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Review

Lipids and polymers in pharmaceutical technology: Lifelong companions

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ABSTRACT

In pharmaceutical technology, lipids and polymers are considered pillar excipients for the fabrication of most dosage forms, irrespective of the administration route. They play various roles ranging from support vehicles to release rate modifiers, stabilizers, solubilizers, permeation enhancers and transfection agents. Focusing on selected applications, which were discussed at the Annual Scientific Meeting of the Gattefossé Foundation 2018, this manuscript recapitulates the fundamental roles of these two important classes of excipients, either employed alone or in combination, and provides insight on their functional properties in various types of drug formulations. Emphasis is placed on oral formulations for the administration of active pharmaceutical ingredients with low aqueous solubilities or poor permeation properties. Additionally, this review article covers the use of lipids and polymers in the design of colloidal injectable delivery systems, and as substrates in additive manufacturing technologies for the production of tailor-made dosage forms.

1. Introduction

Lipids and polymers have always been essential components of pharmaceutical dosage forms. Early civilizations already described the preparation of pills and ointments made with these excipients, incorporating for example gums and waxes in their medicinal mixtures (Allen and Ansel, 2013). The Galen's cerate (AD 200), better known today as cold cream, is a classic example of a lipid-based formulation as it consists of a stabilized dispersion of water in a lipidic continuous phase (Pastore, et al., 2015). In those early days and following centuries, lipids and polymers were obtained from natural sources, and mainly served as support materials or bulking agents for the active compound. With the advent of modern medicine, the progress in chemistry and the industrialization of the manufacturing processes, excipients evolved and gained in purity, becoming exploited for diverse functionalities. In the 19th century, more purified polymeric materials such as gelatin began to be used for the preparation of capsules and tablets (Cowen and Helfand, 1990). Today, drug formulators have at their disposal a wide range of natural, semi-synthetic or completely man-made lipids and polymers that are produced in various pharmaceutical grades, allowing their administration *via* different routes (oral, topical, parenteral or rectal) (Allen and Ansel, 2013).

Despite considerable structural differences, lipids and polymers often fulfill similar functions. They may be used to prepare dispersion/solubilization matrices, controlled release formulations and colloidal targeted systems (nanoparticles and vesicles), and act as permeation

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enhancers (Aulton and Taylor, 2018). Nevertheless, important differences (e.g. mechanical properties, melting point, biodegradability, solubility, etc.) make them suitable for achieving distinct tasks. For example, poly(ethylene glycol) (PEG) is employed to produce water-soluble suppositories, whereas fatty vehicles are used to manufacture suppositories that melt at body temperature (Aulton and Taylor, 2018). Lipids and polymers can also have complementary roles. This is commonly exploited in modern pharmaceutical technology. For instance, lipids are added as antifriction agents to polymeric particle mixtures for the manufacturing of tablets, and hydrocolloids serve as stabilizers in oil-in-water emulsions (Aulton and Taylor, 2018).

This review article provides an overview of recent advances in the use of polymers and lipids in pharmaceutical technology. It stems from the scientific presentations given at the Annual Scientific Meeting of the Gattefossé Foundation 2018 ("*Journées Galéniques of Saint-Rémy de Provence*", France, September 5–8th, 2018) by academic and industry experts, all of whom are coauthors of this manuscript. Given the breadth of the topic, the review focuses on areas of long-standing interest for the pharmaceutical industry and on selected emerging technologies. These include sustained release formulations, oral delivery of poorly water-soluble drugs and peptides, drug targeting technologies, transfection methods, and the on-demand production of customized delivery systems by three-dimensional (3D) printing technologies.

2. Polymer-based oral formulations

The pharmaceutical applications of polymers in oral dosage forms span from their use as binders in tablets to viscosity and flow-controlling agents in liquids. Their wide range of physical (i.e. density, particle size) and chemical properties (i.e. molecular weight, substitutions) is important to overcome formulation challenges. Polymers can be employed as film coatings to mask the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics (Table 1). Moreover, the possibility to combine different polymeric excipients allows the design of novel and robust dosage forms, as well as the production of controlled release drug delivery systems. This section focuses primarily on the application of polymers in controlled release tablets and amorphous solid dispersions (ASDs).

2.1. Controlled release matrix systems

Different formulation strategies can be adopted to prepare controlled release solid dosage forms. Polymeric matrix tablets are the most popular ones for oral drug administration as they are a convenient and relatively low-cost way to modulate the release of active pharmaceutical ingredients (APIs) with a wide range of solubilities and dosage strengths. However, formulating a robust controlled release matrix requires knowledge of the physicochemical properties of both the drug and the polymer. Commonly used polymers for controlled release are reported in Table 1. Some examples of commercialized drugs using these polymers are felodipine, verapamil, nifedipine, and gliclazide (PharmaCircle, August 18th, 2018).

The underlying mass transport mechanisms controlling drug release from polymeric controlled release tablets may vary in complexity (e.g. Borgquist et al., 2006; Caccavo et al., 2017; Chirico et al., 2007; Kaunisto et al., 2011; Siepmann et al., 2010, 2017; Siepmann and Siepmann, 2008, 2012). Depending on the physico-chemical properties of the polymer (e.g., solubility in water, swelling behavior) and the drug (e.g. solubility in the swollen polymeric system and in the surrounding release medium), a variety of phenomena might be involved (Grassi et al., 2004; Kaunisto et al., 2010). These include water penetration into the system, drug dissolution, drug diffusion (with constant or time- and position-dependent diffusion coefficients), polymer swelling, drug–polymer interactions (e.g. ionic, van der Waals), polymer dissolution, polymer degradation and tablet disintegration. Importantly, not all of these processes occur in all cases and even when they occur, they may not contribute significantly to the resulting drug release rate. For instance, if several mass transport processes occur sequentially and one of them is much slower than the others, it will be rate-limiting and dominate the overall transport.

As an example of controlled release polymeric matrix tablets, HPMC-based matrix tablets (Kaunisto et al., 2013; Siepmann and Peppas, 2001) are described in more detail in this section. Fig. 1 illustrates their possible inner structure during drug release. On the left side, the well-stirred release medium (bulk fluid) is shown. On the right side, the inner structure of the still dry tablet core is represented. It consists of a polymer network in which non-dissolved drug particles (represented as black circles) are trapped. Depending on the solubility of the drug in the dry polymer matrix, a certain amount of API (eventually all) might be dissolved (i.e. being in the form of individual drug molecules) in the polymeric system (depicted as stars in Fig. 1). The extent of such drug dissolution in the dry polymeric network can also strongly depend on the manufacturing procedure of the tablet.

Once the tablet comes into contact with aqueous body fluids, water penetrates the system and as soon as a critical water concentration is reached, the HPMC chains undergo a relaxation process (swelling). This

Table 1
Common polymers used in pharmaceutical technology (Jones, 2004; Maderuelo, et al., 2011).

Vinyl polymers	Cellulose ethers	Other polysaccharides	Miscellaneous		
Polymethacrylates, poly(acrylic acids), poly(vinyl alcohol), poly(*N*-vinyl pyrrolidone) (PVP)	Methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), HPMC acetate-succinate, carboxymethylcellulose	Chitosan, carrageenan, xanthan gum, alginic acid, tragacanth, acacia gum	Poly(lactide), poly(lactide-*co*-glycolide),poly(ε-caprolactone)	PEG	Silicone
Primary applications					
Film coating, binders, viscosity modifiers, solubilizers, controlled release	Film coating, binders, films, controlled release, microencapsulation, solubilizers, stabilizers, thickeners	Immediate and controlled release, thickeners, peptide delivery, microencapsulation, permeation enhancer	Controlled release	Controlled release, thickeners, binders	Immediate and controlled release
Common dosage forms					
Oral solid, parenteral, topical	Oral solids, topical, injectables, ophthalmic, disperse systems, wound dressings	Oral solids, injectables, topical	Injectables, vaccines, implants	Oral solids, liquids, semi-solids	Medical devices, implants

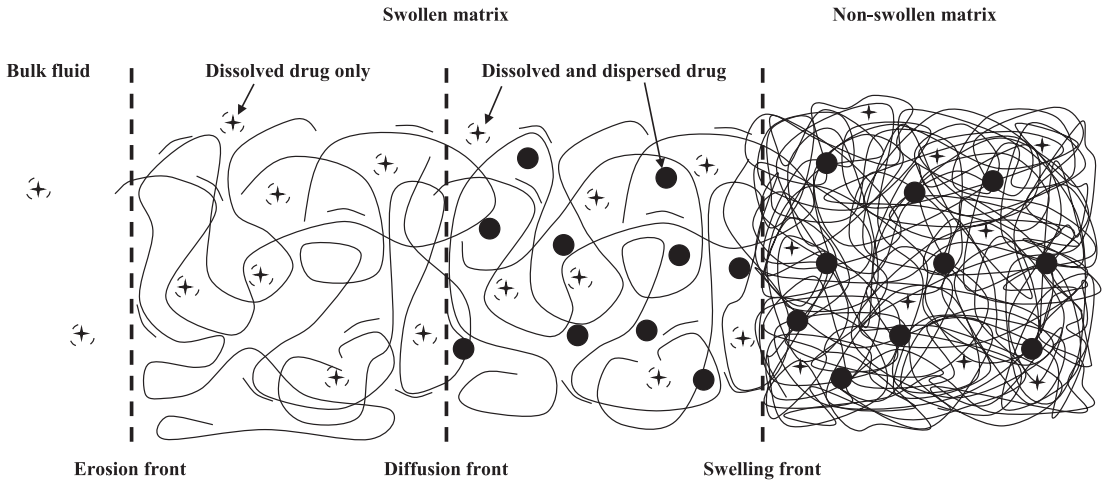

Fig. 1. Schematic representation of a HPMC controlled release matrix tablet during drug release. The stars and black circles represent dissolved and dispersed drug, respectively. The following (moving) boundaries can be distinguished: (i) an "erosion front", separating the bulk fluid from the matrix tablet; (ii) a "diffusion front", separating the swollen polymer matrix containing dissolved drug only and the swollen polymer matrix containing dissolved and dispersed drug; and (iii) a "swelling front", separating the swollen and non-swollen polymer matrix. Details are described in the text. Adapted from Siepmann and Siepmann, 2008, with permission from Elsevier.

creates a boundary called the "swelling front" that separates the swollen and non-swollen matrix, and that moves (often slowly) towards the center of the tablet. Importantly, drug mobility in the swollen matrix is generally substantially greater than in the dry part of the tablet. On the other hand, significant polymer swelling also leads to increased system dimensions, which imposes longer diffusion pathways to be overcome. Hence, substantial polymer matrix swelling might slow down drug release when compared to less intensively swelling polymers. Depending on the type of drug and polymer used, the "*increased drug mobility effect*" or the "*increased diffusion pathway length effect*" might prevail, resulting in faster or slower drug release compared to systems based on less swellable polymers.

Once the drug molecules are dissolved (individualized) and become sufficiently mobile, they diffuse out of the tablet due to concentration gradients. If the drug loading is higher than the drug's solubility in the swollen polymer matrix, dissolved and non-dissolved drug co-exist. Importantly, since only the dissolved drug can diffuse, the absolute release rate is dictated by the concentration of *dissolved* drug (and not by the *total* drug concentration). The swollen polymeric matrix might be saturated with the drug, and the released drug be rapidly replaced by the dissolution of the locally remaining non-dissolved drug excess. Hence, the limited solubility of the drug can play a major role in the control of drug release and the resulting release rate from polymeric matrix tablets. Although often ignored, such "*limited drug solubility effects*" can be of importance even in the case of freely water-soluble drugs and highly swollen polymer matrices; the amount of water present in the swollen hydrogel might be insufficient to dissolve all of the drug (e.g. Siepmann et al., 2017). With time, the amount of non-dissolved drug locally decreases. Once all the drug excess is dissolved at a certain position, the released drug molecules are no more replaced and the concentration of dissolved drug at this position decreases. Consequently, another front can be observed: the so-called "diffusion front". This separates the swollen polymer matrix, which is free of non-dissolved drug, from the swollen polymer matrix, which still contains non-dissolved drug excess (Fig. 1). Furthermore, since HPMC is water-soluble, the macromolecules start to disentangle from the polymeric network above a critical water threshold concentration (Ju et al., 1995). This occurs at the "matrix – release medium interface", which is also called the "erosion front".

The importance of the above described mass transport phenomena occurring in HPMC matrix tablets depends on the type of HPMC (e.g. polymer molecular weight and degree of substitution), nature of the drug (e.g. with a specific solubility and mobility in the polymeric matrix) and composition of the system (e.g. drug and polymer contents as well as potential presence of other compounds) (e.g. Viridén et al., 2011a,b). In addition, the conditions in the surrounding bulk fluid can affect the importance of the involved mass transport phenomena and resulting drug release kinetics (e.g. Williams et al., 2009). Generally, the drug release rate from hydrophilic matrix tablets is determined by several parameters such as the composition of the formulation, the manufacturing process, and the properties of the drug itself and of the polymers in the matrix. Indeed, molecular weight, hydrophilicity, degree of cross linking and degree of substitution are all polymer parameters known to influence the swelling and erosion of the matrices.

One of the major potential challenges encountered during formulation development involves minimizing undesired burst effects and achieving constant drug release rates (zero order kinetics, if these are targeted), since generally release rates are initially higher and monotonically decrease with time. Often, curve-shaped release profiles are obtained, not linear profiles. Moreover, providing robust drug release kinetics in the human body constitutes another significant challenge. For example, the mechanical stress experienced in the gastrointestinal tract might accelerate the destruction of the swollen polymer matrix, which may in turn lead to variable drug release rates in the patient.

2.2. Amorphous solid dispersions

ASDs have become key enabling tools for formulating poorly water-soluble drug molecules (Baghel et al., 2016; Huang and Dai, 2014; Paudel, et al., 2013). As such, they are of great value as it has been estimated that 70% of new drug molecules under development are insoluble yet highly permeable drug compounds (Biopharmaceutical Classification System (BCS)-II), and another 20% are insoluble and poorly permeable (BCS-IV) (Benet et al., 2011; Thayer, 2010). In pharmaceutical sciences, the term ASD is generally used to describe a glassy solid solution of an amorphous homogeneous miscible blend composed of a drug compound and a polymer excipient (Fig. 2) (Breitenbach and Magerlein, 2003; Chiou and Riegelman, 1970). In ASDs, the disordered amorphous phase is kinetically more soluble, providing sufficient driving force to enhance plasma concentrations as long as drug crystallization can be prevented *in vivo* (Hancock and Parks, 2000). This higher solubility and higher dissolution rate may

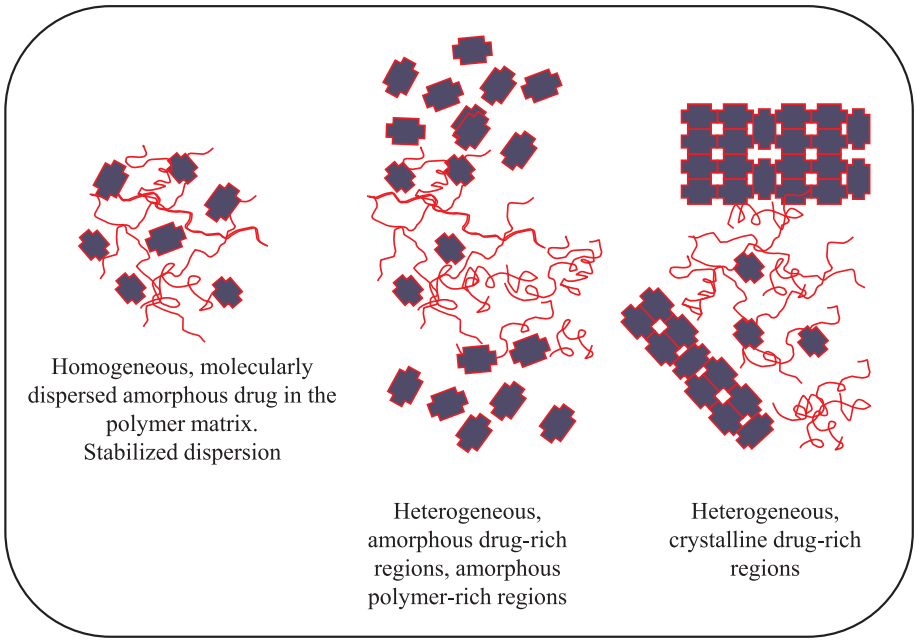

Fig. 2. Possible structures for drug-polymer dispersions. **Left**: drug is molecularly dispersed (amorphous) in the polymer matrix; a preferred stabilized ASD (single glass transition temperature). **Middle**: phase separated with amorphous drug-rich and amorphous polymer-rich phase (likely two glass transition temperatures). **Right**: phase separated with a crystalline drug-rich phase and an amorphous polymer-rich phase (Huang and Dai, 2014; Meere, et al., 2017).

enhance bioavailability, as a drug must be in solution to be orally absorbed in the gastrointestinal tract and reach systemic circulation. The solubility enhancement may be low, one to two-fold, or more significant such as the 10-fold achieved with amorphous novobiocin. It may also reach as much as 1600-fold or higher (Hancock and Parks, 2000); although, most supersaturations achieve concentrations between 10 and 60-fold the crystalline solubility (Almeida e Sousa et al., 2015).

While it is possible to develop a dosage form using an amorphous drug substance, addition of anti-nucleating polymers is often required to stabilize the drug compound in the amorphous phase. Nabilone (Cesamet®) and verapamil (Isoptin-SR-E®) are examples of early-marketed ASDs, consisting of the API melt-extruded in PVP and HPC/HPMC, respectively (Huang and Dai, 2014; Ting et al., 2018).

ASDs are prepared using several techniques including grinding, solvent evaporation (e.g. lyophilization, spray-drying, spray-freezing, spray-congealing), fusion (e.g. hot-melt extrusion, HME), co-precipitation (e.g. supercritical fluid precipitation) (Chauhan et al., 2005) and more recently 3D printing (Kyobula et al., 2017). The types of stabilizing polymers used have expanded from the cellulosic polymers and synthetic polymers, such as HPMC and PVP, to novel ones designed specifically to stabilize the ASD (Arca et al., 2018; Ting et al., 2018). Arca et al. (2018) synthesized ω-carboxyalkanoate-modified cellulose polymers to stabilize rifampin, which prevented the acid-catalyzed degradation occurring under gastric conditions, ensuring complete release of the API and increasing bioavailability. Moreover, combinations of polymers, binary and ternary systems, have been explored to further optimize polymer dispersions. In these cases, the main challenge lies in maintaining miscibility of all the components without leading to crystallization of the drug compound and changes in the release profiles of the ASD. The additional components may also include surfactants and lipids which are added to enhance dissolution rates and solubilization *in vivo* (vitamin E TPGS, Gelucire® 44/14, polysorbate 80, Kolliphor® EL and HS15). The inclusion of these solubilizers has demonstrated improved drug release and enhanced bioavailability (Bley et al., 2010). However, the addition of dissolution enhancers can also create the risk of phase separation, immiscibility in the polymer blends, and precipitation of the crystalline drug molecule either in the matrix or upon dissolution; and may also reduce *in vivo* release of the API reducing absorption (Chen et al., 2016; Deshpande et al., 2018; Harmon et al., 2016). Other modifications involve the incorporation of cyclodextrin inclusion complexes or spraying onto a substrate such as mannitol. A high surface area material such as magnesium aluminometasilicate or silicon dioxide may be added to enhance stability and bioavailability (Alhijjaj et al., 2017; Bley et al., 2010). Despite the numerous publications on ASDs, the number of polymers used in products remains limited to a few (HPMC, HPC, HPMC acetate succinate, PVP, PVP-vinyl acetate, PEG, poloxamer), reflecting the complexity behind regulatory approvals of novel polymers and their adoption by the pharmaceutical industry (Huang and Dai, 2014).

The melting temperature can be considered the most important parameter of the crystalline state, however in the case of ASDs the glass transition temperature, an indicator of the onset of molecular mobility, defines the significant properties of the amorphous state (Eisenberg, 1993). A miscible homogeneous solid dispersion with a single glass transition temperature is preferred over an immiscible dispersion with multiple glass transition temperatures because of its enhanced stability due to the favorable drug-polymer interactions and reduced molecular mobility (antiplasticization). Non-homogeneous or phase-separated dispersions, consisting of drug-rich amorphous domains in the amorphous polymer (two glass transition temperatures) as well as polymer dispersions containing crystalline drug (Fig. 2), do not provide the desired stability or solubility enhancement. The strength of the non-covalent drug-polymer interactions (H-bonding, van der Waals, ionic interactions, electrostatic, hydrophobic, ion-dipole) (Baghel et al., 2016) is critical as these inhibit the potential for crystallization; however, they may also reduce the liberation of the drug molecule from the polymer matrix. Generally, higher molecular weight polymers with reduced hygroscopicity are preferred (Huang and Dai, 2014). However, plasticization by water as the polymer dissolves, can increase mobility and migration of drug molecules, and may subsequently result in crystallization. The success of a drug-polymer amorphous dispersion is often described in terms of a *spring* and *parachute* (Fig. 3). As the fluid penetrates the solid amorphous dispersion, the polymer dissolves along with the amorphous drug molecules to create a supersaturated solution with respect to the solubility of the crystalline solid (*spring*). The prolonged duration of this supersaturation is described as the *parachute* and contributes to the success of the ASD in enhancing the absorption of the drug molecule *in vivo*. However, the challenge is to maintain the supersaturation. Bergstrom and coworkers (Edueng et al., 2017) showed that modifying surface properties was important; indeed, even low amounts of polymer (0.001 to 0.01% of HPMC) could reduce the crystallization at the water interface. However, in practice, the

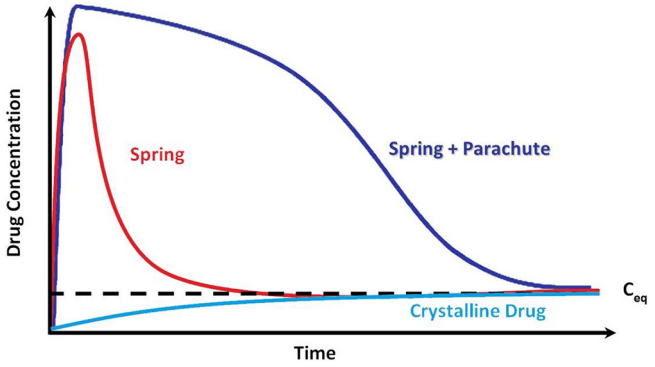

Fig. 3. Dissolution to form a supersaturated solution followed by rapid crystallization (*spring*) or prolonged supersaturation (*spring* + *parachute*) of a drug compound with an equilibrium solubility, C_{eq}. (Brough and Williams, 2013; Meere, et al., 2017). Reproduced from Brough and Williams (2013) with permission from Elsevier.

preferred drug loads in ASDs vary from 20% to 50% depending on the crystallization risk of the drug compound, whether it is a fast or slow crystallizer (Friesen et al., 2008).

Various modeling attempts to aid in the rational selection of the ASD polymer excipients have included Hildebrand Solubility Parameters, δ, Flory-Huggins χ-interaction parameter, and different molecular descriptors such as mobility, enthalpic driving force, hydrogen bonding, entropic barrier to crystallization, molecular weight, number of rotating bonds, etc. (DeBoyace and Wildfong, 2018). A recent molecular modeling study by Fridgeirsdottir et al. (2018) evaluating the results of 60 solid dispersions with 10 molecularly different drug molecules (see Section 5), three different polymers and two manufacturing processing methods (spray-drying and HME), suggested that the key important parameters for achieving higher ASD stability were: (1) increased glass transition of the ASDs relative to that of the drug molecule; (2) increased molecular flexibility of the drug molecule (lower propensity to crystallize); and (3) decreased number of drug molecule donor H-bonds. The latter parameter was attributed to the enhanced drug-drug molecular interactions or drug-water molecular interactions resulting from APIs with increased H-bond donors compared to those with lower H-bond donor capabilities. These molecules did not form enhanced drug-polymer interactions, thus reducing stability (Fridgeirsdottir et al., 2018). Future research should focus on better understanding the selection of polymer combinations, with or without additives such as surfactants and lipids, to further enhance bioavailability and facilitate the development of standard prototype formulations based on the physicochemical properties of the drug molecules. The challenges with ASDs are several and include the selection of polymers and combinations, and the accommodation of high API doses into a single dosage form. In addition to the above, it is important to ensure chemical and physical stability in the solid state over the shelf-life of the drug product, and to maintain sufficient supersaturation of the drug *in vivo* to provide higher bioavailability. Despite the significant interest and the number of publications on amorphous solid dispersions, there have been less than 35 FDA-approved ASDs to date (Huang and Dai, 2014, Huang and Williams, 2018). Yet, ASDs have become an important part of a formulator's armamentarium, enabling non-clinical safety and toxicity studies as well as bringing insoluble, poorly orally bioavailable drug compounds to the market particularly in cases where molecular design does not permit amelioration of the properties of potent drug compounds.

3. Lipid-based oral formulations

Lipids play an essential role in the oral delivery of a wide variety of APIs. They are highly versatile in terms of structure – a fact often recognized with polymers, but rarely highlighted for lipids. Lipids are natural dietary components and besides serving as sources of energy, they are suitable carriers for the delivery of poorly water-soluble vitamins and nutrients to the body through favorable interactions with endogenous bile components. Lipid structures are digested by lipases to form smaller absorbable components (monoglycerides and fatty acids). These provide the specific and non-specific interactions with lipophilic drugs that enable their solubilization and absorption (Porter et al., 2007). This section of the article focuses on the dynamic self-assembly structures that lipids adopt in aqueous environments following administration, and on their impact on drug delivery.

Lipid-based excipients are ingredients derived from vegetable oils, fatty acids or waxes. Vegetable oils comprise triacylglycerols (fatty acid esters of glycerol), phospholipids and lipophilic vitamins (Jannin et al., 2008). They are used to produce a wide variety of ingredients by various processes such as hydrogenation, esterification (of the fatty acids), transesterification, and ethoxylation. The latter three processes use alcohols to produce more hydrophilic ingredients. Alcohols can be either small molecules such as glycerol or propylene glycol, or polymers like PEG or polyglycerols. The physical properties of these lipid-based ingredients are mainly influenced by the unsaturation in fatty acids, the fatty acid chain length and potential ramification, the type of alcohol selected and the number of ester/ether functions (polarity). Hence, these ingredients can be either liquid or solid, exhibiting various polymorphic phases (Brubach et al., 2004), polar but insoluble (swelling – forming liquid crystalline phases - or not in contact with aqueous environment) or water-soluble (forming micelles) (Small, 1968). The critical material attributes of lipid-based excipients are linked to the origin and quality of the fatty acids and alcohols as well as process conditions to minimize the creation of impurities potentially affecting the functionality of those excipients (Jannin et al., 2014).

3.1. Oily solutions and self-emulsifying drug delivery system

The functionality of lipid systems with respect to transport and oral delivery of poorly water-soluble APIs is critically linked to their propensity to self-assemble in aqueous environments (Fig. 4). The structures formed depend on the specific lipids present, and the way in which the molecules can geometrically pack together in the self-assembled structure. The geometry of packing of the lipids can be predicted using the concept known as the 'critical packing parameter' which relates the effective molecular dimensions (headgroup size, tail length and volume) to the likely structures formed (Israelachvili et al., 1976), and can be probed using conventional colloidal characterization approaches. The structure of the particles formed also dictates their surface characteristics and consequent interaction with bio-interfaces such as mucus. Drugs have differential affinities for these structures (Kossena et al., 2003), and understanding the formation and significance of the latter has been a holy grail in the field. Importantly, it is the pre-absorptive environment and not necessarily the formulation itself that ultimately dictates drug absorption. In the case of poorly water-soluble, weakly basic drugs, digestion of ester-containing lipids is key for drug solubilization prior to absorption from the small intestine. Characterizing this highly dynamic and complex system is key to understanding the determinants of lipid self-assembly, drug solubilization and absorption, and constitutes an evolving field that is currently being addressed using advanced time-resolved techniques (Warren et al., 2011).

Lipid-based excipients are currently used in various oral dosage forms, such as oily solutions and self-emulsifying drug delivery systems (SEDDS), to increase the bioavailability of poorly soluble drugs (Table 2). The enhancement in bioavailability by oily solutions and SEDDS is, for poorly water-soluble lipophilic drugs, mainly due to the pre-dissolution of the drug in the formulation, which spares the need for this step in the gastrointestinal tract. The performance of such systems is dependent on their ability to form colloidal phases intraluminally

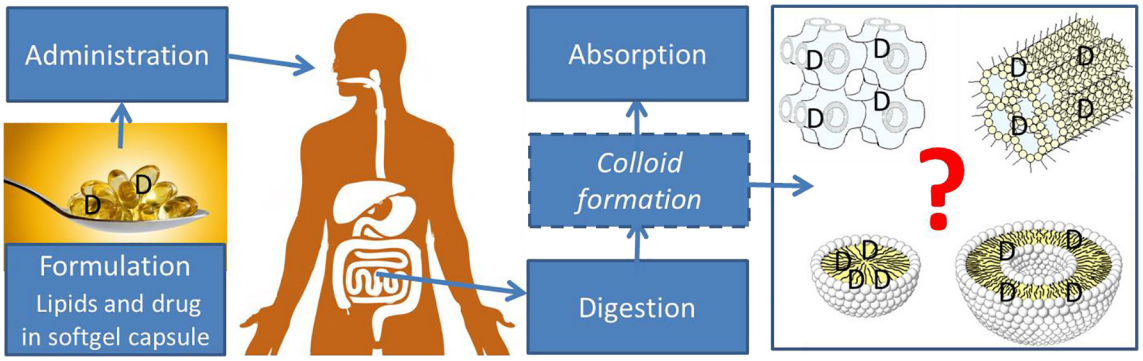

Fig. 4. Lipid formulations, often filled into a soft gelatin capsule, undergo dispersion and digestion of the lipids by lipases in the gut, followed by self-assembly of the lipid digestion products into colloidal structures. The fate of the co-administered drug (D) is dictated by its interaction with those structures prior to absorption (as illustrated in last panel on the right).

that maintain the drug in a solubilized state. These systems also increase the kinetics of drug absorption by creating a local supersaturation close to the intestinal epithelium through the absorption of lipid metabolites (Yeap et al., 2013). The translation of this technique into commercial drug products is important as over 150 oral products are currently marketed with the technology referred as 'lipid & SEDDS' in PharmaCircle. Most of these formulations are composed of liquid lipid excipients that are encapsulated in either soft or hard gelatin capsules.

In the last decade, the interest in 'solid SEDDS' has risen and currently various solidification techniques or processing technologies of semi-solid or solid excipients are being investigated. Among these, the HME process (Vithani et al., 2017) and 3D printing (see Section 5) (Jannin et al., 2017) allow solid SEDDS to be obtained directly without a solid phase carrier, while maintaining their self-emulsifying and solubilizing properties. The same approach is now being used to enhance the oral bioavailability of therapeutic peptides (Section 3.2) (Menzel et al., 2018) and nucleic acid-based therapeutics (Hauptstein et al., 2015), given their ability to limit the metabolic degradation of these molecules and increase the intestinal absorption. Upon contact with body fluids such as the intestinal fluid, SEDDS spontaneously form oily droplets in the range of 50–500 nm. Drugs (e.g. peptides and nucleic acids) exhibiting a log $D_{SEDDS/release\ medium} < 2$ are immediately released from these oily droplets (Bernkop-Schnürch and Jalil, 2018). Therefore, a sustained release can likely only be achieved by the formation of hydrophobic ion pairs with a preferred log D > 3 (Griesser et al., 2017b). In case of a low log D, the release from the oily droplets is mainly dictated by the drug absorption process from the gastrointestinal mucosa. Alternatively, in case of a log D > 3, the drug release can be controlled by the degradation of the oily droplets in the intestine by lipases. Furthermore, a controlled drug release can be achieved by the incorporation of amphiphilic polymers in SEDDS keeping the drug for a prolonged time period in the oily droplets due to ionic interactions such as between a hydrophobized polycation and an anionic drug.

Even with adequate dissolution, the bioavailability of many drugs is limited by efflux mechanisms that non-specifically shuttle xenobiotics back out of the absorptive enterocytes. Lipids (and some amphiphilic polymers) can interact with the proteins that facilitate these processes as a decoy to enable the drug to passage further into the enterocytes and avoid this obstacle to bioavailability (Li et al., 2013; Werle, 2008). Most absorbed molecules, including drugs, will then exit the cellular environment through the dominant passage into the portal blood supply, due to the high blood flow acting as an effective sink. However, highly lipophilic drugs with a defined set of physicochemical properties, and in the presence of certain lipids, may also take the less dominant route of entering the bloodstream *via* the lymphatic system (Porter et al., 2007).

3.2. SEDDS for the delivery of poorly permeable drugs

SEDDS have the potential to facilitate the delivery of poorly permeable drugs. Emerging data shows that their combination with polymers could improve the oral absorption of therapeutic peptides (Mahmood and Bernkop-Schnürch, 2018). Polymeric excipients can grant SEDDS diverse properties, such as drug release control, mucus permeation or mucoadhesion, zeta potential modulation and cell penetration.

The ability to permeate the mucus gel layer and reach the underlying epithelial membrane is essential for certain drug delivery systems. In comparison to other types of nanocarriers such as nanoparticles and liposomes, SEDDS exhibit greater mucus-permeating properties (Griesser et al., 2018). In particular PEGylated surfactants like Kolliphor® and polysorbates seem to provide a slippery surface for SEDDS as their hydrophilic PEG substructures exhibiting muco-inert properties

Table 2
Examples of oily solutions and SEDDS in marketed drug products (extracted from a PharmaCircle search with the technology keyword 'lipid & SEDDS' performed on August 23rd, 2018).

Type of formulation	Composition (excluding antioxidants)	API (Marketed drug products, manufacturer)
Oily solution	Medium chain triglycerides	Calcitriol (Rocaltrol, Roche Laboratories)
Oily solution	Medium chain triglycerides, lecithin, caprylic/capric mono/diglycerides, PEG	Dutasteride (Avodart, GlaxoSmithKline)
SEDDS	Linoleyl polyoxyl-6 glycerides	Ethinylestradiol / norethindrone acetate (Taytulla, Allergan)
SEDDS	Ethanol, linoleyl polyoxyl-6 glycerides, corn oil	Cyclosporine A (Sandimmune, Novartis)
SEDDS	Ethanol, propylene glycol, corn oil, polyoxyl-40 hydrogenated castor oil (Cremophor* RH40)	Cyclosporine A (Neoral, Novartis)
SEDDS	Caprylocaproyl polyoxyl-8 glycerides (Labrasol ALF)	Enzalutamide (Xtandi, Astellas)
SEDDS	Lauroyl polyoxyl-32 glycerides (Gelucire 44/14), PEG, HPC, sodium starch glycolate	Fenofibrate (Lipofen, Kowa Pharm.)
SEDDS	Polyoxyl-35 castor oil (Cremophor* EL), oleic acid, Ethanol	Ritonavir (Norvir, Abbott) - discontinued
SEDDS	Stearoyl polyoxyl-32 glycerides (Gelucire 50/13), sorbitan monooleate, soybean oil	Isotretinoin (Absorica, Sun Pharma)

* Cremophor® has been rebranded as Kolliphor®.

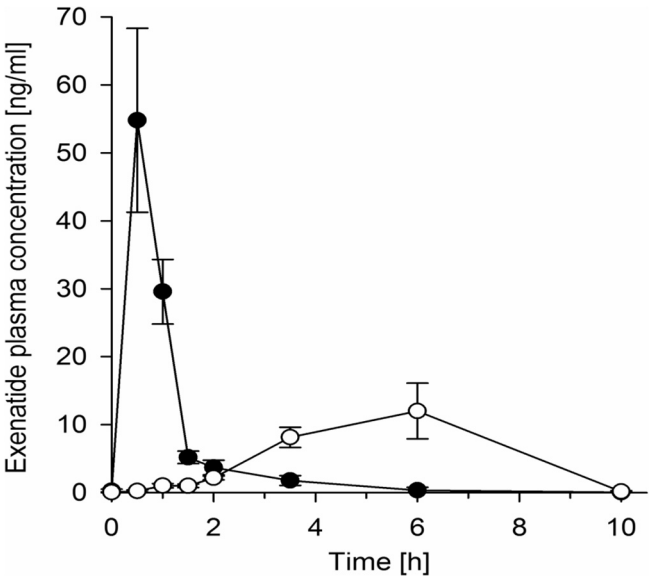

Fig. 5. Plasma concentration–time curve of exenatide in rats after oral administration *via* highly mucus-permeating SEDDS (dose: 150 μg) (○) and after subcutaneous injection of exenatide solution (dose: 20 μg) (●). Indicated values are the means of at least three experiments ± standard deviation; adapted with permission from Elsevier (Menzel, et al., 2018).

assemble on the surface of the oily droplets. Menzel et al. (2018), for instance, reported highly mucus-permeating SEDDS for the administration of exenatide, achieving an oral bioavailability of 14.6% *vs.* subcutaneous injection (Fig. 5) (Menzel et al., 2018). As an alternative to PEG-coating, SEDDS can be coated with mucolytic enzymes such as papain. *Via* hydrophobic ion-pairing with oppositely-charged ionic surfactants (e.g. deoxycholate), the proteolytic enzyme can be anchored on the surface of the oily droplets from where it will cleave mucus glycoproteins as the droplets make their way to the epithelium (Menzel and Bernkop-Schnürch, 2018).

In addition to mucus-permeating capabilities, mucoadhesive properties can improve SEDDS' efficacy. Increasing their residence time on mucosal membranes extends the time that is available for drug absorption, which may in turn lead to a prolonged therapeutic effect. By incorporating hydrophobized mucoadhesive polymers into SEDDS, their bioadhesion can be dramatically increased. Chitosan-fatty acid conjugates may be used for this purpose (Efiana et al., 2017), as well as hydrophobic thiolated polymers capable of forming covalent bonds with cysteine-rich mucus substructures, such as thiolated Eudragit® S100 (Leonaviciute et al., 2017). Sakloetsakun et al. (2013), for instance, showed a significantly increased systemic insulin exposure in rats after oral administration of insulin-loaded SEDDS containing a thiolated polymer (Sakloetsakun et al., 2013).

As mucus carries a net negative charge because of sialic and sulfonic acid residues, oily droplets exhibiting a positive zeta potential get retained in the mucus due to ionic interactions. In contrast, uncharged or negatively charged oily droplets exhibit comparatively higher mucus-permeating properties. In close proximity to the cell membrane, however, the situation changes completely as now adhesion rather than repulsion is the aim. Similar to the mucus, intestinal epithelial cells exhibit a negative surface charge due to the presence of high-density negatively charged molecular species (including polar carbohydrates and charged amino acid side chains), which repel negatively charged nanocarrier systems from the membrane (Bennett et al., 2014). To overcome this repulsion, a positive zeta potential seems to be advantageous. For this purpose, SEDDS that change their zeta potential from a negative charge throughout the mucus gel layer towards a positive zeta potential on the absorption membrane have been developed. Zeta potential-shifting SEDDS have been designed by combining a cationic surfactant and a phospholipid (1,2-dipalmitoyl-*sn*-glycero-3-phosphatidic acid) in the SEDDS pre-concentrate. Due to the enzymatic cleavage of the phosphate ester on the phospholipid by intestinal alkaline phosphatase, the oily droplets were shown to change their zeta potential in the demanded manner (Suchaoin et al., 2016). The shift in zeta potential was even more pronounced when phosphorylated hydroxypropyl starch was incorporated in the SEDDS (Griesser et al., 2017a). Unfortunately, the inclusion of polymers in SEDDS is in many cases limited by their poor solubility in the lipophilic phase. Because of this limitation, certain polymers cannot be incorporated at all or only to a minor extent, meaning that the desired effect cannot be achieved.

Another strategy intended to improve attachment and uptake by mucosal epithelial cells involves the use of cell-penetrating peptides. The HIV-1 Tat-protein 49–57 cell-penetrating peptide, for instance, has been covalently attached to oleic acid, providing a lipophilic anchor in the oily droplets formed by SEDDS. Improved cellular uptake of Tat-decorated SEDDS was confirmed through confocal microscopy, which revealed clathrin- and caveolae-mediated endocytosis as the major pathways for internalization (Mahmood et al., 2016).

4. Nanocarriers based on lipids and polymers

4.1. Lipidic and polymeric vesicles

Vesicles consist of an aqueous lumen enclosed by bilayer membranes, which can be composed of supramolecular amphiphilic lipids or synthetic block copolymers, forming liposomes or polymersomes, respectively. The first liposomes were reported by Bangham et al. (1965), who demonstrated the very slow diffusion of ionic species through phospholipidic bilayers with the aim of mimicking biological cell membranes. Based on the number of bilayers, vesicles can be classified as unilamellar or multilamellar. Unilamellar vesicles are of particular interest in biomedical applications, and can be further classified according to their size as small, large and giant unilamellar vesicles. Three decades later, Zhang and Eisenberg (1995) published the first report on vesicle formation with amphiphilic poly(styrene)-*b*-poly(acrylic acid) copolymers, which were later on named polymersomes by Discher et al. (1999). The latter established robust relationships between amphiphilic molar mass, bilayer thickness and membrane properties on PEG-*b*-polybutadiene copolymers (Discher and Eisenberg, 2002). Since then, polymersomes have emerged as promising bioinspired compartments for various applications (De Oliveira et al., 2012).

Liposomes and polymersomes are extensively investigated as nanocarriers for loading, delivering and releasing hydrophobic or hydrophilic drugs, biologics and diagnostic agents in a controlled manner (Palivan et al., 2016; Torchilin, 2005; Upadhyay et al., 2009). In the case of liposomes, given their resemblance to cellular structures, they are also widely exploited to study the biophysical properties of biological membranes (e.g. stability, permeability, phases, domains and curvature), and to develop membrane-based biosensors (Osaki and Takeuchi, 2017). Today, liposomes are part of vaccine and cosmetic formulations, but perhaps the most popular application remains their use as nanomedicines (Allen and Cullis, 2013). Liposomes have provided clinical benefits for over 20 years since the approval of Doxil® in 1995 (Fig. 6). The latter is an injectable PEGylated liposomal formulation of doxorubicin (ca. 80 nm) (Wibroe et al., 2016) with an improved therapeutic index compared to free doxorubicin. It is currently approved for the treatment of AIDS/HIV Kaposi's sarcoma, multiple myeloma and ovarian cancer. The PEG coating reduces the uptake of the liposomes by the mononuclear phagocytic system, extending the circulation time (elimination half-life of 20–30 h in human), and in some cases increasing doxorubicin deposition in permeable tumoral areas that exhibit the so-called enhanced permeability and retention (EPR) effect (Barenholz, 2012; Maeda, 2010). There are currently ca. 15 types of liposome-based pharmaceutical products on the market, and intensive development of liposomal formulations is

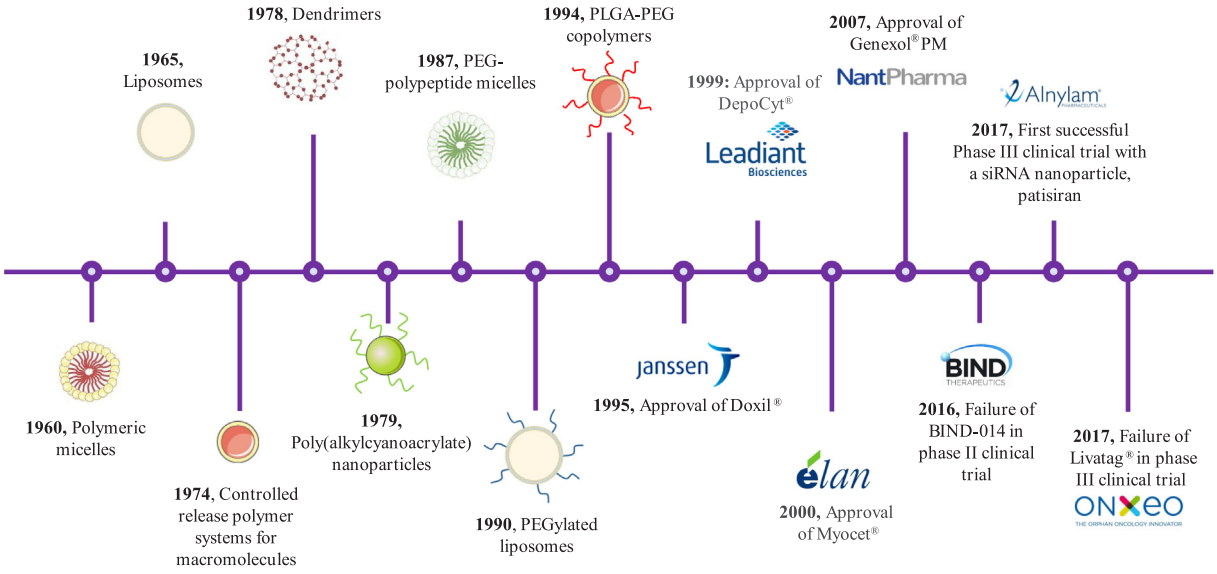

Fig. 6. Timeline of polymeric and liposome-based nanoparticles' discovery, clinical development, failures and approvals. From 1960 to the mid-1990's, there was a surge in the development of nanoparticle delivery systems including polymeric micelles, liposomes, dendrimers, poly(lactide-*co*-glycolide) (PLGA)-PEG and poly (alkylcyanoacrylate) nanoparticles (Bangham, et al., 1965; Blume and Cevc, 1990; Buhleier, et al., 1978; Elworthy, 1960; Gref, et al., 1994; Klibanov, et al., 1990; Langer and Folkman, 1976; Vauthier, et al., 2003; Yokoyama, et al., 1987). Several successes since that time have included Doxil®, Depotcyt®, Myocet®, Genexol®PM and patisiran (Pillai, 2014) (Adams, et al., 2018). Despite these, several high-profile failures have been reported in recent years including BIND-014 (Ledford, 2016) and Livatag® (Reig, et al., 2017).

ongoing worldwide with 28 products under clinical evaluation (Bulbake et al., 2017).

Although liposomes possess advantageous attributes in terms of safety and biodegradability, the fragile nature of their lipid bilayer and difficulties in formulation and functionalization of lipids may restrict their development in certain cases (e.g. delivery to the gastrointestinal tract) (Le Meins et al., 2013; Wibroe et al., 2016; Yingchoncharoen et al., 2016). The emergence of polymersomes, which are characterized by chemical versatility, high stability and toughness, has brought new delivery opportunities (Discher and Ahmed, 2006; Le Meins et al., 2011; Lee and Feijen, 2012). Owing to their unique properties, polymeric vesicles may offer some advantages over liposomes: i) a broad range of diffusion properties can be easily achieved by chemistry (Discher and Eisenberg, 2002); ii) very long circulation times can potentially be attained due to the high density of PEG chains; iii) high loading efficiency of hydrophobic drugs can be obtained within the thicker membrane (up to 10-fold increase compared to lipid bilayers), additionally allowing for multiple drug loadings (Ahmed et al., 2006); iv) accurate engineering of a responsive building block that allows specific and controlled release properties can be done. Nevertheless, polymersomes have not yet made it into the market, which probably reflects the inherent difficulty to approve any novel excipient. Another possible factor slowing down polymersome translation into the clinic may be the technical difficulty in scaling-up the manufacturing of monodisperse nano-sized polymersomes, even if emerging technologies such as microfluidics constitute promising fabrication alternatives (Upadhyay et al., 2009).

Polymersome and liposome formulations are expected to further evolve and find their utility in newer indications (e.g. cancer immunotherapy, inflammatory diseases, etc.) (Alaarg et al., 2017; Dianat-Moghadam et al., 2018). In particular, the possibility to incorporate both diagnostics agents and drugs as well as to control the release rate and endow these vesicles with targeting moieties makes them particularly attractive for the development of personalized therapies. The option to combine both lipids and polymers in the membrane structure further adds to the versatility of these systems. Interestingly, hybrid bilayer vesicles (polymer/polymer or polymer/lipid) (Le Meins et al., 2013) have attracted particular attention in which the polymer supports mechanical stability, whereas the lipid provides domains with specific interactions or permeability. Flexible assembly of these amphiphiles in bilayers where lipid/polymer deposits at inner-leaflet or outer-monolayer creates a new class of vesicle-based systems aiming to improve the delivery efficacy (Peyret et al., 2018a,b).

In conclusion, the main arguments in favor of liposomes are that they have a long history with decades of research to understand their structure/properties relationships, they are generally bio-based, biocompatible, metabolizable and very well tolerated. The main drawback of liposomes originates from their general instability, especially during certain functionalization steps. Polymersomes offer the general scaling laws of polymer and the specificity of the chemistry, allowing accurate design of structures with controlled and predictable properties, in terms of diffusion, stability and degradability.

4.2. Polymer-based nanoparticles and micelles

While liposomal formulations of anti-cancer drugs still dominate the oncology nanomedicine field (Barenholz, 2012), several polymer-based nanosystems are either currently approved for use or in clinical development for various types of cancers (Fig. 6) (Houdaihed et al., 2017). Due to the unparalleled diversity associated with the design and synthesis of polymers, their integration into a nanotechnology platform offers many exciting possibilities. The polymeric nanosystems that are most advanced in terms of pharmaceutical development include nanoparticles and spherical block copolymer micelles (BCMs), albeit other types such as dendrimers are also under investigation (Prabhu et al., 2015). Polymeric nanoparticles are solid colloidal systems on which a drug is adsorbed, entrapped or chemically conjugated. BCMs are generally composed of di- or tri- block amphiphilic polymers that self-assemble in aqueous media to entrap (either physically or chemically) a hydrophobic drug within its hydrophobic core. With respect to success in the clinic, this has mainly been confined to micelle-based systems thus far.

In 1974, the first controlled release polymer system for macromolecules and other drugs (in this case hormones) was reported (Davis,

1974). Over 30 years later, the first polymer-based nanosystem was approved for use in humans. In 2007, Genexol®-PM (a paclitaxel micelle formulation) received approval in South Korea for the treatment of patients with metastatic breast cancer, non-small cell lung cancer and ovarian cancer (Van Gaal and Crommelin, 2015). Genexol®-PM is an example of a spherical polymeric micelle system that effectively solubilizes its hydrophobic cargo. Using block copolymers to formulate the drug spares the need for potentially harmful surfactants, such as Kolliphor® EL (in Taxol®) and polysorbate 80 (in Taxotere®), which have been shown to cause hypersensitivity reactions and other forms of toxicity (Baur et al., 2008; Gelderblom et al., 2001; Szebeni et al., 1998).

A major advantage of polymeric nanosystems is the improvement in the toxicity profile of their chemotherapeutic cargo. NC-6004 (Nanocarrier Co.) is a PEG-*b*-poly(glutamic acid) BCM formulation of cisplatin currently being evaluated in Phase III clinical trials for the treatment of head and neck as well as pancreatic cancer. In a Phase I clinical trial, NC-6004 demonstrated less severe and less frequent toxicities including nephrotoxicity, neurotoxicity and ototoxicity when compared to free cisplatin (Plummer et al., 2011). Improved toxicity profiles relative to the free drug were also observed with other formulations, including NC-4016 (Nanocarrier Co.), NK105 (Nanocarrier Co.), Cynviloq™ (Nantworks™), Nanoxel™-PM (Samyang Biopharm) and CriPec® (Cristal Therapeutics) (Houdaihed et al., 2017).

Another benefit to using polymeric nanosystems is the extension of the circulation half-life of the encapsulated drugs, which allows for the exploitation of the EPR effect to increase their deposition at the tumor site (Matsumura and Maeda, 1986). Several polymer-based nanoparticles have shown in clinical trials an inherent ability to exploit this phenomenon. In a Phase I clinical trial, NanoCarrier's NC-6004 demonstrated a 230-fold increase in the plasma half-life relative to free cisplatin (Plummer et al., 2011). In addition, the administration of paclitaxel formulated in NanoCarrier's NK105 (BCM of PEG and poly (aspartic acid) esterified with 4-phenyl-1-butanol) in a Phase I clinical trial resulted in an increased area under the curve for plasma concentration *vs.* time and tumor exposure relative to paclitaxel as Taxol® (Hamaguchi et al., 2007). The improvement of the pharmacokinetic profiles of these drugs in polymeric nanoparticle systems increases the likelihood that they will accumulate at the tumor site at a therapeutically relevant dose.

Besides acting as carriers, polymeric nanosystems are amenable to the co-delivery of combinations of drugs at specific molar ratios. Triolimus (Co-D Therapeutics) is a PEG-*b*-poly(D,L lactide) (PEG-*b*-PLA) micelle system encapsulating three hydrophobic drugs at a synergistic ratio: paclitaxel, rapamycin and 17-N-allylamino-17-demethoxygeldanamycin. This nanosystem has demonstrated superior efficacy relative to free drugs and mono- and di- encapsulated systems in several preclinical models of cancer (Hasenstein et al., 2012; Shin et al., 2011; Tomoda et al., 2017).

A major barrier to overcome with regards to polymeric micelle systems is thermodynamic instability when diluted following intravenous administration to concentrations below the critical micelle concentration of the polymer (Fahr and Liu, 2007). For less stable micelle systems, this dilution results in the dissociation of the micelle structure and premature release of the drug before the tumor site is reached. This inherent instability is often the major limitation of polymeric micelle systems over their lipidic counterparts. Therefore, it is critical to design BCM systems with adequate thermodynamic and/or kinetic stability.

The field of polymer-based nanomedicine was negatively impacted in May 2016 when BIND therapeutics (a nanotechnology company based in Cambridge, Massachusetts) went bankrupt as a result of a failed high-profile clinical trial (Weisman, 2016). The company's lead compound BIND-014 was a PEG-*b*-PLA nanoparticle formulation encapsulating docetaxel and targeting the PSMA, which is overexpressed in prostate cancer as well as on the neovasculature of several non-prostatic solid tumors (Chang et al., 1999; Rajasekaran et al., 2005). BIND-014 was the first targeted controlled release polymeric nanoparticle to enter clinical trials (Von Hoff et al., 2016). A successful Phase II clinical trial in 64 patients with non-small cell lung cancer (NCT01792479) spurred its development. However, a disappointing Phase II clinical trial (NCT02479178) in head and neck cancer, halted its progression in the clinic. Pfizer picked up BIND's assets in 2016 but the fate of this technology remains unclear (Boyle, 2016). Despite this setback, the versatility as a platform technology combined with several promising clinical trials to date suggests a bright future for polymeric based drug delivery in oncology and other indications.

4.3. Nucleic acids – The pulmonary route example

Since the beginnings of nucleic acid delivery using DNA antisense oligonucleotides (AON) to modulate target gene expression in the 1970 s, the vision of exploiting nucleic acids as a form of therapeutics rather than just an *in vitro* tool has grown substantially (Séguin and Ferrari, 2009). In 2006, Fire and Mello were awarded the Nobel Prize in physiology for discovering gene silencing by long double-stranded RNA (dsRNA) (Fire et al., 1998) in a process called RNA interference (RNAi). By the time the prize was attributed, RNAi had already advanced well beyond its early application in functional genomics and had entered drug development (Dorsett and Tuschl, 2004; Gomase and Tagore, 2008). Many hoped that by inducing transient and reversible gene knockdown with short interfering RNA (siRNA), a drug-like approach for the treatment of so far "undruggable" diseases might have been found (Verdine and Walensky, 2007). Unfortunately, shortly after many of the leading pharmaceutical companies shut down their efforts and research groups focusing on siRNA delivery (Ledford, 2010), the main reason being delivery difficulties. While several of the initial clinical trials on therapeutic siRNA used "naked", unformulated siRNA for direct administration in the eye (Shen et al., 2005; Tolentino et al., 2004) or for nasal and pulmonary delivery (DeVincenzo et al., 2008; Ozcan et al., 2015), it was soon acknowledged that for most administration routes, a delivery system was necessary. However, formulations optimized for DNA delivery did not hold the promise for siRNA (Merkel et al., 2011), and the characteristics of short double-stranded RNA had to be taken into consideration for developing siRNA-specific delivery systems.

Stable nucleic acid lipid particles (SNALP) were amongst the first nano-enabled formulations that entered clinical settings. Alnylam in collaboration with Tekmira targeted what could be considered the low-hanging fruit, exploiting liver accumulation of the nanoparticles for gene silencing in the liver (Zimmermann et al., 2006), an approach that resulted in the approval of patisiran in 2018 (Fig. 6). However, siRNA was expected to address more than liver diseases. Due to the inefficient targeting of siRNA to organs other than the liver, rapid degradation by nucleases, and fast excretion upon systemic injection (Dykxhoorn et al., 2006), other administration routes were explored in academia and industry. As an example of local administration, pulmonary siRNA delivery has been extensively tested in preclinical settings using animal models of viral infection, acute lung injury, asthma, cystic fibrosis, tuberculosis, and lung cancer (Merkel et al., 2014; Ruigrok et al., 2016). Since a variety of lethal lung disorders are among the top ten causes of death worldwide, it is clear that pulmonary medical needs remain unmet despite the fact that the lung is directly accessible by inhalation (WHO, 2011). Aerosol delivery has numerous advantages over systemic administration such as local targeting, immediate availability, decreased systemic side effects and non-invasive application. Hence, several obstacles encountered in systemic drug delivery can be overcome by pulmonary delivery (Durcan et al., 2008). Pulmonary formulations also feature a history of patient acceptability and compliance because localized aerosol delivery allows for non-invasive ease of access (Birchall, 2007). After more than a decade of research on therapeutic siRNA delivery, clinical success stories are still sparse and the

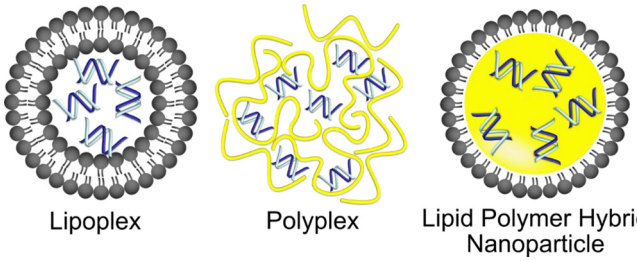

Fig. 7. Lipid- and polymer-based nanocarriers for pulmonary nucleic acid delivery. While lipoplexes consist of cationic lipids and polyplexes of cationic polymers that electrostatically interact with nucleic acids, lipid polymer hybrid nanoparticles can be made by lipids encapsulating a polymeric core that contain the nucleic acid load.

pulmonary route is not an exception (Bobbin and Rossi, 2016). While engineering dry powders for inhalation from nanoparticle suspensions containing nucleic acids by spray-drying (Bielski et al., 2017) or spray-freeze-drying (Okuda et al., 2018) has successfully been described, the question of a suitable nanocarrier has yet to be answered. While the low concentration of nucleases in the lung may be advantageous for nucleic acid administration, the presence of mucus and surfactant poses physical and chemical barriers, on the other hand, for non-viral carriers of nucleic acids (Sanders et al., 2009).

Traditionally, liposomes have been amongst the most prevalent nanocarriers for nucleic acid delivery in the lung. However, lipoplexes (cationic lipid-based particles, Fig. 7) have gained popularity because liposome stability is negatively affected by surfactants (Rudolph et al., 2000; Alton et al., 2013). Unfortunately, lipoplexes bear the potential for inducing dose-dependent cellular toxicity (Lv et al., 2006; Weber et al., 2014). Thus, anionic liposomes have been developed for gene delivery (Lee and Huang, 1996); however, they require the use of cationic helper molecules such as calcium chloride, poly(amino acid) or some arginine-rich oligomer to initially compact nucleic acids for encapsulation. Another type of nanocarriers that is being evaluated in clinical trials for other administration routes includes solid lipid nanoparticles (SLNs), which have higher stability in biological environments and offer controlled drug release. In addition, they present improved chemical stability of the encapsulated nucleic acids and entail an inexpensive and scalable production (Mehnert and Mäder, 2001). Their performance in pulmonary nucleic acid delivery has yet to be investigated. Two potential hurdles could be their destabilization upon interacting with lung surfactants or their lack of mobility in mucus (Sanders et al., 2009).

Polymers as nucleic acid nanocarriers, most importantly suffer from polydispersity concerns that can cause poor reproducibility of a formulation. Cationic polyplexes logically encounter the same toxicity problems as cationic lipoplexes, while synthetic cationic polymers are additionally often non-degradable and can be immune-stimulatory (Beyerle et al., 2011; Merkel et al., 2011; Sanders et al., 2009). In an approach similar to anionic lipoplexes, PLGA, which is negatively charged, has been modified with hydrophilic and cationic polymers, such as poly(ethylenimine) and chitosan, for electrostatic adsorption of nucleic acids (Su et al., 2012). However, this kludge neither addresses the endogenous toxicity of polycations nor the overall rather low encapsulation efficacy of nucleic acids in the resulting modified PLGA nanoparticles.

One approach that may hold promise, however, is pursued by combining the advantages of lipid formulations that offer better monodispersity and a natural endosomal escape mechanism with the muco-inertness and stability of polymer particles in lung lining fluids. Core-shell hybrid particles of lipid–PLGA (Fig. 7) have therefore been especially designed for siRNA delivery (d'Angelo et al., 2018; Raemdonck et al., 2014). Such hybrid nanoparticles have yet to be investigated in preclinical and later in clinical settings. Currently, the main limitation of this approach is their comparably low loading capacity of nucleic acids, considering that the carrier material is at least twice as much as in a conventional liposome or polymer particle. Another downside to this approach is the more laborious and costly preparation, which follows several steps and may not be easily scalable. In light of the latest discoveries in genome editing including the CRISPR-Cas9 technology, efficient formulations for nucleic acids are urgently needed. While the pulmonary route certainly is only one possible example of promising local administration routes, many other routes are currently being investigated.

5. 3D-printed dosage forms made from lipids and polymers

The processes used to produce tablets, the dominant form of medicine taken by patients, have changed relatively little for many years. Whilst these approaches serve the industry and patients well, they remain limited in some clinical areas and moreover, cannot create complex dosage forms or bespoke medications tailored for an individual or sub-population (i.e. personalized medicines). 3D printing in its many different forms (extrusion, ink-jet, stereolithography, etc.), offers a possible route to address these issues (Konta et al., 2017). Indeed, several laboratories around the world have now convincingly demonstrated that 3D printing may be used to manufacture small batches of functional medicines that could be expected to be safe for patients and to pass standard regulatory tests (Norman et al., 2017).

3D printers continue to develop rapidly, and we can expect to see the quality and speed of production improve significantly. To date, a number of studies have shown that currently approved materials for pharmaceutical manufacture can be used in various different types of 3D printing processes, such as fused deposition modelling (FDM) (Liang et al., 2018b; Sadia et al., 2018a; Solanki et al., 2018), extrusion (Khaled et al., 2015a,b), hot-melt ink jet (Kyobula et al., 2017) and selective laser sintering (Fina et al., 2018; Prasad and Smyth, 2016). There, nevertheless, remains significant material challenges and opportunities for the formulation and manufacture of medicines by 3D printing (and in particular for solvent ink-jet approaches), both for optimization of properties for printing and achieving new functionalities that 3D printing can enable. The consequent need to establish an expanded pallet of materials suited for 3D printing of medicines in general, and for ink-jet based methods in particular, is perhaps one of the most important technical challenges ahead of the field.

The most commonly applied 3D printing method for research in pharmaceutical manufacture is FDM, whereby a pre-formed polymeric filament is melted and extruded to form a defined three-dimensional object on freezing. Many studies have shown the potential of incorporating drugs into the polymer filament (Sadia et al., 2016; Solanki et al., 2018). FDM work has included a demonstration of the use of dosage form geometry to control drug release *via* manipulation of tablet surface area and diffusion lengths (Goyanes et al., 2015).

It has also been shown that 3D printing *via* paste-extrusion and ink-jet methods can be used to produce tablets with novel 3D architecture and compositions, designed to control drug release and allow personalization for a given patient. For example, 'polypill' tablets have been printed using an extrusion method that contains the different drugs (up to 5) in separate compartments, each of which can have its release controlled independently through the use of alternate release membranes or matrices (Khaled et al., 2015a,b). In an alternate strategy, the geometry and surface area of a tablet may be used to modulate drug release, as these parameters can be set differently for every tablet using 3D printing (Kyobula et al., 2017). Notably, polypills have also been produced using alternative 3D printing approaches such as FDM, once again indicating the potential for exploiting these different routes, and hence mechanisms of manufacture that this family of approaches offer (Sadia et al., 2018b).

Until now, the main excipients used in the 3D printing of medicines have been polymers. For example, 3D-printed dosage forms have been

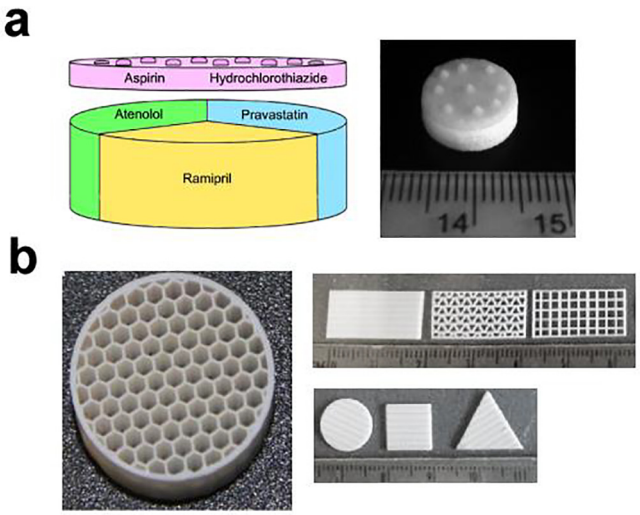

Fig. 8. Examples of dosage forms produced by 3D printing (a) Paste extrusion, (Khaled, et al., 2015a), reproduced with permission from Elsevier, (b) Hot-melt ink-jet (Kyobula, et al., 2017) demonstrating the ability to produce complex multi-drug tablets and controlled geometry dosage forms respectively.

prepared with various commonly employed and approved natural and synthetic polymeric materials such as PVP, microcrystalline cellulose, sodium starch glycolate, poly(acrylic acid), PEG and HPMC. These have primarily been used in formulations of pastes for extrusion 3D printing (Clark et al., 2017; Khaled et al., 2018; Khaled et al., 2015a,b; Kyobula et al., 2017) (Fig. 8). For hot-melt ink-jet-based printing, natural waxes such as beeswax (Kyobula et al., 2017) and candelilla, which have the appropriate rheological and thermal properties to be printed from the melt whilst incorporating a thermally stable drug (in much the same manner as standard HME) have also been exploited. Such natural products can present difficulties in terms of reproducibility and adaptability in formulating for 3D printing due to their potential variability in properties. Currently available pharmaceutical grade lipid-based materials such as Compritol® (Aburahma and Badr-Eldin, 2014) represent viable regulatory approved alternatives with suitable physical (melting point, rheology) and chemical properties.

Ink-jet printing from a solution or a suspension (as in personal desktop printers), presents a significant formulation challenge in comparison to printing from the melt because the solidification methodologies currently employed rarely use safe materials for human consumption. In recent work, high throughput methods to identify new inks based on a range of properties related to their application were investigated (Louzao et al., 2018). For example, > 250 new ink formulations in a high-throughput format were assessed for the release of the drug, paroxetine. The selected candidates with the desirable properties were scaled up using 3D printing into a range of object architectures (Fig. 9) (Louzao et al., 2018).

Another approach, which shows promise for the future on how to screen for suitable excipient materials, is statistical modelling. When combined with long-term stability studies it was used to assist formulation selection, and identify the most suitable manufacturing process for the preparation of solid dispersions of poorly soluble drugs, as is typically formed in ink-jet based printing. For example, in a proof-of-principle study, 60 solid dispersion formulations were produced using ten chemically diverse, neutral, poorly soluble drugs, three commonly used polymers, and two manufacturing techniques (spray drying and melt extrusion). The extensive experimental dataset was used to build multiple linear regression models to correlate physicochemical properties of the drug with stability data. These models indicate which combination of processing method and polymer carrier is most likely to give a stable solid dispersion (Fridgeirsdottir et al., 2018).

Many challenges remain to be solved before 3D printing can be applied to the manufacture of solid dosage forms, particularly, in scalability/business model, quality control, regulatory approval for any process which devolves the manufacture away from a central facility towards the patient and in the new constraints it brings to formulation. A number of excellent extensive reviews address these important issues that must be addressed if products are to reach patients (Alhnan et al., 2016; Liang et al., 2018a; Trenfield et al., 2018) that along with this work, illustrate that there are clear opportunities for 3D printing of medicines provided the right clinical need can be identified. In relation to polymers and lipid- based materials, many familiar requirements remain (e.g. material properties, stability, safety) with the additional constraints associated to the 3D printing processes such as suitable flow in solution, paste or molten, form and ability to retain in solid form a printed structure with the adequate spatial resolution.

6. Conclusions

Despite centuries of use in human health history, lipids and polymers have not yet unraveled their full potential as pharmaceutical excipients. Both exhibit great versatility in terms of structures and functionalities and allow formulators to solve complex drug delivery challenges, whether used individually or in combination with each other. Nowadays, the physical combination of lipids and polymers is commonly exploited in the design of traditional and sophisticated dosage forms. As discussed above, lipids and their amphiphilic derivatives can improve the solubilization capacity of polymeric solid dispersions, allowing higher doses of water-insoluble drugs to be administered. Similarly, polymers may endow SEDDS with mucus-penetrating properties, thereby promoting the absorption of poorly bioavailable APIs. Moreover, recent progress in chemistry and material sciences has allowed the design of lipids and polymers with unique functional characteristics, making them responsive to stimuli (e.g. pH, temperature) or capable of exerting a biological action (e.g. possible inhibition of P-

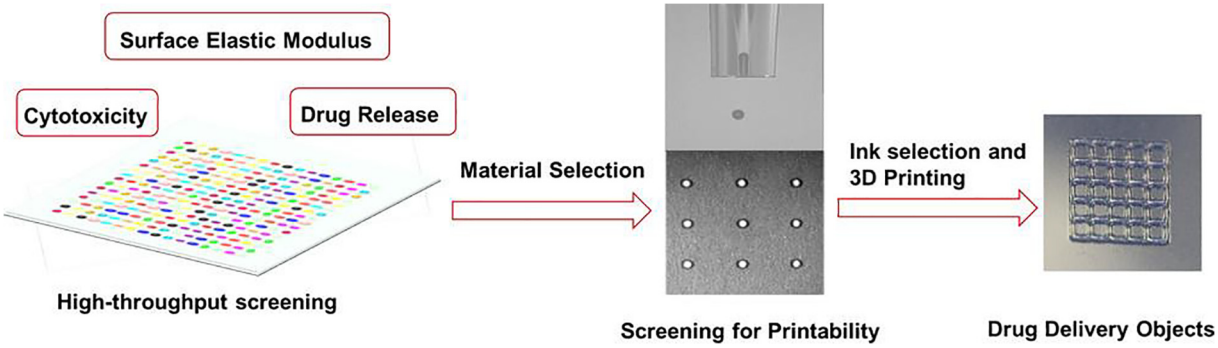

Fig. 9. Summary of the high-throughput method for identifying printable inks (Louzao, et al., 2018), reproduced with permission from the American Chemical Society.

glycoprotein) (Constantinides and Wasan, 2006). Polymers and lipids are now often being chemically linked to impart drug delivery systems with improved or novel features. Aside from the well-established PEG-phospholipids that, as discussed above, enter in the composition of long-circulating liposomes, newer polymer-lipid hybrids such as pullulan-cholesterol or alkylated poly(*N*-isopropylacrylamide) are emerging as alternative solubilizers for lipophilic APIs or as smart self-assembling systems in drug targeting applications (Bertrand et al., 2017; Morimoto et al., 2013; Yingchoncharoen et al., 2016). With the rapid evolution of 3D printing technologies, it can be expected that hybrid polymer-lipid excipients will allow the design of drug delivery systems with new characteristics and unprecedented control over the drug release patterns. For drug delivery scientists, polymers and lipids are set to remain indispensable tools to address the challenges posed by medicine of tomorrow and the formulation of ever more complex APIs.

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Conflicts of interest

The Editor-in-Chief of the journal is one of the co-authors of this article. The manuscript has been subject to all of the journal's usual procedures, including peer review, which has been handled independently of the Editor-in-Chief.

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