processes

MDPI

Review

The Importance of Drug Delivery in the Clinical Development and Lifecycle of Drug Products with Examples from Authorised Medicinal Products

Maria Malamatari

Department of Pharmacy, School of Health Sciences, Frederick University, Nicosia 1036, Cyprus; hsc.mm@frederick.ac.cy

Abstract: Drug delivery systems (DDS) are formulations or devices that enable the introduction of a therapeutic into the body and its delivery to its target site, potentially enhancing its efficacy and safety. Advances in formulation approaches related to the enhancement of solubility, permeability and thus bioavailability of drugs have already been successfully implemented by the pharmaceutical industry. This review highlights the importance of formulations/DDS in the clinical development and the lifecycle of drug products. Examples from already authorised drug products have been used to showcase how the development of appropriate formulations/DDS could deliver drugs to the site of action (e.g., pulmonary and nasal drug delivery) and enhance patient adherence to medication (e.g., long-acting injectables, 3D-printed tablets). Moreover, examples from authorised products have been provided to highlight how formulation can improve safety (e.g., liposomes, abuse-deterrent opioid formulations) and efficacy (e.g., albumin-based nanoparticles, permeation enhancers for oral delivery of peptides).

Keywords: drug delivery; formulation; pharmacokinetics; adherence; safety; efficacy

check for updates

Citation: Malamatari, M. The Importance of Drug Delivery in the Clinical Development and Lifecycle of Drug Products with Examples from Authorised Medicinal Products. *Processes* **2023**, *11*, 2919. https://doi.org/10.3390/pr11102919

Academic Editor: Mahesh Narayan

Received: 20 September 2023
Revised: 29 September 2023
Accepted: 4 October 2023
Published: 5 October 2023

Copyright: © 2023 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

The term drug delivery refers to the approaches/technologies used to present the drug to the desired site of the body for drug release and absorption [1]. Drug delivery systems (DDS) are formulations or devices that enable the introduction of a therapeutic into the body and its delivery to its target site, potentially enhancing its efficacy and safety [2,3].

Therapeutics include small-molecule drugs and biologics. The first category encompasses pharmaceutical compounds with low molecular weight, while the biologics category includes proteins and peptides, antibodies, nucleic acids, and cell therapies [3]. Each category has its own advantages and challenges. For example, small-molecule drugs have simpler manufacturing methods, increased stability and are economically more sustainable than biologics [4]. In contrast, biologics are highly targeted drugs with limited off-target effects compared to small-molecule drugs, addressing unmet needs especially in the fields of oncology and immunotherapy. Most drug products in the market contain small-molecule drugs as the active pharmaceutical ingredient (API). However, a steady increase in the number of biologics approved by Regulatory Authorities has been observed over the last 25 years [5]. Such trends support the opinion that both small-molecule drugs and biologics have important roles in the therapeutic armamentarium of the future [6].

Focusing on small-molecule drugs, the reasons for attrition of pharmaceutical compounds are presented in Figure 1. In 1991, problems related to poor pharmacokinetic (PK) properties and erratic bioavailability were the main reasons for candidate failure followed by efficacy and clinical safety. A different picture can be observed in 2000 and 2017, as PK and bioavailability account for only ~10% of attrition, while the lack of efficacy and safety remain the leading causes of attrition [7–9].

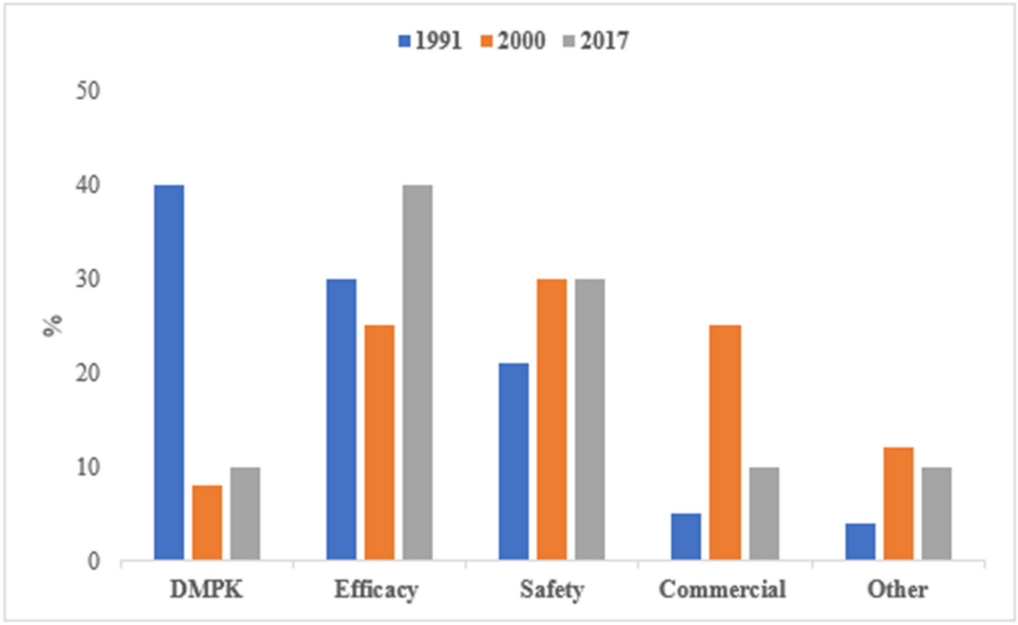

Figure 1. Reasons for attrition in drug development in 1991, 2000 and 2017. Adapted from [7–9]. (DMPK: drug metabolism and pharmacokinetics).

The reasons for attrition in drug development and their shift over the years constitute a recurrent theme of this review as they show the following:

i. Inability to develop an appropriate DDS/formulation fit for the intended purpose of the drug product could be a reason for attrition of a new chemical entity (NCE) in drug development.
ii. Advances in formulation strategies related to the enhancement of solubility, permeability and thus bioavailability of drugs have been successfully used by the pharmaceutical industry to reduce attrition due to the poor PK and erratic bioavailability of NCEs.
iii. Focus should be given on the development of formulations/DDS that could improve the efficacy and safety of NCEs and currently approved APIs. Such formulations could improve the benefit–risk ratio of drugs facilitating their clinical development and could also be used to re-purpose already established medicines.

In general, formulation approaches do not alter the pharmacodynamic properties of a drug, but they could change its pharmacokinetic properties (e.g., bioavailability, area under the concentration–time profile curve (AUC), maximum plasma concentration (Cmax), time to reach Cmax (Tmax), elimination half-life) and thus subsequently impact its pharmacodynamic performance. By changing the route of administration of a drug, different exposures over time can be achieved. For example, when 800 mg of ibuprofen is administered intravenously (IV), the Cmax is double that of the Cmax upon oral administration, while the tmax is 0.11 h and 1.50 h, respectively (Figure 2) [10]. The significantly shorter Tmax achieved by IV administration is because the drug is injected directly into the bloodstream and is linked to the fast onset of action.

The aim of this review is to highlight the importance of formulations/DDS in the clinical development and the lifecycle of drug products. To do so, examples from already authorised drug products will be used to showcase how the development of appropriate formulations/DDS could deliver drugs to the site of action, address issues related to patient adherence, improve safety and efficacy of APIs. Special focus will be given on how formulations could achieve these aspects by modifying the PK profile of the medicinal product.

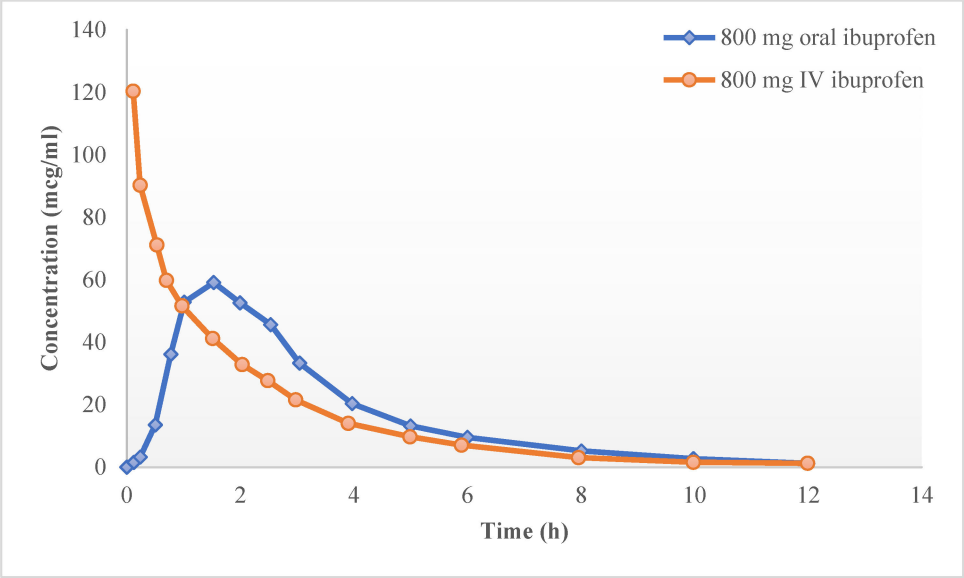

Figure 2. PK profile of a single dose of IV ibuprofen (800 mg) infused over 5 to 7 min vs. a single dose of oral ibuprofen (800 mg) in healthy volunteers. Adapted from [10] using the PlotDigitizer online app.

2. Drug Formulations to Deliver the Drug to the Site of Action

In this section, the examples of two authorised medicinal products administered via the pulmonary and nasal route will be presented. The examples showcase how the selection of an appropriate route of administration could offer targeted delivery to the site of action.

Pulmonary drug delivery is the preferred route of administration for the treatment of lung diseases. As the drug is delivered to or close to its site of action, pulmonary delivery offers rapid onset of action, targeted delivery, lower systemic exposure, and hence less systemic side effects [11]. Several inhaled antibiotics have been authorised by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) (Table 1).

Table 1. Inhaled antibiotics authorised in Europe and US.

Antibiotic	Approved Indications	References
Amikacin (Arikayce®)	Treatment of non-tuberculous mycobacteria lung infections caused by *Mycobacterium avium Complex* in adults with limited treatment options who do not have cystic fibrosis	[12]
Aztreonam powder and solvent for nebuliser solution (Cayston®)	Therapy of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis aged 6 years and older	[13]
Colistimethate inhalation powder (Colobreathe®)		[14]
Colistimethate powder for nebuliser solution (Promixin)	Management in adult and paediatric of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis	[15]
Levofloxacin nebuliser solution (Quinsair®)	Management of chronic pulmonary infections due to *P. aeruginosa* in adult patients with cystic fibrosis	[16]
Tobramycin nebuliser solution	Therapy of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis aged 6 years and older	[17]
Tobramycin inhalation powder (Tobi Podhaler®)		[18]

Amikacin is an aminoglycoside antibiotic which is active against a broad spectrum of Gram-negative bacteria including *P. aeruginosa* and *E.coli*. Amikacin is available as solution for injection or infusion and is indicated in the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria [19]. The incidence of infections of the lungs due to nontuberculous mycobacteria (NMT) such as Mycobacterium avium complex (MAC) is increasing worldwide, becoming a public health problem. The disease is associated with high morbidity and mortality, while prolonged combination therapy is required for the eradication of the disease [20].

Amikacin liposome inhalation suspension (Arikayce liposomal 590 mg nebuliser suspension; Insmed Limited) is indicated for the treatment of NMT lung infections caused by MAC in adults with limited treatment options and who do not have cystic fibrosis [12]. In the formulation, amikacin is encapsulated in liposomes (200–300 nm), which are formed by two lipids, dipalmitoylphosphatidylcholine (DPPC) and cholesterol in a 2:1 w/w ratio [21]. The formulation is administered to the lungs using a Lamira Nebuliser System. Formulating amikacin as an inhalable dosage form allows the delivery of sufficiently high concentrations of amikacin to the site of infection while concentrations elsewhere are kept to a minimum, resulting in a reduction in the side effects due to systemic exposure.

Given that NMT form biofilms and accumulate in the macrophages, formulation of amikacin as liposomes was a rational approach to increase the concentration of the drug in the airways and uptake by the pulmonary macrophages. Zhang et al. [22] found that in rats, inhaled liposomal amikacin achieves significantly higher concentrations in the macrophages, airways and lung tissue compared to IV amikacin and inhaled free amikacin, while concentrations in the plasma remain low. The therapeutic efficacy of inhaled liposomal amikacin has also been demonstrated in the pivotal Phase III CONVERT trial, where a once daily administration of the drug product as an add-on to guideline-based therapy (GBT) met the primary endpoint of increased sputum culture conversion by month six compared with GBT in patients with treatment-refractory MAC lung disease [23]. The example of inhaled liposomal amikacin highlights how the route of administration but also the formulation itself could be tailored to extend the use of a drug for a new indication and provide a useful treatment option for a life-threatening condition.

The nasal route of administration has also been explored as an alternative route to oral and parenteral delivery for systemic delivery. Systemic delivery by nasal administration is particularly attractive for diseases where rapid onset of action is required, as it would translate to fast relief of symptoms. Moreover, intranasal delivery is investigated as an alternative approach to deliver therapeutics to the central nervous system (CNS). Specifically, the olfactory region, which is situated in the roof of the nasal cavity, exclusively connects the external environment to the brain, unimpeded by the blood–brain barrier (BBB). Thus, drugs administered to this area may be transported directly into the brain, bypassing the BBB [24,25]. Currently, nasal drug products have been authorised for the acute treatment of migraine (e.g., zolmitriptan), management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain (e.g., fentanyl citrate) and relief of withdrawal symptoms as an aid to smoking cessation (e.g., nicotine).

In 2019, FDA and EMA approved Spravato® (esketamine HCl) nasal spray, in conjunction with an oral antidepressant, for treatment-resistant depression (TRD) [26]. Spravato nasal spray (Janssen-Cilag International NV) is self-administered by the patient under the supervision of a healthcare provider in a clinic or doctor's office and the spray cannot be taken home. Compared to other available treatments that have a lengthy time to response, the addition of nasal esketamine, in conjunction with an antidepressant, exhibits rapid onset of action and generally transient adverse effects, increasing rates of response and remission in TRD [27,28]. The example of intranasal antidepressants shows how by selecting the route of administration, drug targeting can be achieved, leading to rapid onset of action.

3. Drug Formulations to Enhance Patient Adherence to Medication

In this section, the examples of two authorised products (i.e., long-acting injectables and 3D printing) will be discussed as delivery approaches to improve patient adherence to medication.

The World Health Organisation (WHO) defines adherence to long-term therapy as 'the extent to which a person's behaviour [. . .] corresponds with agreed recommendations from a health care provider' [29]. It is estimated that between 30% and 50% of all medicines prescribed for long-term therapy are not taken as recommended, leading to poorer clinical outcomes, and increased economic costs [30]. Non-adherence to medications is common in severe mental disorders such as bipolar disorder and schizophrenia, with such non-adherent behaviours that increase the risk of relapses and re-hospitalisation [31].

Development of innovative DDS is a well-established strategy to overcome barriers to patient adherence [32]. Specifically, long-acting injectables (LAI) of several antipsychotic drugs have been developed as a strategy for the treatment of schizophrenia by providing sustained therapeutic plasma concentrations from several weeks up to several months. The LAIs can be administered either via intramuscular (IM) or subcutaneous (SC) administration. LAIs belong to one of the following formulations: oil-based systems, suspensions, polymeric microspheres and in situ forming gels [33].

LAIs of antipsychotic drugs exhibit different PK profiles compared to oral medication. Absorption from the injection site into the circulation is slow. Specifically, LAIs exhibit 'flip-flop' kinetics where the rate of absorption is significantly slower than the rate of elimination. This means that the rate of absorption is the rate-limiting step in the disposition of the drug. In this way, the LAIs antipsychotic exhibit very slow and gradual absorption from the injection site leading to extended therapeutic plasma concentrations [34]. The slower absorption rate of the LAIs compared to oral antipsychotics also results in reduced peak-to-trough fluctuations, which in turn means reduced peak concentrations and increased trough concentrations. In this way, the potential for adverse effects due to peak concentrations above the maximum therapeutic concentrations and the potential for subtherapeutic concentrations due to trough concentrations below the minimum effective concentration are both reduced, enhancing both adherence and the overall benefit–risk ratio of the drug product.

Paliperidone is an atypical antipsychotic indicated for the treatment of schizophrenia and schizoaffective disorders. It is available in the form of prolonged-release tablets for administration once daily (Invega prolonged-release tablets, Janssen and Cilag Ltd.). Paliperidone palmitate is available as a prolonged-release suspension for injection for administration once monthly (Xeplion prolonged-release suspension for injection) and once every three months (Trevicta prolonged-release suspension for injection) [35–37]. Paliperidone palmitate prolonged-release suspension for injection once every three months exhibits a Tmax ranging from 24 to 34 days and an apparent half-life of 2–4 months after a single IM deltoid administration (Figure 3) [38].

Mathews et al. [39] performed a post-hoc analysis of three similarly designed, randomised relapse prevention studies in adult patients with schizophrenia to indirectly compare paliperidone prolonged-release tablets, paliperidone palmitate once monthly and paliperidone palmitate once every three months formulations and to determine whether the LAIs provide longer protection from relapse due to premature discontinuation (analogous to 'non-adherent' patients in the real world). The analysis showed that time-to-relapse was longer with longer-duration LAIs (i.e., LAI once three monthly > LAI once monthly > oral paliperidone). Such observations support the early initiation of LAI antipsychotics in the maintenance treatment of schizophrenia. Several real-world studies have demonstrated that LAIs improve patient adherence and patient outcomes in schizophrenia [40–42]. LAIs of antipsychotics are a characteristic example on how developing formulations with suitable PK characteristics could play an important role in overcoming barriers to patient adherence.

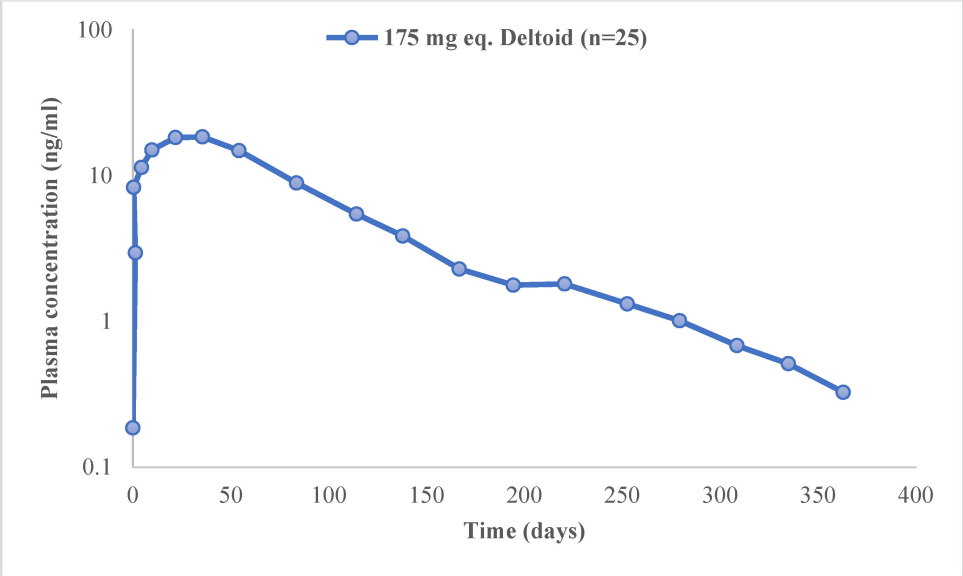

Figure 3. Median plasma–time profiles of paliperidone after deltoid injection in patients. Adapted from [38] using the PlotDigitizer online app.

Epilepsy is a chronic neurological condition where a high prevalence of non-adherence to medication has been identified. Specifically, antiepileptic non-adherence rates among adults with epilepsy range from 29% to 39% [43]. Non-adherence to antiepileptic medication can result in breakthrough seizures and can impact individual's perceived quality of life [44]. Poor adherence to antiepileptic medication is associated with increased mortality, morbidity, and healthcare costs [45].

Epilepsy is one of the neurological conditions associated with dysphagia (i.e., difficulty in swallowing). Based on the study of Plessinger et al. [46], epilepsy patients with dysphagia were significantly older than the epilepsy patients without dysphagia. Moreover, patients with dysphagia had reduced adherence to antiepileptic medication and a higher healthcare burden with an estimated incremental cost of USD 16,000 per year [46]. Several patient-centred pharmaceutical design approaches exist to improve the acceptability of medicines in the geriatric population (Table 2).

Table 2. Patient-centred pharmaceutical design approaches to improve acceptability of medicines in the geriatric population [47–49].

Formulation	Improved Acceptability	Examples
Fixed-dose combination	Reduction in complexity of treatment regimen and pill burden	Amlodipine/Valsartan tablets
Multiparticulates	Multi-unit systems of minitablets, pellets or granules that are filled into capsules or compressed into tablets. They can be swallowed as whole or may be sprinkled onto soft food. Good choice for the development of fixed-dose combination products	Pancreatin gastro-resistant granules
Orodispersible dosage forms	Rapid disintegration or dissolution in the oral cavity without the need for water. Ability to be administered to those with swallowing difficulties	Donepezil orodispersible tablets

Levetiracetam is an antiepileptic medication indicated as monotherapy in the treatment of partial onset seizures and as adjunct therapy in the treatment of partial onset seizures,

monoclinic seizures, and primary generalised tonic–clonic seizures [50]. In a recent study by Silva et al. [51], non-adherence to levetiracetam was reported as 42.6% among the study participants.

Spritam® levetiracetam tablets for oral solution are the first and only 3D-printed medicinal product approved by the FDA in 2015 [52]. The product uses Aprecia's proprietary ZipDose® technology, which is based on powder bed fusion 3D printing. Using an aqueous fluid to bind together multiple layers of powder, this technology can produce highly porous orodisperible tablets with high-dose loads [53]. Spritam® tablets disintegrate in the mouth within 10 s when taken with a sip of liquid to produce small particles that are easy to be swallowed. In this way, Spritam® tablets facilitate the adherence of patients with dysphagia to their antiepileptic medication. Given its high precision and the fact that no compression is required, ZipDose® Technology is an example of a platform that can be used to produce formulations that can offer patients with swallowing difficulties or a high pill burden an easier way to take their medication.

4. Drug Formulations to Improve Safety

This section will focus on two authorised medicinal products (i.e., PEGylated liposomal amphotericin and abuse-deterrent extended-release opioid formulations). These examples highlight how drug formulation can play an important role in modifying PK and thus enhancing drug safety by eliminating adverse events and the potential for abuse.

Conventional cancer chemotherapy works by directly or indirectly interfering with a biological process (e.g., DNA synthesis, mitosis) that is more important to the survival and proliferation of tumour cells than normal cells. However, chemotherapy agents due to non-selectivity can also cause severe adverse effects (e.g., neutropenia, mouth sores, alopecia). In addition, poor drug uptake and penetration into tumours is an important barrier in cancer chemotherapy associated with therapeutic failure. To overcome this problem, increased doses are given to patients resulting in elevated toxicity and adverse effects [54].

Doxorubicin is an anthracycline antitumour agent indicated against a wide range of neoplastic conditions including leukaemia, lymphomas, paediatric malignancies, breast and lung carcinomas [55]. Two mechanisms have been proposed for the antitumour action of doxorubicin: (i) intercalation into DNA and disruption of topoisomerase-II-mediated DNA repair and (ii) generation of Reactive Oxygen Species (ROS), which in turn damage the cellular membrane, DNA, and proteins [56]. However, a side effect induced by doxorubicin is cardiotoxicity, potentially leading to congestive heart failure. Even though the specific mechanism of cardiotoxicity of anthracyclines is still not fully understood, the generation of ROS and changes in iron metabolism are listed among the potential mechanisms [57]. The cardiotoxicity of the currently available doxorubicin solution for injection leads these drug products to be contraindicated in patients with severe myocardial insufficiency, recent myocardial infraction and severe arrythmias. Cardiac function must be monitored in patients receiving high cumulative doses in those with risk factors [55].

Formulating doxorubicin in liposomes was used as an approach to alter the tissue distribution of doxorubicin. Coating the liposomes with polyethylene glycol (PEG) further improved the PK of doxorubicin. Specifically, PEG-coated liposomes of doxorubicin exhibited a long half-life, slow clearance from the plasma and a reduced volume of distribution compared to free doxorubicin and conventional liposomal doxorubicin [58]. While conventional liposomal formulations tend to be 'leaky' when in circulation and they are extensively taken up and subsequently destroyed by the cells of the reticuloendothelial system (RES), incorporation of the PEG coating resulted in sterically stable liposomes with a reduced tendency to leak and reduced extent of RES uptake [58].

PEGylated liposomal doxorubicin (Doxil® liposome injection, Sequus Pharmaceuticals Inc.) was the first nanomedicine to be approved by the FDA in 1995 [59]. The drug product is currently available in the EU as Caelyx® pegylated liposomal 2 mg/mL concentrate for solution for infusion (Baxter Healthcare Ltd.). It is indicated for the treatment of several

tumours including metastatic breast cancer, ovarian cancer, myeloma, and Kaposi's sarcoma. In contrast to conventional doxorubicin formulations, it is indicated as a monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk [60].

The increased tolerability and safety profile of PEGylated liposomal doxorubicin compared to the free drug has been reported by several studies [61,62]. In an open-label, Phase III multi-centre trial, PEGylated liposomal doxorubicin was found to provide comparable efficacy versus conventional doxorubicin as first-line treatment for metastatic breast cancer, with significantly reduced cardiotoxicity, myelosuppression, alopecia and vomiting [63]. The example of PEGylated liposomal doxorubicin sheds light on how the design of nanomedicines can be used to improve the safety of a drug product.

Another example of using DDS to improve drug safety is related to pain management using opioids. Opioid analgesics are an established treatment for acute and chronic pain. However, inappropriate use of opioids is common and is associated with serious risks such as deaths and hospitalisations. Around 450,000 Americans died of an opioid-related overdose between 1999 and 2018, while a rise in opioid use and attributed deaths has been also observed in the UK, making the opioid crisis a global concern for public health [64,65].

Extended-release (ER) formulations offer several advantages over immediate-release (IR) formulations, including less frequent dosing and reduced fluctuation in plasma concentrations leading to more consistent analgesia. Even though opioid abuse is markedly higher for IR compared to ER formulations, abuse of ER opioid formulations may be more desirable and dangerous to manipulating (e.g., crushing, chewing) as by destroying the ER mechanism provides a greater amount of the drug to be absorbed quickly [66,67]. In addition, unintentional misuse of ER opioid formulations may take place by patients with dysphagia to facilitate swallowing [68].

Abuse-deterrent formulations (ADFs) is one approach that could reduce the risk of abuse and misuse while maintaining access to opioids (Table 3). ADFs make it more difficult to be manipulated and to extract the opioid from the drug product. Xtampza ER® (Collegium Pharmaceutical Inc.) is an ER ADF of oxycodone, which was approved by the FDA in 2016. Xtampza ER® is a microsphere-in-capsule formulation using the proprietary DETERx® technology that makes it less susceptible to manipulation using a variety of tools and solvents relative to IR oxycodone tablets [69]. Brennan et al. [70] reported that after oral administration of crushed IR oxycodone, a rapid increase in oxycodone concentration was observed. In contrast, crushed Xtampza ER managed to retain the same plasma concentration profiles as the intact capsules (Figure 4). Similar results were obtained when Xtampza ER was crushed and administered intranasally, indicating its low human abuse potential [71]. A post-marketing analysis revealed that Xtampza ER abuse and misuse were relatively low compared to other prescription opioid analgesics [67]. Thus, the example of ADFs shows the importance of formulation on reducing the human abuse potential of drugs.

Table 3. Opioids with FDA-approved labelling describing abuse-deterrent properties [72,73].

Drug Product	Drug	Abuse-Deterrence Mechanism
OxyContin™	Oxycodone	Upon dissolution, a viscous gel is formed that is difficult to inject through a hypodermic needle
Hysingla™ ER	Hydrocodone	
Xtampza™ ER	Oxycodone	Capsules containing microspheres formulated with oxycodone base and excipients that make the formulation harder to manipulate
RoxyBond™		Contains excipients that make the tablet harder to misuse by physical manipulation and/or chemical extraction

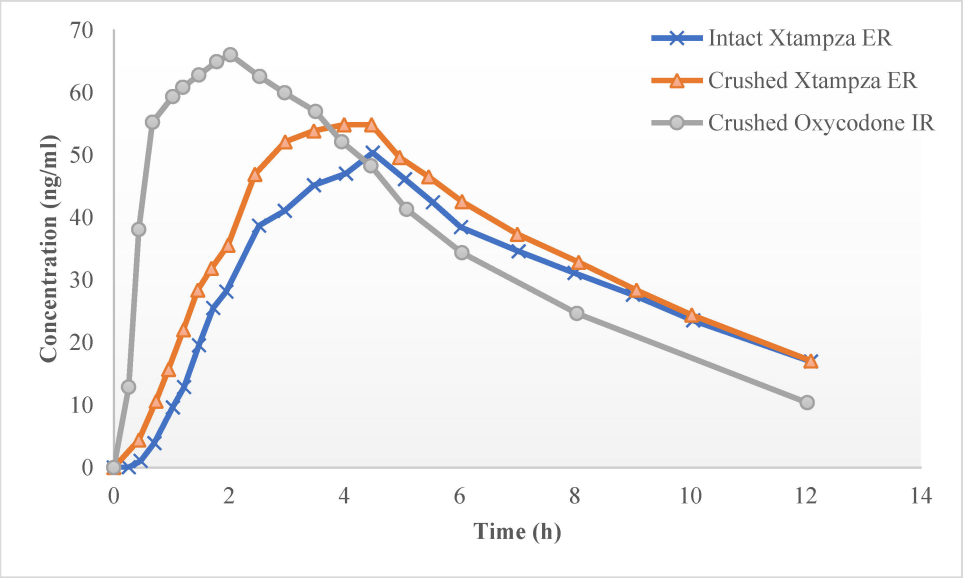

Figure 4. Mean plasma oxycodone concentration over time following administration of Xtampza^{TM} ER (intact and crushed). Adapted from [70] using the PlotDigitizer online app.

5. Drug Formulations to Improve Efficacy

In this section, examples from two authorised products will be presented showing how formulation can improve the efficacy of medicinal products.

Paclitaxel is a chemotherapeutic agent used as first-line chemotherapy for ovarian cancer, breast cancer, advanced non-small cell lung cancer (NSCLC) and AIDS-related Kaposi's sarcoma [74]. Paclitaxel exhibits very low aqueous solubility. To improve its solubility, paclitaxel was formulated in a mixture of polyethoxylated castor oil (Cremophor EL) and ethanol [75]. In such formulations, paclitaxel is available as a concentrated solution for infusion. However, in such formulations, paclitaxel is known to exhibit severe adverse effects, mainly linked to hypersensitivity reactions to the Cremophor EL and ethanol [42]. Prolonged infusion time and premedication with dexamethasone and histamine have been used as measures to reduce the incidence of hypersensitivity reactions [76].

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) was developed to increase the solubility of paclitaxel and thus reduce the need for Cremophor EL. Human serum albumin, apart from stabilising the particle size to the nanometre range (i.e., 130 nm) and thus increasing solubility, also acts as a natural carrier for several molecules in the body (e.g., fatty acids, hormones etc.) [77]. Nab-paclitaxel exhibits a higher uptake by tumour cells compared to conventional paclitaxel formulations. Initially, this was attributed to its transport through Gp60, an albumin receptor on the surface of vascular endothelia cells, while based on the study of Hama et al. [78], nab-paclitaxel is taken up into endothelial or tumour cells via a denatured albumin transport system.

Nab-paclitaxel is the first tumour-targeted chemotherapy approved for metastatic breast cancer by FDA that combines the approaches of nanotechnology along with the natural transport properties of albumin [79]. The drug product is currently available as Abraxane 5 mg/mL powder for dispersion for infusion (Bristol Myers Squibb Pharmaceuticals Ltd.) [80]. Abraxane® has shown increased antitumour activity, higher uptake by tumour cells and endothelial cell transport compared to conventional paclitaxel formulations [81]. The nab-based formulation platform is a characteristic example of how the distribution and targeting of an anticancer drug can be tailored and thus its efficacy and safety be improved.

Another example of using formulation to improve efficacy comes from the oral delivery of peptides. Semaglutide is a peptide consisting of 31 amino acids, which can be manufactured using a solid-phase approach [82]. It is a glucagon-like peptide-1 receptor

agonist (GLP-1RA). Semaglutide as a subcutaneous injection (Ozempic® solution for injection in pre-filled pen; Novo Nordisk Ltd.) was approved by the FDA in December 2018 for the treatment of type 2 diabetes mellitus as an adjunct therapy to diet and exercise [83]. The invasive route of subcutaneous administration is limiting the acceptability of the drug product.

A major barrier related to the oral delivery of peptides is their poor permeability through the intestinal epithelium. One way to overcome this issue is to co-formulate the peptide with a permeation enhancer (Table 4) [84]. Rybelsus ® is the first oral peptide drug that is approved by the FDA and EMA, and it is based on the transient permeation enhancement strategy [85]. In Rybelsus® tablets, semaglutide is co-formulated with the permeation enhancer, sodium salcaprozate (SNAC). SNAC increases the transcellular absorption of semaglutide by increasing its permeability but also by increasing the local pH around the tablet in the stomach. By doing so, it protects the peptide by degradation from pepsin [86]. Despite having an oral availability of 0.8%, oral peptide delivery is efficacious [87].

Table 4. Mechanisms of intestinal absorption enhancement [88].

Mechanism
Prevention of degradation/metabolism
Enhancement of membrane permeability by:
i. Transient opening of tight junction
ii. Disruption of lipid bilayer packing
iii. Complexation/carrier/ion pairing

6. Conclusions

Apart from the initial discovery of a new drug, the stage of formulation development is a make-or-break moment for drugs. Currently, there are several formulation approaches that can be used to ensure that the drug delivery system is fit for its intended use. In deciding the formulation to be used, a patient-centred approach should be followed where the characteristics and challenges of the specific patient population are considered. Using examples of authorised drug products, this review has demonstrated the important role that formulation and DDS play in the clinical development of drugs and throughout their lifecycle. Choosing the appropriate route of administration, as well as developing a suitable formulation, could lead to the delivery of the drug substance to its site of action, amend its PK and distribution characteristics and in turn enhance patient compliance and the overall benefit–risk ratio of a drug product. Advances in drug delivery as well as the advent of new technologies (e.g., machine-learning directed drug formulation development) are expected to facilitate more efficient drug product development processes.

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Bruschi, M.L. *Strategies to Modify the Drug Release from Pharmaceutical Systems*; Woodhead Publishing: Cambridge, UK, 2015; pp. 15–28.
2. Wen, H.; Jung, H.; Li, X. Drug Delivery Approaches in Addressing Clinical Pharmacology-Related Issues: Opportunities and Challenges. *AAPS J.* **2015**, *17*, 1327–1340. [CrossRef]
3. Vargason, A.M.; Anselmo, A.C.; Mitragotri, S. The Evolution of Commercial Drug Delivery Technologies. *Nat. Biomed. Eng.* **2021**, *5*, 951–967. [CrossRef] [PubMed]
4. Makurvet, F.D. Biologics vs. *Small Molecules: Drug Costs and Patient Access. Med. Drug Discov.* **2021**, *9*, 100075.
5. De la Torre, B.G.; Albericio, F. The Pharmaceutical Industry in 2021. An Analysis of FDA Drug Approvals from the Perspective of Molecules. *Molecules* **2022**, *27*, 1075.
6. Ngo, H.X.; Garneau-Tsodikova, S. What Are the Drugs of the Future? *Med. Chem. Commun.* **2018**, *9*, 757–758. [CrossRef] [PubMed]
7. Kola, I.; Landis, J. Can the Pharmaceutical Industry Reduce Attrition Rates? *Nat. Rev. Drug Discov.* **2004**, *3*, 711–716. [CrossRef]

8. Sun, D.; Gao, W.; Hu, H.; Zhou, S. Why 90% of Clinical Drug Development Fails and How to Improve It? *Acta Pharm. Sin. B* **2022**, *12*, 3049–3062. [CrossRef]
9. Dowden, H.; Munro, J. Trends in Clinical Success Rates and Therapeutic Focus. *Nat. Rev. Drug Discov.* **2019**, *18*, 495–496. [CrossRef]
10. Pavliv, L.; Voss, B.; Rock, A. Pharmacokinetics, Safety, and Tolerability of a Rapid Infusion of i.v. Ibuprofen in Healthy Adults. *Am. J. Health-Syst. Pharm.* **2011**, *68*, 47–51. [CrossRef]
11. Labiris, N.R.; Dolovich, M.B. Pulmonary Drug Delivery. *Part I: Physiological Factors Affecting Therapeutic Effectiveness of Aerosolized Medications. Br. J. Clin. Pharmacol.* **2003**, *56*, 588–599.
12. Arikayce Liposomal 590 mg Nebuliser Dispersion—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/12067/smpc (accessed on 9 July 2023).
13. Cayston 75 mg Powder and Solvent for Nebuliser Solution—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/4456/smpc (accessed on 28 September 2023).
14. Colobreathe 1,662,500 IU Inhalation Powder, Hard Capsules—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/3063/smpc (accessed on 28 September 2023).
15. Promixin 1 Million International Units (IU) Powder for Nebuliser Solution—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/4/smpc (accessed on 28 September 2023).
16. Quinsair 240 mg Nebuliser Solution—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/7202/smpc (accessed on 28 September 2023).
17. Tobi 300 mg/5 mL Nebuliser Solution—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/262/smpc (accessed on 28 September 2023).
18. Tobi Podhaler 28 mg Inhalation Powder, Hard Capsules—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/4757/smpc (accessed on 28 September 2023).
19. Amikacin 250 mg/mL Injection—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/3784/smpc (accessed on 9 July 2023).
20. Johnson, M.M.; Odell, J.A. Nontuberculous Mycobacterial Pulmonary Infections. *J. Thorac. Dis.* **2014**, *6*, 210–220. [PubMed]
21. Li, Z.; Perkins, W.; Cipolla, D. Robustness of Aerosol Delivery of Amikacin Liposome Inhalation Suspension Using the eFlow®Technology. *Eur. J. Pharm. Biopharm.* **2021**, *166*, 10–18. [CrossRef]
22. Zhang, J.; Leifer, F.; Rose, S.; Chun, D.Y.; Thaisz, J.; Herr, T.; Nashed, M.; Joseph, J.; Perkins, W.R.; DiPetrillo, K. Amikacin Liposome Inhalation Suspension (ALIS) Penetrates Non-Tuberculous Mycobacterial Biofilms and Enhances Amikacin Uptake Into Macrophages. *Front. Microbiol.* **2018**, *9*, 915. [CrossRef] [PubMed]
23. Shirley, M. Amikacin Liposome Inhalation Suspension: A Review in Mycobacterium Avium Complex Lung Disease. *Drugs* **2019**, *79*, 555–562. [CrossRef] [PubMed]
24. Gänger, S.; Schindowski, K. Tailoring Formulations for Intranasal Nose-to-Brain Delivery: A Review on Architecture, Physico-Chemical Characteristics and Mucociliary Clearance of the Nasal Olfactory Mucosa. *Pharmaceutics* **2018**, *10*, 116. [CrossRef] [PubMed]
25. Costa, C.P.; Moreira, J.N.; Sousa Lobo, J.M.; Silva, A.C. Intranasal Delivery of Nanostructured Lipid Carriers, Solid Lipid Nanoparticles and Nanoemulsions: A Current Overview of in Vivo Studies. *Acta Pharm. Sin. B* **2021**, *11*, 925–940. [CrossRef]
26. SPRAVATO®(Esketamine). Available online: https://www.spravato.com/ (accessed on 9 July 2023).
27. Swainson, J.; Thomas, R.K.; Archer, S.; Chrenek, C.; MacKay, M.-A.; Baker, G.; Dursun, S.; Klassen, L.J.; Chokka, P.; Demas, M.L. Esketamine for Treatment Resistant Depression. *Expert Rev. Neurother.* **2019**, *19*, 899–911. [CrossRef] [PubMed]
28. Kasper, S.; Cubała, W.J.; Fagiolini, A.; Ramos-Quiroga, J.A.; Souery, D.; Young, A.H. Practical Recommendations for the Management of Treatment-Resistant Depression with Esketamine Nasal Spray Therapy: Basic Science, Evidence-Based Knowledge and Expert Guidance. *World J. Biol. Psychiatry* **2021**, *22*, 468–482. [CrossRef] [PubMed]
29. World Health Organization. *Adherence to Long-Term Therapies: Evidence for Action*; World Health Organization: Geneva, Switzerland, 2003.
30. National Institute for Health and Care Excellence. *Medicines Adherence: Involving Patients in Decisions about Prescribed Medicines and Supporting Adherence*; National Institute for Health and Care Excellence: Manchester, UK, 2009.
31. Stentzel, U.; van den Berg, N.; Schulze, L.N.; Schwaneberg, T.; Radicke, F.; Langosch, J.M.; Freyberger, H.J.; Hoffmann, W.; Grabe, H.-J. Predictors of Medication Adherence among Patients with Severe Psychiatric Disorders: Findings from the Baseline Assessment of a Randomized Controlled Trial (Tecla). *BMC Psychiatry* **2018**, *18*, 155. [CrossRef]
32. Baryakova, T.H.; Pogostin, B.H.; Langer, R.; McHugh, K.J. Overcoming Barriers to Patient Adherence: The Case for Developing Innovative Drug Delivery Systems. *Nat. Rev. Drug Discov.* **2023**, *22*, 387–409. [CrossRef]
33. Wilkinson, J.; Ajulo, D.; Tamburrini, V.; Gall, G.L.; Kimpe, K.; Holm, R.; Belton, P.; Qi, S. Lipid Based Intramuscular Long-Acting Injectables: Current State of the Art. *Eur. J. Pharm. Sci.* **2022**, *178*, 106253. [CrossRef]
34. Correll, C.U.; Kim, E.; Sliwa, J.K.; Hamm, W.; Gopal, S.; Mathews, M.; Venkatasubramanian, R.; Saklad, S.R. Pharmacokinetic Characteristics of Long-Acting Injectable Antipsychotics for Schizophrenia: An Overview. *CNS Drugs* **2021**, *35*, 39–59. [CrossRef]
35. Invega 3 mg Prolonged-Release Tablets—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/6816/smpc#gref (accessed on 9 July 2023).

36. Xeplion 100 mg Prolonged-Release Suspension for Injection—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/7653/smpc#gref (accessed on 9 July 2023).
37. TREVICTA 175 mg Prolonged Release Suspension for Injection—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/7230/smpc#gref (accessed on 9 July 2023).
38. Ravenstijn, P.; Remmerie, B.; Savitz, A.; Samtani, M.N.; Nuamah, I.; Chang, C.-T.; De Meulder, M.; Hough, D.; Gopal, S. Pharmacokinetics, Safety, and Tolerability of Paliperidone Palmitate 3-Month Formulation in Patients with Schizophrenia: A Phase-1, Single-Dose, Randomized, Open-Label Study. *J. Clin. Pharmacol.* **2016**, *56*, 330–339. [CrossRef]
39. Mathews, M.; Gopal, S.; Singh, A.; Nuamah, I.; Pungor, K.; Tan, W.; Soares, B.; Kim, E.; Savitz, A.J. Comparison of Relapse Prevention with 3 Different Paliperidone Formulations in Patients with Schizophrenia Continuing versus Discontinuing Active Antipsychotic Treatment: A Post-hoc Analysis of 3 Similarly Designed Randomized Studies. *Neuropsychiatr. Dis. Treat.* **2020**, *16*, 1533–1542. [CrossRef]
40. Lin, D.; Thompson-Leduc, P.; Ghelerter, I.; Nguyen, H.; Lafeuille, M.-H.; Benson, C.; Mavros, P.; Lefebvre, P. Real-World Evidence of the Clinical and Economic Impact of Long-Acting Injectable Versus Oral Antipsychotics Among Patients with Schizophrenia in the United States: A Systematic Review and Meta-Analysis. *CNS Drugs* **2021**, *35*, 469–481. [CrossRef] [PubMed]
41. Greene, M.; Yan, T.; Chang, E.; Hartry, A.; Touya, M.; Broder, M.S. Medication Adherence and Discontinuation of Long-Acting Injectable versus Oral Antipsychotics in Patients with Schizophrenia or Bipolar Disorder. *J. Med. Econ.* **2018**, *21*, 127–134. [CrossRef]
42. Kim, H.O.; Seo, G.H.; Lee, B.C. Real-World Effectiveness of Long-Acting Injections for Reducing Recurrent Hospitalizations in Patients with Schizophrenia. *Ann. Gen. Psychiatry* **2020**, *19*, 1. [CrossRef] [PubMed]
43. O' Rourke, G.; O' Brien, J.J. Identifying the Barriers to Antiepileptic Drug Adherence among Adults with Epilepsy. *Seizure* **2017**, *45*, 160–168. [CrossRef]
44. Eatock, J.; Baker, G.A. Managing Patient Adherence and Quality of Life in Epilepsy. *Neuropsychiatr. Dis. Treat.* **2007**, *3*, 117–131. [CrossRef]
45. Al-Aqeel, S.; Gershuni, O.; Al-Sabhan, J.; Hiligsmann, M. Strategies for Improving Adherence to Antiepileptic Drug Treatment in People with Epilepsy. *Cochrane Database Syst. Rev.* **2020**, *10*, CD008312. [CrossRef] [PubMed]
46. Plessinger, D.; Ryan, M.; Gache, L.; Gunnarsson, C.; Faugh, E. Estimating the Incremental Burden of Dysphagia in Epilepsy Patients: A Retrospective Payer Database Analysis. Presented at the 2016 American Epilepsy Society Annual Meeting, Houston TX, USA, 2–6 December 2016.
47. Liu, F.; Ranmal, S.; Batchelor, H.K.; Orlu-Gul, M.; Ernest, T.B.; Thomas, I.W.; Flanagan, T.; Tuleu, C. Patient-Centered Pharmaceutical Design to Improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations. *Drugs* **2014**, *74*, 1871–1889. [CrossRef]
48. Hanning, S.M.; Lopez, F.L.; Wong, I.C.K.; Ernest, T.B.; Tuleu, C.; Orlu Gul, M. Patient Centric Formulations for Paediatrics and Geriatrics: Similarities and Differences. *Int. J. Pharm.* **2016**, *512*, 355–359. [CrossRef] [PubMed]
49. Lee, H.S.; Lee, J.-J.; Kim, M.-G.; Kim, K.-T.; Cho, C.-W.; Kim, D.-D.; Lee, J.-Y. Sprinkle Formulations—A Review of Commercially Available Products. *Asian J. Pharm. Sci.* **2020**, *15*, 292–310. [CrossRef] [PubMed]
50. Keppra 250 mg Film-Coated Tablets—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/2294/smpc (accessed on 15 September 2023).
51. Silva, R.; Bicker, J.; Almeida, A.; Carona, A.; Silva, A.; Sales, F.; Santana, I.; Falcão, A.; Fortuna, A. Clinical Application of Pharmacokinetics to Appraise Adherence to Levetiracetam in Portuguese Epileptic Patients. *Biomedicines* **2022**, *10*, 2127. [CrossRef]
52. FDA Approves the First 3D Printed Drug Product. Available online: https://www.aprecia.com/news/fda-approves-the-first-3d-printed-drug-product (accessed on 15 September 2023).
53. ZipDose Technology. Available online: https://www.aprecia.com/technology/zipdose (accessed on 15 September 2023).
54. Senapati, S.; Mahanta, A.K.; Kumar, S.; Maiti, P. Controlled Drug Delivery Vehicles for Cancer Treatment and Their Performance. *Sig. Transduct. Target Ther.* **2018**, *3*, 7. [CrossRef]
55. Doxorubicin Solution for Injection—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/6184/smpc#gref (accessed on 9 July 2023).
56. Thorn, C.F.; Oshiro, C.; Marsh, S.; Hernandez-Boussard, T.; McLeod, H.; Klein, T.E.; Altman, R.B. Doxorubicin Pathways: Pharmacodynamics and Adverse Effects. *Pharmacogenet. Genom.* **2011**, *21*, 440–446. [CrossRef] [PubMed]
57. Cardinale, D.; Iacopo, F.; Cipolla, C.M. Cardiotoxicity of Anthracyclines. *Front. Cardiovasc. Med.* **2020**, *7*, 26. [CrossRef]
58. Gabizon, A.; Martin, F. Polyethylene Glycol-Coated (Pegylated) Liposomal Doxorubicin—Rationale for Use in Solid Tumours. *Drugs* **1997**, *54* (Suppl. S4), 15–21. [CrossRef] [PubMed]
59. Gabizon, A.; Shmeeda, H.; Barenholz, Y. Pharmacokinetics of Pegylated Liposomal Doxorubicin: Review of Animal and Human Studies. *Clin. Pharmacokinet.* **2003**, *42*, 419–436. [CrossRef]
60. Caelyx Pegylated Liposomal 2 mg/mL Concentrate for Solution for Infusion—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/12931/smpc#gref (accessed on 9 July 2023).
61. Yildirim, Y.; Gultekin, E.; Avci, M.E.; Inal, M.M.; Yunus, S.; Tinar, S. Cardiac Safety Profile of Pegylated Liposomal Doxorubicin Reaching or Exceeding Lifetime Cumulative Doses of 550 mg/m^2 in Patients with Recurrent Ovarian and Peritoneal Cancer. *Int. J. Gynecol. Cancer* **2008**, *18*, 223–227. [CrossRef]

62. Gabizon, A.A.; Lyass, O.; Berry, G.J.; Wildgust, M. Cardiac Safety of Pegylated Liposomal Doxorubicin (Doxil/Caelyx) Demonstrated by Endomyocardial Biopsy in Patients with Advanced Malignancies. *Cancer Investig.* **2004**, *22*, 663–669. [CrossRef]
63. O'Brien, M.E.R.; Wigler, N.; Inbar, M.; Rosso, R.; Grischke, E.; Santoro, A.; Catane, R.; Kieback, D.G.; Tomczak, P.; Ackland, S.P.; et al. Reduced Cardiotoxicity and Comparable Efficacy in a Phase III Trial of Pegylated Liposomal Doxorubicin HCl (CAELYX/Doxil) versus Conventional Doxorubicin for First-Line Treatment of Metastatic Breast Cancer. *Ann. Oncol.* **2004**, *15*, 440–449. [CrossRef]
64. Hornberger, J.; Chhatwal, J. Opioid Misuse: A Global Crisis. *Value Health* **2021**, *24*, 145–146. [CrossRef]
65. Alenezi, A.; Yahyouche, A.; Paudyal, V. Current Status of Opioid Epidemic in the United Kingdom and Strategies for Treatment Optimisation in Chronic Pain. *Int. J. Clin. Pharm.* **2021**, *43*, 318–322. [CrossRef]
66. Iwanicki, J.L.; Severtson, S.G.; McDaniel, H.; Rosenblum, A.; Fong, C.; Cicero, T.J.; Ellis, M.S.; Kurtz, S.P.; Buttram, M.E.; Dart, R.C. Abuse and Diversion of Immediate Release Opioid Analgesics as Compared to Extended Release Formulations in the United States. *PLoS ONE* **2016**, *11*, e0167499. [CrossRef]
67. Geoffrey Severtson, S.; Kreider, S.E.D.; Amioka, E.C.; Margolin, Z.R.; Iwanicki, J.L.; Dart, R.C. Postmarketing Analysis of Misuse, Abuse, and Diversion of Xtampza ER. *Pain Med.* **2020**, *21*, 3660–3668. [CrossRef]
68. Argoff, C.E.; Kopecky, E.A. Patients with Chronic Pain and Dysphagia (CPD): Unmet Medical Needs and Pharmacologic Treatment Options. *Curr. Med. Res. Opin.* **2014**, *30*, 2543–2559. [CrossRef] [PubMed]
69. Gudin, J. Effect of Physical Manipulation on the Oral Pharmacokinetic Profile of Xtampza®ER (Oxycodone DETERx®Formulation): A Review of Published Studies. *J. Opioid Manag.* **2020**, *16*, 127–139. [CrossRef] [PubMed]
70. Brennan, M.J.; Kopecky, E.A.; Marseilles, A.; O'Connor, M.; Fleming, A.B. The Comparative Pharmacokinetics of Physical Manipulation by Crushing of Xtampza®ER Compared with OxyContin®. *Pain Manag.* **2017**, *7*, 461–472. [CrossRef] [PubMed]
71. Webster, L.R.; Kopecky, E.A.; Smith, M.D.; Fleming, A.B. A Randomized, Double-Blind, Double-Dummy Study to Evaluate the Intranasal Human Abuse Potential and Pharmacokinetics of a Novel Extended-Release Abuse-Deterrent Formulation of Oxycodone. *Pain Med.* **2016**, *17*, 1112–1130. [CrossRef] [PubMed]
72. Becker, W.C.; Fiellin, D.A. Abuse-Deterrent Opioid Formulations—Putting the Potential Benefits into Perspective. *N. Engl. J. Med.* **2017**, *376*, 2103–2105. [CrossRef] [PubMed]
73. Abuse-Deterrent Opioid Analgesics. Available online: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics (accessed on 29 September 2023).
74. Paclitaxel 6 mg/mL Concentrate for Solution for Infusion—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/10076/smpc#gref (accessed on 9 July 2023).
75. Sharma, U.S.; Balasubramanian, S.V.; Straubinger, R.M. Pharmaceutical and Physical Properties of Paclitaxel (Taxol) Complexes with Cyclodextrins. *J. Pharm. Sci.* **1995**, *84*, 1223–1230. [CrossRef] [PubMed]
76. Kumar, P.; Aditya, K. Paclitaxel Hypersensitivity. *Cancer Res. Stat. Treat.* **2020**, *3*, 419. [CrossRef]
77. Miele, E.; Spinelli, G.P.; Miele, E.; Tomao, F.; Tomao, S. Albumin-Bound Formulation of Paclitaxel (Abraxane ABI-007) in the Treatment of Breast Cancer. *Int. J. Nanomed.* **2009**, *4*, 99–105.
78. Hama, M.; Ishima, Y.; Chuang, V.T.G.; Ando, H.; Shimizu, T.; Ishida, T. Evidence for Delivery of Abraxane via a Denatured-Albumin Transport System. *ACS Appl. Mater Interfaces* **2021**, *13*, 19736–19744. [CrossRef]
79. Kratz, F. Albumin as a Drug Carrier: Design of Prodrugs, Drug Conjugates and Nanoparticles. *J. Control Release* **2008**, *132*, 171–183. [CrossRef] [PubMed]
80. Abraxane 5 mg/mL Powder for Dispersion for Infusion—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/6438/smpc#gref (accessed on 9 July 2023).
81. Desai, N.; Trieu, V.; Yao, Z.; Louie, L.; Ci, S.; Yang, A.; Tao, C.; De, T.; Beals, B.; Dykes, D.; et al. Increased Antitumor Activity, Intratumor Paclitaxel Concentrations, and Endothelial Cell Transport of Cremophor-Free, Albumin-Bound Paclitaxel, ABI-007, Compared with Cremophor-Based Paclitaxel. *Clin. Cancer Res.* **2006**, *12*, 1317–1324. [CrossRef]
82. Al Musaimi, O.; Al Shaer, D.; de la Torre, B.G.; Albericio, F. 2017 FDA Peptide Harvest. *Pharmaceuticals* **2018**, *11*, 42. [CrossRef]
83. Ozempic 0.25 mg Solution for Injection in Pre-Filled Pen—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/9748/smpc (accessed on 20 September 2023).
84. Maher, S.; Mrsny, R.J.; Brayden, D.J. Intestinal Permeation Enhancers for Oral Peptide Delivery. *Adv. Drug Deliv. Rev.* **2016**, *106*, 277–319. [CrossRef]
85. Rybelsus 14 mg—Summary of Product Characteristics (SmPC)—(Emc). Available online: https://www.medicines.org.uk/emc/product/14389 (accessed on 20 September 2023).
86. Kim, J.C.; Park, E.J.; Na, D.H. Gastrointestinal Permeation Enhancers for the Development of Oral Peptide Pharmaceuticals. *Pharmaceuticals* **2022**, *15*, 1585. [CrossRef]
87. Overgaard, R.V.; Navarria, A.; Ingwersen, S.H.; Bækdal, T.A.; Kildemoes, R.J. Clinical Pharmacokinetics of Oral Semaglutide: Analyses of Data from Clinical Pharmacology Trials. *Clin. Pharmacokinet.* **2021**, *60*, 1335–1348. [CrossRef] [PubMed]
88. Aungst, B.J. Absorption Enhancers: Applications and Advances. *AAPS J.* **2012**, *14*, 10–18. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.