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PHARMACEUTICALLY USED PLASTICIZERS: A REVIEW

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ABSTRACT
A plasticizer is a substance the addition of which to another material makes that material softer and more flexible. Most often plasticizers are materials which, when added to a polymer, cause an increase in the flexibility and workability, brought about by a decrease in the glass-transition temperature of the polymer. This article provides an overview of the important types of plasticizers which exist, and gives details of properties of the plasticizers. The choice of an appropriate plasticizer requires a wide background of information. This is because they are incorporated into drug delivery systems containing an assortment of ingredients which may have different reactions to the presence of plasticizers. The mechanism of action of plasticizers is described, in terms of plasticization theory and the chemical modifications that occur during this process, which account for the excellent performance of some plasticizer molecules and the apparently poor softening ability of others. The current legislative and toxicological status of plasticizers is thoroughly reviewed to provide information about the environmental effects of this widespread use of these products.

KEY WORDS: Plasticizer, Polymer, Release, Flexibility.

INTRODUCTION
Now a day the plasticized polymers are used as a modern pharmaceutical technology to modify and control the drug release characteristics in therapeutic systems. Recently, a great variety of plasticized polymeric systems have been studied as microparticles, matrices, free membranes, membranes for transdermal systems and *in situ* forming implants. Not only the polymer itself but thorough choice of other ingredients of the polymer system is necessary for required quality of drug delivery system.[1] Plasticizers can be added to polymers to make them more flexible. Plasticizers are small lubricating molecules that can change polymer properties and processability.[2,3] Plasticizers are generally used to improve the mechanical properties of a polymer matrix also modify the thermal property, water absorption behaviour, and adhesive property of polymeric films. All of these properties affect the strength of coating films and the integrity of final products, which further affect drug release performance.[4]

WHAT IS A PLASTICIZER?
A plasticizer is a chemical which is added to a polymer to increase its flexibility. The plasticizer gets between the polymer chains and keeps them further apart which reduces the forces of attraction between them and makes the material more flexible. The polymer will probably have a reduced strength and stiffness because of the plasticizer but the material will be more useful where flexibility is required.[5]

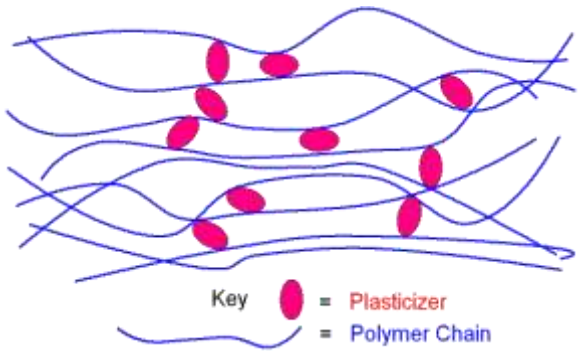

Figure No. 1: Principle of chain folding

There are many plasticizers used in thechemical 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 now a days 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 lost 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 propyleneglycol, citric acid (tributylcitrate, triethylcitrate) or glycerol (triacetin, tributyrin) are used as Plasticizer. Even liquid drugs or liquids with a potential pharmacodynamic effect can serve as plasticizers.[6]

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 systemand 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 toan increase in water diffusion into the polymer, thus diffusivity parameters of the systemare 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 bellow50 °C is necessary for easy manipulation and simply and harmless application of implants in situ via an injection needle or trocar device.[7]

MECHANISM ACTION OF PLASTICIZERS

For better plasticizing effect, it must be thoroughly mixed and incorporated into the PVC polymer matrix. This is typically obtained by heating and mixing until either the resin dissolves in the plasticizer or the plasticizer dissolves in the resin. The plasticized material is then molded or shaped into the useful product and cooled. Different plasticizers will exhibit different characteristics in both the ease with which they form the plasticized material and in the resulting mechanical and physical properties of the flexible product.[8]

The mechanism of action of plasticizers is defined as to interpose between every individual strand of polymer and thereby causing breakdown of polymer-polymer interactions. The tertiary structure of the polymer is modified into more porous, flexible and with less cohesive structure. Plasticizers soften and swell the polymer which aids in overcoming their resistance to deformation. Plasticized polymer would deform at a lower tensile force as compared to without plasticizer. This enhances the polymer – plasticizer interaction. This effect in turn enhances the film elongation effect. The interaction to a greater extend depends upon the glass transition temperature of polymers. Glass transition temperature (Tg) is the temperature at which hard glassy polymer is converted into a rubbery material. All polymers have higher glass transition temperature and addition of plasticizers reduces the glass transition temperature.[9]

Some theories have been proposed to explain the mechanisms of plasticization process as follows,

The lubrication theory postulates that plasticizers act as internal lubricants by reducing frictional forces by interspersing themselves between polymer chains.

The gel theory postulates that the rigidity of polymer comes from three dimensional structure through the centre of force and plasticizers take effect by breaking polymer -polymer interaction.

The free volume theory states plasticization as a study of ways to increase free volume and is useful in explaining the lowering of the Tg by a plasticizer. The free volume or free space of a crystal, glass or liquid may be defined as the difference between the volume observed at absolute zero temperature and the volume measured for the real crystal, glass or liquid at a given temperature.

In specific volume of material and temperature relationship, the glassy matter becomes rubbery or fluid (obviously increasing specific volume). When the temperature is above Tg, the molecules have enough energy to move, bend or rotate. The Brownian motion of molecules or segments of molecules produces a greater amount of free volume (the torsional or hole free volume).

Free volume comes from three principal sources:

1. The motion of chain ends
2. The motion of side chains
3. The motion of the main chain.

The free volume of a resin system may be increased by:

1. Increasing the number of end groups (lower the molecular weight).
2. Increasing the number or length of (proper) side chains (internal plasticization)
3. Increasing the chance for main chain movement by inclusion of segments of low steric hindrance and low intermolecular attraction (low polarity and H bonding) (Internal plasticization).
4. Inclusion of a compatible compound of lower molecular weight that acts as though it does all of 1 through 3 above. (external plasticization)
5. Raising the temperature.[9]

PLASTICIZER REQUIREMENTS[10]

In addition to such general requirements as low volatility, temperature stability, light stability, little, or no odor, etc., there are a number of more basic requirements. One of these has been mentioned as all the intermolecular forces involved (between plasticizer and plasticizer, between polymer and polymer, between plasticizer and polymer) be of the same order of magnitude. The other important criteria are as follows;

Solvent Power

The plasticizer should, in most cases, have a high degree of solvent power for the polymer. With crystalline polymers, only a solvent type plasticizer will be able to penetrate both the ordered and the disordered regions, whereas a nonsolvent plasticizer (softener) will only be able to enter the amorphous regions. It should be realized, however, that when a low molecular weight compound penetrates the crystalline regions certain properties which depend on crystallinity -e.g., tensile strength, and modulus-will deteriorate. With materials where these properties are of prime importance, it may therefore be more advantageous to use only a secondary plasticizer, or softener.

Compatibility

The plasticizer should be compatible with the polymer system over both the processing and the use temperature ranges; and it is desirable that subsequent exposure of the plasticized article to common substances or conditions, such as water, oil, oxygen, or sunlight, should not disturb the compatibility balance. Factors affecting compatibility, in addition to polarity, are the size (molecular weight) and shape of the plasticizer. An example of good compatibility due to similar chemical structure (polarity, shape, size) is the oldest known plasticizer- polymer system: camphor and cellulose nitrate.

Efficiency

The term plasticizer efficiency is used to relate a desirable modification of the properties of a given product to the amount of plasticizer required to achieve this effect. For example, the efficiency of various plasticizers in plasticizing a given polymer may be expressed in terms of the depression of the glass temperature by a given mole, or volume fraction of plasticizer. Therefore, there is no absolute value for the efficiency of a certain plasticizer, and the relative efficiency of different plasticizers will depend on which polymer property is used to measure plasticizer efficiency. In addition to size and molecular weight, one of the most important factors which determine plasticizer efficiency is the rate of diffusion of the plasticizer in the polymer matrix. In view of the dynamic solvation-desolvation between the plasticizer molecules and the polymer chains, the higher the diffusion rate, the greater the efficiency of the compound as a plasticizer. However, high diffusion rates are usually encountered with small molecules; the smaller the plasticizer molecule, the greater its volatility and, therefore, the rate at which it is lost from the plasticized product.

Permanence

The permanence of a plasticizer-i.e., its tendency to remain in the plasticized material, depends on the size of the plasticizer molecule and on its rate of diffusion in the polymer. The larger the plasticizer molecule, the lower its vapour pressure, or volatility and, therefore the greater its permanence. This accounts for the popularity of certain polymeric plasticizers, such as polyesters, in spite of their relatively high price. Other factors, such as polarity and hydrogen bonding, will also, of course, affect the vapour pressure of the plasticizer. The rate of diffusion of the plasticizer molecules within the polymer matrix will also determine plasticizer permanence. Unfortunately, while a high rate of diffusion provides for greater plasticizer efficiency, it results in low plasticizer permanence.

The choice of a plasticizer, therefore, usually involves a compromise since the requirements for good solvent power, compatibility, efficiency, and permanence, cannot all be met simultaneously. This has been clearly illustrated by Boyer with the aid of the diagram in Figure**.**

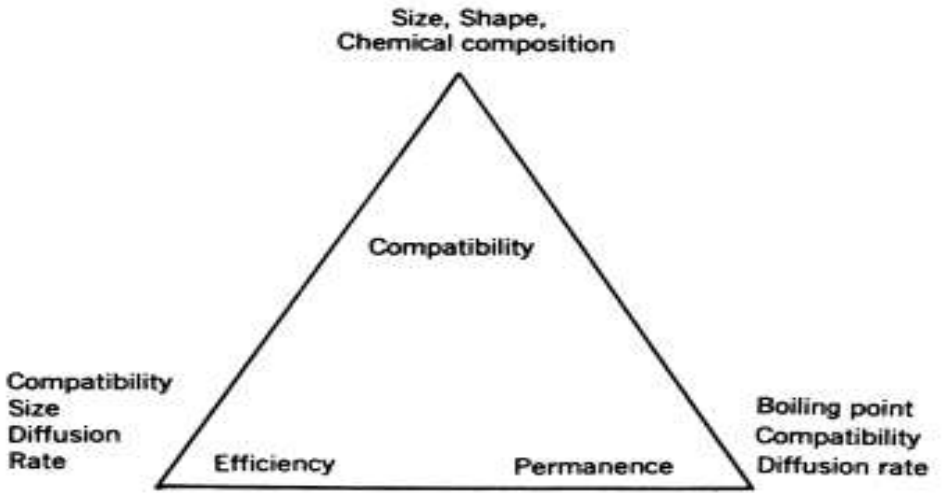

Figure No.2: Schematic representation of relationships between three important properties of the plasticizer: compatibility, efficiency, and permanence[11]

PHARMACEUTICALLY USED PLASTICIZERS

In the field of pharmaceutical science and drug development, there are important and particular

challenges related to the selection of suitable and compatible ingredients as well as the design of successful formulations. As plasticization is a phenomenon widely exploited in all formulation fields, plasticizers should be recognized as a critical aspect for drug delivery. The choice of an appropriate plasticizer requires a wide background of information. This is because they are incorporated into drug delivery systems containing an assortment of ingredients which may have different reactions to the presence of plasticizers.[12]

Plasticizers are simply relatively low molecular weight materials which have the capacity to alter the physical properties of a polymer to render it more useful in performing its function as a film-coating material. Generally the effect will be to make it softer and more pliable. There are often chemical similarities between a polymer and its plasticizer—for instance, glycerol and propylene glycol, which are plasticizers for several cellulosic systems, possess —OH groups, a feature in common with the polymer.

One fundamental property of a polymer which can be determined by several techniques is the glass transition temperature (Tg). This is the temperature at which a polymer changes from a hard glassy material to a softer rubbery material. The action of a plasticizer is to lower the glass transition temperature. The transition can be followed by examining the temperature dependence of such properties as modulus of elasticity, film hardness, specific heat, etc.

Criterions 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:

- 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.

EFFECT OF PLASTICIZERS ON OTHER COMPONENTS OF FORMULATION

Several factors influence consumption of plasticizers by fillers. These include:

- ✓ Particle size distribution − combination of small and large particle sizes leaves less free space between filler particles and thus less plasticizer is required to fill this space.
- ✓ Particle shape − closer the shape of particle to the spherical shape better packing and less free space between particles to fill. Particle shape of fillers can be conveniently measured by the aspect ratio which for majority of fillers is within the range of 1 to 3 but may be much larger for flaky fillers (10 to 100) and largest for fibers (above 100)
- ✓ particle size distribution and particle shape both contribute to packing volume of filler which is a fraction of total volume occupied by fillers. This may vary widely depending on filler design. For ordinary mineral fillers maximum packing volume is usually within the range of 0.3 to 0.5. It is usually much lower for flakes and fume silica (below 0.1) but can be above 0.5 for glass beads and other fillers produced with well controlled geometry
- ✓ surface roughness and pore volume and size contribute to plasticizer uptake by filler. Small pores (e.g., molecular sieves) do not permit plasticizer to enter them because plasticizer molecule is too bulky to fit small diameters of pores. On the end of spectrum, diatomaceous earth is made of pores and voids which occupy 85% of its volume
- ✓ many physical and chemical interactions reduce or increase plasticizer uptake. These include: interactions between filler particles, formation of agglomerates and aggregates, flocculation, zeta potential, acid/base interactions, surface energy, chemical interactions between filler and plasticizer.[13]

CLASSIFICATION OF PHARMACEUTICALLY USED PLASTICIZERS

Pharmaceutically used plasticizers are often distinguished into hydrophilic andhydrophobic, or low molecular weight, oligomeric and polymeric. Water insolubleplasticizers have to be emulsified in the aqueous phase of the polymer dispersions.Plasticizers are incorporated in the amorphous phase of polymers while the structure andsize of any crystalline part remains unaffected.

Water as a plasticizer

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 Tg 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 anti-plasticizer.

Water can increases the of diffusion of a small molecule in iota-carrageenan biopolymer films for edible coating application was studied by Karbowiak T et. al.[14]

Hydrophilic plasticizers

Hydrophilic plasticizers include the compounds which are without limitations or in asufficient degree miscible with water. They are on the rule substances with very good biocompatibility, some are components of metabolic processes, and others can be easilyeliminated from the organism. The most widely used are polyhydric alcohols namely, glycerol (GLY), ethylene glycol (EG), poly(ethylene glycol) (PEG), and propylene glycol (PG)[15]. 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. 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. In the temperatures of 150 to 180 °C the granules melt and a plastic amorphous material is produced. Glycerol and xylitol are important plasticizers of starch; in their presence the starch film is flexible regardless of the water content in it. 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 Tg. Between the individual plasticizers there occurs competitive plasticization with three types of interactions: starch/plasticizer, plasticizer/water and starch/water. Pharmaceutically used plasticizers 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 to20 %. On the basis of water sorption, the competition of the plasticizer and water under different activities of water was evaluated.

Suyatma NE was evaluated the plasticizer effect on chitosen film. It was found that GLY and PEG were more suitable as chitosan plasticizers than EG and PG by taking into account their plasticization efficiency and storage stability.[15]

Plasticizers with limited miscibility with water

The border between hydrophilic and hydrophobic plasticizers is not sharp, being connectedwith 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 solutionsor 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, (depression of the glass transition temperature and 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.

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. 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 states 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), and polyesteramides were also proposed. Polyethylene glycols (PEG) are also suitable for these purposes, their miscibility decreases with molecular mass (PEG with a value of Mn 20 000 very effectively plasticized in a 40 % concentration of poly(L-lactic acid). PEG in a concentration above 50 % possesses increased crystallinity, an increased module and decreased ductility. Polypropylene glycol also exerts a plasticizing effect on poly(L-lactic acid), its effect on a decrease in crystallinity is lower than in PEG plasticizers called multiple plasticizer, triacetin and oligomeric poly(1,3-butanediol), significantly influences the elastic properties and tensile strength some excipients.

Non traditional plasticizer

Non-traditional, non-conventional, or multifunctional plasticizers are advantageous to utilize plasticization effect of some pharmaceutical active agents or of possessing other functions in the formulated composition. Several studies report the plasticization of polymers by ibuprofen,[16] theophylline, salts of metoprolol and chlorpheniramin and other active ingredients. From the auxiliarycompounds 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 withthe consequence of ameliorated thermal and mechanical properties, distensibility, adhesion, viscosity etc.

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 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 anon-porous polymer drug delivery system or (ii) from a porous polymer drug deliverysystem, and (iii) disintegration controlled systems. 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 deliverysystem 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.[7]

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. Incontrast, 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.

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, dibutylsebacate 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.

Effect of Plasticizer Type and Level on Drug Release

Plasticizers are added to enhance ethylcellulose film forming properties, render it more pliable and provide films with adequate mechanical properties.[17] Type of plasticizer used determines the intrinsic properties of the polymeric system consequently affecting drug release characteristics, as well as surface and mechanical properties of the applied film coat. The influence of type and level of plasticizers on chlorpheniramine maleate release from ethylcellulose barrier membrane coated beads was investigated. Type and amount of plasticizer can significantly influence drug release rates. Selection of type and amount of plasticizer requires careful consideration and can be used as an effective tool to tailor drug release.[18]

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

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, adesired 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 drugrelease phase was surmounted by addition of a plasticizer. There might be a hydrogenbonds formation between the indomethacin hydroxyl group and PMMA, no interaction between triacetin and indomethacin or

PMMA as the effects of secondary bonds wasobserved. The release enhancement of indomethacin from microspheres was attributed tothe physical plasticization effect of triacetin on PMMA and, to some extent, theamorphous 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 an example of how drug-polymer interaction can affect the drug release can be piroxicamloaded 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.

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 uniformmixing of the polymer and plasticizer, to effectively reduce the polymer Tg, and to lower the processing temperatures. For instance, citric acid monohydrate combined with triethylcitrate in the powder blend was found to plasticize Eudragit S 100. Tablets containingcitric acid released drug at a slower rate as a result of the suppression of polymerionization due to a decrease in the micro-environmental pH of the tablet. The drug releaseprofiles of the extruded tablets were found to fit both diffusion and surface erosion models (Theophylline or chlorpheniramine maleate pellets were coated with an aqueous ethyl cellulose dispersion, Aquacoat. The influence of the plasticization time, curingconditions, storage time, and core properties on the drug release were investigated. The plasticization time (time between plasticizer addition to the polymer dispersion and thespraying process) did not affect the drug release, when the water-soluble plasticizer triethylcitrate was used, because of its rapid uptake by the colloidal polymer particles. In contrast, with the water-insoluble plasticizer acetyltributyl citrate, plasticization time (½ h vs 24 h) influenced the drug release, the longer plasticization time resulted in a slower drug releasebecause of a more complete plasticizer uptake prior to the coating step. However, a thermalaftertreatment of the coated pellets at elevated temperatures (curing step) eliminated theeffect of the plasticization time with acetyltributyl citrate. In general, curing reduced thedrug release and resulted in stable drug release profiles. The time period between thecoating 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) stronglyaffected the drug release. A slow, zero-order drug release was obtained with high dosetheophylline pellets, while a more rapid, first-order release pattern was obtained with lowdose theophylline-layered nonpareil pellets active ingredient such as an additivesubstance a control release agent and suitable carrier was patented. 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 pulserelease 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.

Drug Release From Plasticized Polyesters

Heparin-loaded polymer films of poly-L-lactide (PLLA) and poly-L-lactide-co-glycolide (PLLGA) as well as poly-DL-lactide-co-glycolide (PLGA) were produced. A plasticizer, PEG, was added to the polymers. It was found that the release profile in general consisted of a burst effect, a diffusion-controlled phase and a degradation-controlled phase. The plasticizer accelerated the onset of degradation in all cases, but its effect on the release profile differed significantly depending on the polymer. The plasticizer depressed the burst effect for PLLA, and accelerated the kinetics of the diffusion-controlled phase. For the PLLGA 80/20, however, the plasticizer had no significant effect on the release profile or kinetics.[7, 19]

Table. List of plasticized polymers reviewed in presented chapter[1]

Pharmaceutically used polymer	Plasticizer	Applied as
Cellulose nitrate (collodion)	castor oil	historically the first plasticized polymer used as a medicinal preparation (wounds covering)
PVC	di(2-ethylhexyl) phthalate, diisononyl phthalate, diisodecyl phthalate, epoxidized triglyceride, vegetable oils from soybean oil, linseed oil, castor oil, sunflower oil, fatty acid esters	medical devices (bags, catheters, gloves, intravenous fluid containers, blood bags, medical tubings)
Ethyl cellulose	dibutyl sebacate	coatings free membranes
Cellulose acetate	dibutyl phthalate, PEG 600, propylene glycol, poly(caprolactone triol)	polymeric membranes for transdermal system
Blends of hydroxypropyl	diethyl phthalate	microparticles

methylcellulose and ethylcellulose		
Cellulose acetate phthalate Cellulose acetate trimellitate Hydroxypropyl methylcellulose phthalate Polyvinyl acetate phthalate Shellac	triacetin, acetylated monoglyceride, diethyl phthalate	enteric or colonic drug delivery
Hydroxypropyl methylcellulose acetate succinate	triethyl citrate, triacetin, acetyltriethyl citrate	press-coated tablets for colon targeting
Blends of ethyl cellulose and Eudragit® L	dibutyl sebacate	enteric film coatings
Chitosan salts (chloride, lactate, gluconate)	glycerol, ethylenglycol, propylenglycol, PEGs	free membrane
Blend of native rice starch and chitosan	sorbitol, glycerol, PEG 400	free membrane
Thermoplastic starch Amylose Cassava starch	polyhydric alcohols (glycerol, xylitol, sorbitol), secondary plasticizers (stearic acid, sucrose, urea)	polymeric matrices
Gelatin	glycerol, sorbitol, mannitol, sucrose, citric acid, tartaric acid, maleic acid, PEGs	free membrane
Whey protein Sunflower protein	triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate, glycerol, ethylene glycol, propylene glycol, PEGs	particulate systems
Poly(lactic acid) Poly(lactide-co-glycolide)	oligoesters or low-molecular polyesters, polyesteramides, PEGs, polypropylene glycol, blend of triacetin and oligomeric poly(1,3-butanediol), active ingredients (ibuprofen, theophylline, salts of metoprolol and chlorpheniramine), ethanol, polysorbate 80, water, tricaprin, peanut oil, isopropyl myristate	free membranes polymeric matrices in situ forming systems microparticles
Star-like branched terpolymers of dipentaeythritol, D,L-lactic acid and glycolic acids	triethyl citrate, methyl salicylate, ethyl salicylate, hexyl salicylate, ethyl pyruvate	bioadhesive drug delivery systems
Copolymers of methacrylate esters ammoniated (Eudragit® E grades)	tributyl citrate, triacetin, PEG 200, secondary plasticizer (propylene glycol, diethyl phthalate, oleic acid)	moisture protection and odor/taste masking coatings bioadhesive drug delivery systems
Copolymers of ethyl acrylate and methyl methacrylate (Eudragit® RL and RS grades)	water (relative humidity), citric acid monohydrate, active ingredients (metoprolol tartrate, chlorpheniramine maleate), auxiliary compounds (surfactants, preservatives- methylparaben, solvents, cosolvents, desolvating and coacervating agents)	time-controlled drug release polymeric matrices
Poly(methyl methacrylate)	Triacetin, supercritical carbon dioxide, dibutyl phthalate	microparticles intraocular lenses hard contact lenses
Blend of polyvinyl alcohol and polyvinylpyrrolidon	glycerol, PEG 200 or 400	polymeric membranes for transdermal system
Kollicoat SR30D (aqueous colloidal dispersion of PVA)	triethyl citrate	polymeric matrices
Various non-soluble polymers	benzyl alcohol, benzyl benzoate, ethyl heptanoate, propylene carbonate, triacetin, triethyl citrate	In situ implants

LIMITATIONS

Leaching Effect

The risk of leaching out of certain plasticizers during storage or end-user application constitutes a major safety risk. This leaching effect of Plasticizer is dependent on the type and concentration of dissolution medium. This coupled with other shortcomings (*e.g.* toxicity, poor compatibility) limits some plasticizers from application in the medical, pharmaceutical and food packaging fields. The ideal plasticizer significantly lowers the glass transition temperature (*T*g), is biodegradable, non-volatile, and nontoxic, and exhibits minimal leaching or migration during use or aging.[20]

CONCLUSION

The plasticization of polymers used in pharmaceutical technology can solve a lot of problems during the dosage forms formulation and can improve the quality of the final polymeric drug delivery system. The processing disadvantages can be thus overcome, or even a new technology can be enabled. 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. They do enhance flexibity and plasticity of films so modifying and controlling the drug release characteristics in drug delivery systems.

REFERENCES

1. E. Snejdrova, M. Dittrich, Pharmaceutical Applications of Plasticized Polymers, *Recent Advances in Plasticizers*, Dr. Mohammad Luqman (Ed.), 2012; ISBN: 978-953-51-0363-9, 69-80.
2. G. Wypach, *Handbook of Plasticizers*, Canada: Published by ChemTec, William Andrew Inc; 2004.
3. N. Platzer, The technology of plasticizers, *Journal of Polymer Science: Polymer Letters Edition*, 1982; 20(8): 459.
4. S. B Somwanshi, R. T Dolas et.al., Effects of Drug-Polymer Ratio And Plasticizer Concentration on The Release of Metoprolol Polymeric Microspheres, *Int J Pharm Res Dev*, 2011; 3(3): 139 – 146.
5. http://www.gcsescience.com/o59.htm.
6. C.A. Harper, *Modern Plastics Handbook*, Published by McGraw-Hill, 2000; 2.1-2.88.
7. E. Snejdrova, M. Dittrich, Pharmaceutical used plasticizers, *Recent Advances in Plasticizers*, 2012; 45-68.
8. L.G. Krauskopf, A. Godwin, Plasticizers, In. Charles E. Wilkes, Charles A. Daniels, James W. Summers, *PVC Handbook*, Published by Hanser, ISBN 3-446-22714-8, 173-193
9. http://www.formulation.vinensia.com/2011/08/mechanism-action-of-plasticizers-in.html
10. H. Edmund, Immergut and F. Herman, Mark, Principles of Plasticization, In. *Plasticization and Plasticizer Processes; Advances in Chemistry*, American Chemical Society: Washington, DC, 1965; 6-10.
11. R. F.Boyer, *Plasticization and Plasticizer Processes*, Tappi, 1951; 34: 357.
12. N. A. El-Gendy, Pharmaceutical plasticizers for drug delivery systems, *Curr Drug Deliv.* 2012; 9(2): 148-63.
13. G. Wypych, Effect of Plasticizers on Other Components of Formulation, *Handbook of Plasticizers* (2nd Ed.), Published by ChemTech, 2012; ISBN: 978-1-895198-50-8, p.187-194.
14. T. Karbowiak, H. Hervet, L. Léger, D. Champion, F. Debeaufort, A. Voilley, Effect of plasticizers (water and glycerol) on the diffusion of a small molecule in iota-carrageenan biopolymer films for edible coating application, *Biomacromolecules*, 2006; 7(6): 2011-9.
15. N.E. Suyatma, L. Tighzert, A. Copinet, V. Coma, Effects of hydrophilic plasticizers on mechanical, thermal, and surface properties of chitosan films, *J Agric Food Chem*, 2005; 53(10): 3950-7.
16. C. De Brabander, V. D. Mooter, C. Vervaet, J.P. Remon, Characterization of ibuprofen as a nontraditional plasticizer of ethyl cellulose, *J Pharm Sci.*, 2002; 91(7): 1678-85.
17. G. Rekhi, S. Jambhekar, Ethylcellulose- A polymer review, *Drug Dev Ind Pharm*, 1995; 21(1): 61-77.
18. https://www.colorcon.com/literature/marketing/ex/Suglets%C2%AE/ex_suglet_ads_influ_plast_type_V3_11_2012_1.pdf.
19. L.P. Tan, S.S. Venkatraman, P.F. Sung, X.T. Wang, Effect of plasticization on heparin release from biodegradable matrices, *Int J Pharm*, 2004; 283(1-2): 89-96.
20. Y. Li, C. Wang, G. Wang and Z. Qu, *J. Wuhan Univ. Technol.*, Mater. Sci. Ed., 2008: 23: 100–104.