in drastic alteration in all the functions of the plasticizer, and thus the properties of the initially plasticized polymer system, notably the incorporated drug release patterns.

Plasticized polymers used in drug delivery systems come to contact with liquid after application into the body. Plasticizers tend to diffuse down the concentration gradient to the interface between the polymer surface and the external medium. The interfacial mass transport to the surrounding medium has been found to be the limiting step rather than diffusion of the plasticizer through the matrix to the surface. This rate is usually a function of temperature and initial plasticizer concentration (Foldes, 1998). If plasticizers leach out to a liquid, polymers fail to retain their flexibility while the loss of plasticizers leaves the polymers inappropriate for the desired application. Leaching issue is one of the toughest challenges regarding the research of plasticizers today.

The most effective approaches how to reduce the leaching of plasticizers into physiological fluids are particularly surface modifications. Among a variety of surface modification techniques, (i) surface cross-linking, (ii) modification of surface hydrophilicity/lipophilicity

by grafting of water soluble polymers to the surface of biomaterials, (iii) surface coating and (iv) surface extraction have been used.

Surface modification of polymers not only prevents the plasticizer from leaching but also improve the biocompatibility of a polymer without compromising. Coating the polymer surface with some non-migrating material may often cause a reduction in flexibility of the polymeric materials due to the thickness of the coating layer. During surface extraction, a material is shortly exposed to some solvent for the plasticizer, and then dried. Subsequently the plasticizer distribution in the polymer is not homogenous and interfacial mass transfer of the plasticizer is blocked with the rigid surface. It follows that the mechanical properties of the polymer system are very often influenced in a negative way.

Leaching resistance of flexible PVC has also been improved by grafting polyethylene glycol, which is often used in biomaterials to prevent biological recognition and protein adhesion. The decrease in plasticizer leaching after polyethylene glycol-grafting is presumably due to the hydrophilic polyethylene glycol surface acting as a barrier to the diffusion of di(2-ethylhexyl) phthalate (DEHP) from the PVC matrix. (Lakshmi & Jayakrishnan 1998). There are radical possibilities of how to solve the plasticizer migration out, namely the use of polymeric or oligomeric plasticizers instead of the low molecular weight ones, or alternative (so called non-classical, non-traditional, multifunction) plasticizers, even alternative polymers which do not require plasticizers.

2.2 The effect of plasticizers on human health

Phthalic acid esters found applications as plasticizers for the first time in 1920s and continue to be the largest class of plasticizers in the 21st century (Rahman & Brazel 2004). DEHP, also known as dioctyl phthalate (DOP), was introduced in 1930s and has been the most widely used plasticizer up to the present time. Thus, the use of plasticizers is being questioned due to their possible toxicity problems, related to their migration out of the polymer. Nowadays, there is increasing interest in the use of natural-based plasticizers that are characterized by low toxicity and low migration. This group includes epoxidized triglyceride vegetable oils from soybean oil, linseed oil, castor-oil, sunflower oil, and fatty acid esters (Baltacıoğlu & Balkose 1999).

Currently, there is a trend towards replacing DEHP by either diisononyl phthalate or diisodecyl phthalate, which are higher molecular weight phthalates and therefore are more permanent, have lower solubility and present slower migration rates. Although a total replacement of synthetic plasticizers by natural-based plasticizers is just impossible, at least for some specific applications such a replacement seems obvious and useful.

A number of medical devices as bags, catheters and gloves, intravenous (i.v.) fluid containers and blood bags, medical tubings, are made from the PVC plasticized with the use of DEHP. PVC i.v. bags typically contain 30-40% DEHP by weight; other devices may contain much as 80% DEHP by weight. Because DEHP is not chemically bound to the polymer in a PVC medical device, it can be released into the solutions and blood products transported by these devices.

DEHP leaching from medical plastics was first observed in the late 1960s (Jaeger & Rubin, 1970). Extensive research began after the International Agency for Research on Cancer

classified it as 'possibly carcinogenic to humans' in 1980s (Murphy, 2001). The mechanisms by which DEHP may cause various adverse effects in humans are likely to be multiple and variable, and are not well understood. DEHP belongs to a class of chemicals called "peroxisome proliferators". The greater exposure source is particularly relevant for individuals who are ill, and therefore potentially less able to withstand any toxicant exposure (Tickner et al., 1999).

Particular concern has been raised in neonatal care applications because newborns receive among the highest doses of DEHP from blood transfusions, extracorporeal membrane oxygenation and respiratory therapy. (Sjoberg et al., 1985; Loff et al., 2000).

Infants and children receiving intravenous total parenteral nutrition infused using the typical PVC-DEHP tubing and ethylene vinyl acetate bags with PVC-DEHP connections potentially receive considerable amounts of DEHP every day. DEHP is extracted from the bags and tubing due to the high solubility of DEHP in lipids and DEHP extraction by total parenteral nutrition depends on the lipid content of each total parenteral nutrition preparation and the flow rate (Kambia et al., 2003).

Adults can also be subjected to DEHP exposure from medical plastics. Kambia et al. (Kambia et al., 2001) studied the leachability of DEHP from PVC haemodialysis tubing during maintenance haemodialysis of 10 patients with chronic renal failure. The patient blood obtained from the inlet and the outlet of the dialyzer was analyzed during a 4 h dialysis session. An average DEHP quantity of 123 mg was extracted from tubing during a single dialysis session, of which approximately 27 mg was retained in the patient's body. The detrimental dose for humans has been estimated at 69 mg/kg per day whereas the average daily exposure to DEHP is much lower (2.3–2.8 mg/kg in Europe and 4 mg/kg in the US). (Murphy, 2001). Application of DEHP as plasticizer was found to have adverse effects on the biocompatibility of the plastic materials used in medical devices. Upon contact with blood, albumin is instantly absorbed on the polymer surface, followed by globulin (Baier, 1972).

There are a number of techniques which could help minimize health and environmental problems owing to the use of leachable plasticizers. One simple way to do this is to use alternative flexible polymers (e.g. polyolefins), which require less or no plasticizers, to accomplish some surface modification, or use plasticizers that have less volatility and leachability, and thus low toxicity. Because it is cheap, clear, and flexible, PVC remains the most widely used material by manufacturers and end users of medical bags and tubing.

2.3 Classification of pharmaceutically used plasticizers

Pharmaceutically used plasticizers are often distinguished into hydrophilic and hydrophobic, or low molecular weight, oligomeric and polymeric. Water insoluble plasticizers have to be emulsified in the aqueous phase of the polymer dispersions. Plasticizers are incorporated in the amorphous phase of polymers while the structure and size of any crystalline part remains unaffected (Fedorko et al., 2003). The water has an exceptional position as the inherent plasticizer of biopolymers, mainly polysaccharides and proteins.

2.3.1 Water as a plasticizer

Plasticization is a concept which can be understood either as a physical phenomenon, or as a technological process (Kozlov & Papkov, 1982). Water is a natural plasticizer of biopolymers as well as their semisynthetic derivatives. A portion of this water is structural water, which has anomalous properties (Coyle et al., 1996). Cotton cellulose at 60 % to 70 % crystallinity contains 6 % to 8 % of water, viscose does even more, and gelatin as collagen hydrolyzate contains 5 % to 15 % of water, according to atmospheric humidity.

The water content influences also the properties of synthetic polymers. The polyacrylate polymer Eudragit RS used to coat the pellets with theophylline changes its mechanical and dissolution properties with the relative humidity on storage (Wu & McGinity, 2000). T_g values are decreased in the biodegradable poly(lactide-co-glycolide) in the environment of water vapours up to by 15 °C. Water content was within a range from 0.3 % to 2.6 %. It has been demonstrated that water responsible for plasticization effect was non-freezable and only a small fraction of this water absorbed from the environment caused degradation of the polymer in the same manner as bulk water. In dependence on temperature and concentration, water can act as a plasticizer and an antiplasticizer (Blasi et al., 2005).

2.3.2 Hydrophilic plasticizers

Hydrophilic plasticizers include the compounds which are without limitations or in a sufficient degree miscible with water. They are on the rule substances with very good biocompatibility, some are components of metabolic processes, and others can be easily eliminated from the organism. The most widely used are polyhydric alcohols, in the first place glycerol. The polymers plasticized with hygroscopic compounds receive water from the atmosphere in an increased degree and this water also possesses a plasticizing effect.

The thermoplastic starch is a material interesting for the use in pharmacy (Willet et al., 1997; Liu et al., 2009). It is produced by heating under pressure and under shear from a mixture of native granules and 20 % to 50 % glycerol. This composition named as opened starch was patented for implantation (Van De Wijdeven, 2010). In the temperatures of 150 to 180 °C the granules melt and a plastic amorphous material is produced (Carvalho et al. 2003). Glycerol and xylitol are important plasticizers of starch; in their presence the starch film is flexible regardless of the water content in it (Bader & Göritz, 1994). With the use of 11 % of water and glycerol or xylitol in low concentrations, an antiplasticizing action of polyalcohols on starch was observed; when a concentration of 15 % for glycerol and 20 % for xylitol was achieved, there occurred a significant decrease in T_g . Between the individual plasticizers there occurs competitive plasticization with three types of interactions: starch/plasticizer, plasticizer/water and starch/water (Chaudhary et al., 2011).

The tests for starch plasticization (cassava starch) included glycerol, sorbitol and a mixture of these two polyhydric alcohols in a ratio of 1:1 (Mali et al., 2005) in a concentration of 0, 20, and 40 g/100 g of starch. The combined effect of relative humidity and the plasticizer on the mechanical properties of films was tested. The hydrophilicity of the films of the plasticizer was the decisive factor influencing the affinity to water. The films plasticized with glycerol adsorbed more humidity and more rapidly, and they were more influenced by plasticization from the standpoint of mechanical properties. Glycerol in comparison with sorbitol and a

mixture of both was the most effective plasticizer, much reduced the internal hydrogen bonds between the polymer chains and enlarged the internal space in the molecular structure of starch.

Amylose and starch were plasticized with glycerol or xylitol in various concentrations up to 20 %. On the basis of water sorption, the competition of the plasticizer and water under different activities of water was evaluated. Starch interacts with plasticizers and water by changing its crystallinity. The samples of lower concentrations of the plasticizers contain more humidity in the values of the activity of water in a range of 0.11 to 0.65. With a low activity of water there occurs association of amylose and exclusion of the molecules of the plasticizer. With increasing activity of water over 0.55, lower concentrations of the plasticizer exert no effect on a balanced content of water. It was explained by a strong bondings of glycerol and xylitol on starch chains with the development of cross-linking by means of hydroxyl bonds. Water is thus excluded from the polymer matrix. With a lower activity of water, starch binds both the plasticizer and water. Its antiplasticizing limit for glycerol was found between 10 % and 15 %, for xylitol this effect at its concentrations up to 20 % was not demonstrated (Liu et al., 2011).

Chitosan, partially deacetylated chitin is a biopolymer which has been studied very intensively as a potential carrier of active ingredients for more than two decades. Chitosan salts, in particularly chloride, lactate or gluconate are surface active and filmogenic. Elasticity of films can be improved by their plasticizing. Glycerol was used as a plasticizer of chitosan on a 25% concentration. The material was tested as suitable for the preparation of matrices by mechanical kneading as an alternative procedure to the traditional procedures based on the methods of solvent casting (Epure et al., 2011). Sorption of water, changes in crystallinity and thermomechanical properties were examined when the samples with and without the plasticizer were stored in the surroundings with a different relative humidity. Glycerol has been demonstrated to increase the hydrophilic character of films and acts in a plasticizing manner on the mechanical properties. The most suitable for film storage is the environment of the atmosphere with medium values of relative humidity (57 % RH).

The invention provided an orally dissolving capsule comprising pullulan, a plasticizer, and a dissolution enhancing agent (Rajewski & Haslam, 2008). Polyhydric alcohols such as glycerol, propylene glycol, polyvinyl alcohol, sorbitol and maltitol were proposed.

The biodegradable film was prepared from a blend of native rice starch-chitosan with an addition of various plasticizers in concentrations from 20 % to 60 %, using sorbitol, glycerol and polyethylene glycol 400. With an increased activity of water, a higher content of absorbed water was demonstrated. With increasing relative humidity the time of achievement of a balanced concentration of water was prolonged from 13 days to 24 days. Polymer films plasticized with polyethylene glycol 400 did not increase the content of water with increasing atmospheric humidity (Bourtoom, 2008).

Gelatin is a biopolymer produced by hydrolysis of collagen. Its surface activity and ability to form elastic and firm films are used. Its mechanical properties can be improved by adding plasticizers. Permeability of water vapours, mechanical and thermal properties of gelatin films of the gelatin produced from bovine and porcine hides were measured. The films contained 15 g to 65 g of sorbitol per 100 g of gelatin. Permeability of the conditioned films

increased with sorbitol content. The origin of gelatin was important from the standpoint of measured parameters only at a sorbitol concentration higher than 25 g/100 g of gelatin. The samples containing 15 g to 35 g of sorbitol/100 g of gelatin heated in the first cycle possessed a marked glass transition followed by a sol-gel transition. With increasing sorbitol concentration, the glass transition was wider, typical of the system with phase separation. To predict T_g values in the function of sorbitol concentration, the model according to Couchman and Karasz for the ternary system was employed (Sobral et al., 2001).

The effect of glycerol in a concentration of 3 – 7 % and sorbitol 4 – 8 % on the permeability of water vapours, humidity content, solubility and optical transparency of films prepared from the protein isolated from pea seeds was investigated. With an increasing glycerol content the permeability of vapours and humidity content in the films was increased, their solubility was not influenced, films plasticized with sorbitol, on the other hand, possessed lower permeability and humidity content and higher solubility. Different behaviour of plasticized films was explained by different hygroscopic plasticizers. A change in the pH value of solutions in the preparation of films from 7.0 to 11.0 did not influence most parameters (Kovalczyk & Baraniak, 2011).

Glycerol serves a number of functions in soft gelatin capsules – it is a humectant, plasticizer, in a higher concentration it serves as a preservative. It influences the helix formation from linear protein chains of gelatin in dependence on concentration. Its effect on the formation of helices decreases to 10 %, and then increases, on storage the degree of organization of the structure grows more in hard capsules than in the soft ones. With an increasing glycerol concentration, the extent of changes in the structure on storage is increased (Hüttenrauch & Fricke, 1984).

2.3.3 Plasticizers with limited miscibility with water

The border between hydrophilic and hydrophobic plasticizers is not sharp, being connected with its solubility in water. Plasticizers which possess solubility in water lower than 10 % are frequently employed for the formulation of dosage forms either in the form of solutions or they are emulsified in the aqueous phase. On the rule they are highly biocompatible esters of dicarboxylic and tricarboxylic acids or glycerol esters. These items are mentioned below. In the selection of a suitable plasticizer of this category of less polar compounds, two principal criteria are taken into consideration, (1) depression of the glass transition temperature and (2) the parameter of solubility. In the next order of importance are the mechanical properties of plasticized polymers, such as decreased strength, decreased elastic modulus and increased elongation at break. Another parameter for the selection for formulation studies is a decrease in the internal stress or the effect on the permeability of the material and for the release of the active ingredient.

Diesters and triesters of acids:

- Triethyl citrate (TEC)
- Tributyl citrate (TBC)
- Acetyl triethyl citrate (ATEC)
- Dibutyl sebacate (DBS)

- Diethyl phthalate (DEP)
- Dibutyl phthalate (DBP)

Diesters and triesters of alcohols:

- Triacetin (TA)
- Vegetable oils
- Fractionated coconut oil
- Acetylated monoglycerides

They are the plasticizers which are added to synthetic polymers with lower polarity in different fields of human activity. Many of them are encountered in foodstuffs. The team of analytical chemists of the Japanese National Institute of Health Sciences carried out an analysis of 93 samples of foodstuffs from the standpoint of the presence of 10 plasticizers (4 phthalates, 3 adipates, 1 sebacate, 1 citrate, and 1 triglyceride) and used as additives to the covers and vessels of various Japanese manufacturers. The method of gas chromatography/mass spectrometry revealed higher concentrations of diacetylauroyl glycerol, which did not originate from contamination with plastics, but it was used in children's food as an additive. Acetyl tributyl citrate was found in the bottles with sake, migrating from the bottle caps seals. This one as well as the other plasticizers were deep below the maximal tolerated concentrations (Tsumura et al., 2002).

Triesters of citric acid are considered to be very safe. They possess very advantageous parameters of biocompatibility. Their acetylated forms are markedly hydrophobic, mainly acetyl tributyl citrate. In acute, short-term, subchronic and chronic testing they are relatively non-toxic. After ocular and dermal administration to rabbits they were non-irritating, in guinea-pigs acetyl triethyl citrate acted as a sensitizer, whereas acetyl tributyl citrate did not. According to Cosmetic Ingredient Review Expert Panel, esters of citric acid are not considered to be sensitizers (Johnson, 2002). After intravenous administration they decrease blood pressure and spasms of intestinal muscles. The compounds were not genotoxic in the tests on bacteria and on mammals, they did not induce tumours.

Dibutyl sebacate is a widely used plasticizer in pharmacy. Its solubility in water is 40 mg/l at 20 °C, it is odourless and colourless. It possesses very favourable thermal characteristics, above -10 °C it is liquid, at 344 °C is boiling point. The toxicological data indicate that this compound is practically non-toxic after oral administration and also non-irritating in dermal contact (Clayton & Clayton, 1993-1994).

Phthalates are effective plasticizers of many polymers. With regard to the fact that in the case of some pharmaceutical applications, in particular in film coating of tablets, they are used in very small amounts they are still in use; it is, above all, dibutyl phthalate (Lowell Center for Sustainable Production, 2011) and diethyl phthalate (World Health Organization, 2003).

Triacetin has been very often used as a plasticizer and a solvent in pharmaceutical and cosmetic products. It has been affirmed as a GRAS product by FDA for human use in the food industry, and it is safe for cosmetic products (Zondlo & Fiume, 2003). After acute short-term oral administration and dermal exposure it is not toxic or mutagenic; it feebly irritates the guinea pig skin and rabbit eye.

2.3.4 Oligomeric and polymeric plasticizers

An advantage of the plasticizers of this type is a decrease in or a full prevention of their migration from materials (Rasal et al., 2010).

Polyesters derived from aliphatic hydroxy acids are compounds which have been very intensively studied and employed as biodegradable and renewable thermoplastic materials with a potential of replacing the conventional polymers based on mineral oil products. These polyesters are used as carriers of active ingredients with a period of release of these substances for weeks to months. They are the products of polymerization of cyclic dimers, lactones via ring opening method, or the substances developed by a polycondensation reaction, e.g. poly(lactic acid), poly(lactide-co-glycolide). They are mostly polymers which in the glassy state have a small elongation at break. For their plasticization highly biocompatible, if possible completely biodegradable compounds are suitable. As the very suitable ones were demonstrated oligoesters or low-molecular polyesters of identical or similar aliphatic hydroxy acids as plasticized polymers (Martin & Avérous, 2001), and polyesteramides were also proposed (Ljungberg et al., 2005). Polyethylene glycols (PEG) are also suitable for these purposes, their miscibility decreases with molecular mass (Baiardo et al., 2003). PEG with a value of M_n 20 000 very effectively plasticized in a 40 % concentration of poly(L-lactic acid) (Kim et al., 2001). PEG in a concentration above 50 % possesses increased crystallinity, an increased module and decreased ductility (Sheth et al., 1997). Polypropylene glycol also exerts a plasticizing effect on poly(L-lactic acid), its effect on a decrease in crystallinity is lower than in PEG (Kulinski et al., 2006). A blend of two plasticizers called multiple plasticizer, triacetin and oligomeric poly(1,3-butanediol), significantly influences the elastic properties and tensile strength (Ren et al., 2006).

2.3.5 Non-traditional plasticizers

It is advantageous to utilize plasticization effect of some pharmaceutical active agents or of some excipients possessing other functions in the formulated composition. In the literature, these are named as non-traditional, non-conventional, or multifunctional plasticizers. Several studies report the plasticization of polymers by ibuprofen, theophylline, salts of metoprolol and chlorpheniramin and other active ingredients. From the auxiliary compounds it is potentially promising the use of many surfactants, preservatives, solvents, cosolvents, desolvating and coacervating agents as plasticizers. These components of pharmaceutical preparations can act by various mechanisms, as lowering of intermolecular and intramolecular interactions, increasing of macromolecular or segmental mobility with the consequence of ameliorated thermal and mechanical properties, distensibility, adhesion, viscosity etc.

Ibuprofen was found to be very effective in plasticizing of the acrylic film. Ibuprofen interacts with the Eudragit RS 30 D polymer through hydrogen bonding. The glass transition temperature of the Eudragit RS 30 D polymer decreased with the increasing levels of ibuprofen in the polymeric film (Wu & McGinity, 2001). Metoprolol tartrate, chlorpheniramine maleate and ibuprofen are efficient plasticizers for Eudragit RS as shown by the thermal and mechanical properties of drug-loaded polymeric film (Siepmann et al., 2006).

The influence of methylparaben, ibuprofen, chlorpheniramine maleate and theophylline on the mechanical properties of polymeric films of Eudragit® RS 30 D was studied. The results demonstrated that the glass transition temperature of the Eudragit® RS 30 D decreased with increasing levels of methylparaben, ibuprofen and chlorpheniramine maleate in the polymeric coatings. The addition of methylparaben to Eudragit® RS 30 D resulted in significant changes in the mechanical properties, making the polymer softer and more flexible. The T_g of the polymer was significantly reduced (Wu & McGinity, 1999).

3. Drug release influenced by plasticizers

Drug release from polymer drug delivery system is modified by the method of their formation, or by using an appropriate polymer or additive, which could also be a plasticizer. Modified release includes delayed release, extended release (prolonged, sustained), and pulsatile release (Chamarthy & Pinal, 2008).

Dosage forms based on polymeric carriers can be classified according to the mechanism of drug release into the following categories: (i) Diffusion-controlled drug release either from a non-porous polymer drug delivery system or (ii) from a porous polymer drug delivery system, and (iii) disintegration controlled systems (Khandare & Haag, 2010). Diffusion of a drug within a non-porous polymer drug delivery system occurs predominantly through the void spaces between polymer chains, and in the case of a porous polymer drug delivery system by diffusion of a drug through a porous or swelling polymer drug delivery system. The plain fact is that the plasticizer type and concentration must influence the drug release as plasticizers reduce polymer-polymer chain secondary bonding, and provide more mobility for the drug. Plasticizer leaching out of the polymer results in pore formation for burst release of the drug. Subsequent release stage of drug is based on diffusion through the dense polymer phase.

Non-biodegradable polymers are characterized by their durability, tissue compatibility, and mechanical strength, which endure under in vivo conditions without erosion or considerable degradation. Polyurethane, poly(ethylene vinyl acetate), and polydimethylsiloxane are examples of polymer films that follow predictable Fickian diffusion or can be modified for linear or near zero order release. One drawback of these non-biodegradable polymer devices is an occasional need for a second surgical procedure to remove the device, which leads to an increased cost and associated discomfort / inconvenience for the patient.

Drug release from biodegradable polymers is depended on the way of erosion and degradation. The most commonly employed class of biodegradable polymers are the polyesters, which consist mainly of poly(caprolactone), poly(lactic acid), poly(glycolic acid) and copolymers of lactic and glycolic acids. Their degradation mechanism is non-enzymatic random hydrolytic chain scission established. Polymer drug delivery system can be classified in bulk-eroding systems, surface-eroding systems, or systems undergoing both surface and bulk erosion. Polyamides and polyorthoesters degrade only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the drug delivery system. Poly(lactic acid) and poly(lactic-co-glycolic acid) are reported to undergo both surface and bulk erosion which probably disturbs an even rate of drug delivery.

The release profile of the drug from degradable matrices is typically triphasic. The three phases can be summarized by an initial rapid drug release (burst effect) from the matrix surface, followed by a phase where the incorporated drug diffuses more slowly out of the inner bulk matrix and then, the remaining drug release phase due to bulk degradation of the polymer. The extent of the initial burst release can be controlled by plasticizers. High burst release can be minimized by hydrophobic plasticizers; the opposite effect is achieved by hydrophilic plasticizers, which leach out of polymer in the hydrophilic medium.

Biodegradation rate and thus the release of incorporated drugs depend on the polymer molecular weight parameters. Low molecular weight polymers or oligomers are preferred as drug carriers, as their hydrolysis may proceed simultaneously or just somewhat slower than drug release. A low molecular weight poly(D,L-lactic) acid with a linear molecule constitution is not suitable as a carrier due to a lag-time. Star-like copolymers of hydroxy acids with polyhydric alcohols, such as pentaerythritol, mannitol, glucose, polyvinyl alcohol and others are particularly advantageous. These branched carriers unlike the linear are endowed with low gyration radius (Kissel et al. 1991). Drug release from this type of carriers can be modified not only by molecular weight, but also more significantly by the degree of their branching (Pistel et al., 2001).

3.1 Effect of solubility parameters of the plasticizer on drug release

The physicochemical properties, particularly the solubility parameters of the plasticizer and extent of the plasticizer leaching act the major role in the drug release from a plasticized polymer system. The differences in the drug release patterns are observed in the case of using either lipophilic or hydrophilic plasticizers. The lipophilic plasticizers, (e. g. dibutyl sebacate) are shown to remain within the polymeric system upon exposure to the release media, assuring integral and mechanically resistant coatings during drug release. In contrast, hydrophilic plasticizers leached out of the system, resulting either in decreased mechanical resistance and thus cracking, or in facilitated pore formation. As drug release was controlled by diffusion through the intact membrane and/or water-filled cracks (with significantly different diffusion coefficients), the mechanical stability of the polymeric system and the onset of crack formation are of major importance for the resulting drug release profiles.

3.2 Effect of affinity of the plasticizer to the polymer on drug release

Furthermore, the affinity of the plasticizer to the polymer is found to be decisive. The plasticizer redistribution within the polymeric systems during coating, curing and/or storage affects the drug release rate. For instance, dibutyl sebacate has a higher affinity to ethycellulose than to Eudragit RL, resulting in potential redistributions of this plasticizer within the polymeric systems and changes in the release profiles. Importantly, adequate preparation techniques for the coating dispersions and appropriate curing conditions could avoid these effects, providing stable formulations (Bodmeier & Paeratakul, 1997).

3.3 Effect of plasticizer concentration on drug release

The plasticizer concentration has a significant impact on the drug release of a diffusion-controlled drug delivery system. Low concentrations of the plasticizer often result in an

increase in the rigidity of the polymer instead of the expected softening effect. This effect, known as antiplasticization, can be used as a formulation strategy which can modulate drug permeability of polymers used in pharmaceutical systems.

The antiplasticizing effect of water on the transport properties of disintegration controlled systems such as tablets is highly relevant during the manufacturing, handling and storage of the product; water does not antiplasticize during drug release. Once in the body, pharmaceutical formulations are subjected to a water saturated environment. Consequently, water will act exclusively as a plasticizer under such conditions (Chamarthy & Pinal, 2007).

The theophylline release profile from soluble starch plasticized with sorbitol exhibits two valleys, which can be explained as a simultaneous plasticizing effect of water penetrating from the dissolution medium and the antiplasticizing effect of sorbitol contained in the formulation (Chamarthy & Pinal, 2008).

Antiplasticization can be expected to significantly affect drug release and thus a factor that has to be taken into consideration in formulation development.

3.4 Effect of drug-polymer or drug-plasticizer interaction on drug release

The drug-polymer or drug-plasticizer interaction within the polymer drug delivery system can significantly influence the drug release profile. For instance, when triacetin was added to indomethacin loaded poly(methyl methacrylate) (PMMA) microspheres, a desired drug release profile lasting 24 h was achieved. Originally biphasic release profile, an initial burst effect from the surface of the microspheres followed by a slower drug release phase was surmounted by addition of a plasticizer. There might be a hydrogen bonds formation between the indomethacin hydroxyl group and PMMA, no interaction between triacetin and indomethacin or PMMA as the effects of secondary bonds was observed. The release enhancement of indomethacin from microspheres was attributed to the physical plasticization effect of triacetin on PMMA and, to some extent, the amorphous state of the drug.

The plasticization effect of triacetin on PMMA increased the diffusivity of indomethacin from PMMA. However, this effect was not dependent on the formation of secondary bonds between triacetin and PMMA. This indicates that the triacetin molecules physically separate the PMMA chains by locating within them (Yuksel et al., 2011).

An example of how drug-polymer interaction can affect the drug release can be piroxicam-loaded Eudragit E film. The drug-polymer interaction occurring between piroxicam and Eudragit E seems to cause a drag effect, leading to a delay of the piroxicam release from the Eudragit E film (Lin et al., 1995).

Similarly, ibuprofen interacts with the Eudragit RS 30 D polymer through hydrogen bonding, thus ibuprofen acts both as the active ingredient and as the plasticizer for the polymer also. The glass transition temperature of the Eudragit RS 30 D polymer decreased with increasing levels of ibuprofen in the polymeric film. The drug release rate was reduced by increasing the amount of ibuprofen in the polymeric film and by increasing the coating level on the coated beads (Wu & McGinity, 2001).

3.5 Effect of plasticization technology on drug release

Drug release profile can be modified by the preplasticization step, which is often necessary when incorporating plasticizer into the formulation in order to achieve uniform mixing of the polymer and plasticizer, to effectively reduce the polymer T_g , and to lower the processing temperatures. For instance, citric acid monohydrate combined with triethyl citrate in the powder blend was found to plasticize Eudragit S 100. Tablets containing citric acid released drug at a slower rate as a result of the suppression of polymer ionization due to a decrease in the micro-environmental pH of the tablet. The drug release profiles of the extruded tablets were found to fit both diffusion and surface erosion models (Bruce et al., 2005).

Theophylline or chlorpheniramine maleate pellets were coated with an aqueous ethylcellulose dispersion, Aquacoat. The influence of the plasticization time, curing conditions, storage time, and core properties on the drug release were investigated. The plasticization time (time between plasticizer addition to the polymer dispersion and the spraying process) did not affect the drug release, when the water-soluble plasticizer triethyl citrate was used, because of its rapid uptake by the colloidal polymer particles. In contrast, with the water-insoluble plasticizer acetyltributyl citrate, plasticization time (1/2 h vs 24 h) influenced the drug release, the longer plasticization time resulted in a slower drug release because of a more complete plasticizer uptake prior to the coating step. However, a thermal aftertreatment of the coated pellets at elevated temperatures (curing step) eliminated the effect of the plasticization time with acetyltributyl citrate. In general, curing reduced the drug release and resulted in stable drug release profiles. The time period between the coating and the curing step was not critical when the pellets were cured for a longer time. The structure of the pellet core (high dose matrix vs low dose layered pellet) strongly affected the drug release. A slow, zero-order drug release was obtained with high dose theophylline pellets, while a more rapid, first-order release pattern was obtained with low dose theophylline-layered nonpareil pellets (Wesseling & Bodmeier, 2001).

A pharmaceutical paste composition comprising the active ingredient such as an additive substance a control release agent and suitable carrier was patented (Odidi I. & Odidi A., 2009). The composition may be filled into a capsule or other dispensing device. Oily, waxy, or fatty substances were applied as plasticizers. Other invention relates to an oral pulse release comprising a polymer micromatrix, a first active ingredient distributed substantially uniformly within polymer micromatrix and a second active ingredient deposited on the surface of the polymer matrix (Gadre et al., 2006).

3.6 Drug release from plasticized polyesters

Films from poly(L-lactide) and poly(lactide-co-glycolide) were plasticized with polyethylene glycol. The plasticizer accelerated the degradation of polyester, its effect on the beginning of the release of the contained heparin significantly differed in dependence on the parameters of the polymer. In the homopolymer it decreased the burst-effect and accelerated the drug release in the phase controlled by diffusion, in copolymer the plasticizer did not exert a significant effect on the kinetics of release. The differences were explained by the influence of plasticizer on polymer hydrophilicity and crystallinity (Tan et al., 2004).

Thin films of a thickness of 40 μm from poly(lactide-co-glycolide) containing 10 % paclitaxel were plasticized with polyethylene glycols M_w 8,000 and 35,000 in various concentrations. The plasticizer with a lower molecular mass exerted a great influence on a more rapid release of paclitaxel. Polyethylene glycol was phase separated from copolymer (Steele et al., 2011).

The active ingredients were demonstrated to act as plasticizers of the polymer. The kinetics of dissolution in phosphate buffer of pH 7.4 and apparent diffusion coefficient including mathematical analysis of data resulted in the expression of the quantitative relationship between the diffusivity of drugs and the initial composition of medicinal substances with a possibility of prediction of the effect of thickness of the membrane and its composition on the kinetics of drug release (Siepmann et al., 2006).

Oligoester carrier compound of the equimolar ratio of glycolic acid and lactic acid branched with dipentaerythritol was synthesised by polycondensation (Snejdrova, E. & Dittrich, M., 2011). Table 3 shows the basic characteristic of the carrier.

Reactants proportion [weight %]			M_w [g/mol]	T_g [$^{\circ}\text{C}$]
Lactic acid	Glycolic acid	Dipentaerythritol	2,300	16.3
47.5	47.5	5.0		

Table 3. Relevant characteristics of oligoester carrier.

The carrier was plasticized using methyl salicylate in concentration of either 10 %, or 20 %, or 30 %. The increase of methyl salicylate concentration in the oligoester matrices influences the aciclovir release *in vitro* in the obvious manner. At 10 % concentration of the plasticizer the 90 % portion of active substance released was achieved after 15 days, at its 20 % concentration after 9 days, and at 30 % concentration after three days (Fig. 1).

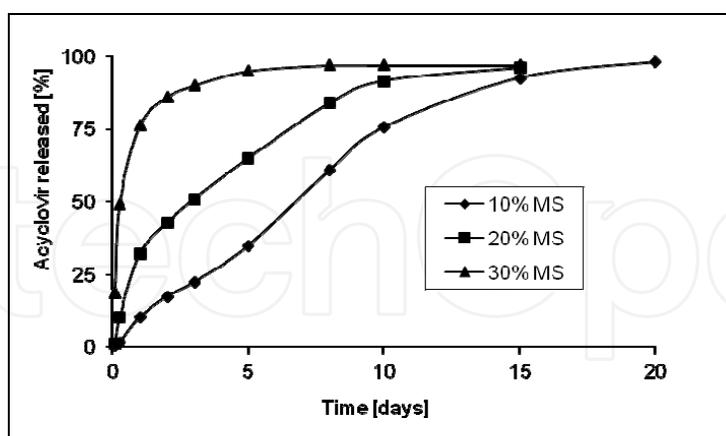


Fig. 1. Aciclovir release from oligoester carrier plasticized by methyl salicylate (MS).

Ethyl salicylate as more hydrophobic plasticizer in comparison to methyl salicylate was used in various concentrations for plasticizing of the oligoester carrier. It influences the aciclovir release kinetics in the more complicated way. The partition coefficient matrix/dissolution medium for drug is in the consequence a character of plasticizer and aqueous medium influx changed. During the drug release process small portion of

plasticizer is separated as liquid heterophase containing aciclovir in the swelled matrices. The viscosity of matrices is dominant factor in the initial phase of drug release (Fig. 2).

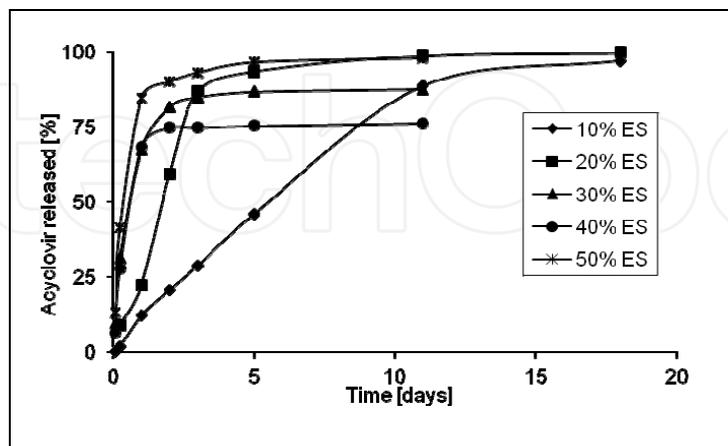


Fig. 2. Acyclovir release from oligoester carrier plasticized by ethyl salicylate (ES).

The influence of triethyl citrate concentration on acyclovir release from the branched oligoester carrier is shown in Fig. 3. Triethyl citrate differs from above mentioned plasticizers, methyl salicylate and ethyl salicylate, by its higher solubility in aqueous medium. The value of triethyl citrate solubility is 6.5 %, whilst for salicylic acid esters it is under 0.1 %. The acceleration of dissolution process after 10 % triethyl citrate addition is expected situation. The hydrophilisation of matrices and their higher swelling is possible explanation for this behaviour. Opposite relation between concentration of triethyl citrate and velocity of drug release is reached at higher plasticizer concentrations. The possible hypothesis of this atypical situation is based on rapid collapse of matrices structure and formation of supramolecular structure based on more dense random coil conformation of molecules.

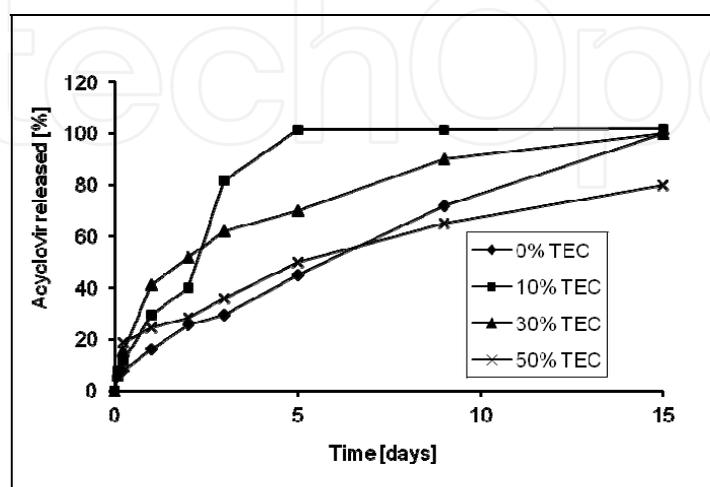


Fig. 3. Effect of triethyl citrate (TEC) on acyclovir release from branched oligoester carrier.

4. Conclusion

The “tailor made method” of selection the proper polymer for drug formulation has its limitations due to the demanding registration procedure of new polymers. Blending of two polymers or mixing of polymers with plasticizers and other additives are relatively simple and promising methods providing new biomaterials used in drug delivery with advantageous properties. Aliphatic polyesters are the most frequently used polymers in drug delivery systems. Star-like copolymers of hydroxy acids with polyhydric alcohols such as dipentaerythritol are particularly interesting. They possess good mechanical properties, however the brittleness is their major drawback for many applications. This is the reason for their blending with common and even non-traditional plasticizers. Viscosity of these drug carriers must be sufficiently low for good workability or in order their application via an injection needle or trocar applicator. The plasticizer type and concentration influence the whole profile of drug release.

5. References

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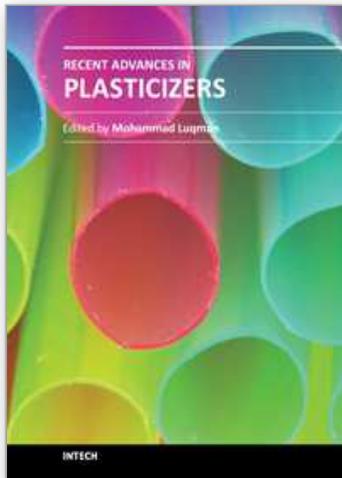
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