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Advanced Drug Delivery Systems in Industrial Pharmacy: From Conventional Dosage Forms to Smart and Targeted Formulations

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Abstract

Advanced drug delivery systems (DDS) are one of the core and challenging areas of contemporary industrial pharmacy aiming to enhance the efficacy, safety, and adherence of the therapy. Conventional dosage forms have been the traditional dosage form for decades; however, these dosage forms have limitations such as bioavailability potential, dosing precision, and site-specific drug delivery which has led to the development of modified, novel, and smart drug delivery platforms. The aim of this narrative review is to gather the pharmaceutic and physicochemical mechanisms associated with the advanced drug delivery systems and link them with industrial production, regulatory requirements, and the clinical performance. A structured literature search was performed based on PubMed, Scopus and Web of Science database with the aim of finding research published in the last 10-15 years. Key search terms were drug delivery systems, modified release, nanoparticles, liposomes, targeted drug delivery, scale-up, Quality by Design and regulatory science. Evidence from formulation science, industrial investigations, and clinical translation is accumulating to show that while advanced DDS can improve the drug targeting, control its release and improve treatment outcome, they also impose strong challenges associated with the complexity of its manufacture, stability and regulatory approval. These dual and sometimes competitive effects point to the need for integrated frameworks for pharmaceutic - industrial evaluation. Future research enjoys linking between formulation design parameters with in vivo performance and industrial reproducibility to help with successful clinical and commercial translation.

Keywords: Drug Delivery Systems; Industrial Pharmacy; Nanoparticles; Liposomes; Bioavailability

1. Introduction

Drug delivery systems (DDS) are of prime importance in the field of pharmaceutical development as they affect the way a drug is released, absorbed, distributed, and finally experienced by the patient in terms of efficacy, safety, and adherence. In industrial pharmacy, conventional dosage forms (e.g., tablets, capsules, oral liquids, and injections) continue to be the manufacturing backbone because they have workflows with much less learning curve, are highly scalable, and have been highly regulated. However, the commercial evolution of DDS has shown a significant shift towards designs with the aim of intentionally engineering drug exposure profiles (time and site dependent) as mandated by modern therapeutic requirements including biologics and complex molecules [1-3].

Despite their success, conventional immediate-release products usually have some recognized shortcomings such as pharmacokinetic variability, frequent dosing needs, poor performance with poorly soluble/unstable drugs and inability to localize therapy to certain tissues. These limitations have led to formulation strategies to be expanded from immediate-release systems into modified/controlled-release systems, carrier-based strategies (including those of

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nanomedicines), as well as "smart" or targeted designs that are responsive to biological or exogenous triggers in order to maximize therapeutic outcomes [3,4].

At the same time, with growing complexity of advanced DDS comes major industry challenges - in particular reproducible manufacturing, robust process control, scale-up/technology transfer, and comprehensive characterization of critical quality attributes (CQAs). This is especially true for nanoparticle-based and other complex formulations, for which controlling consistent size distributions, drug loading, stability, and performance in function at a commercial scale is not so straightforward [4,5]. To overcome some of these challenges, there is a growing trend in industrial pharmaceutics towards Quality-by-Design (QbD) principles and structured and risk- and data-driven development to enhance the robustness and to support the expectations of regulators [6]. Parallel regulatory frameworks also provide another set of influences on feasibility and adoption, such as lifecycle management approaches (predictability of change after approval) and guidance for continuous manufacturing, regarding specific regulatory attention for products containing nanomaterials [7-9].

2. Review

2.1. Categories of Drug Delivery Systems/ Industrial Clinical Distinctions

Drug delivery systems (DDS) can be most appropriately considered in terms of a spectrum rather than a single homogeneous category. At one end are conventional dosage forms (e.g. immediate release tablets, capsules and standard injectables) still widely adopted as they are relatively simple to formulate, may be easy to scale up to facilitate manufacture, and are supported by well-established development and quality pathways. Progressively more complex stages are modified-release systems (sustained/controlled release) and novel carrier-based formulations (e.g., micro-/nano-carriers) and smart/targeted platforms which are designed to react to biological or physicochemical triggers and/or enhance site specific delivery. This "stepwise" evolution has usually increased not only the performance potential, but also increased the characterization, reproducibility, and translational feasibility of these properties from an industrial perspective [10,11].

Importantly, improved performance in vitro (e.g. release profiles, dissolution behavior, stability) is not always translated into clinical benefit highlighting the well-known "translation gap" between formulation design and in vivo behavior. One of the reasons for this is the difficulty of establishing a robust predictive relationship between in vitro release and in vivo exposure (IVIVC/IVIVR)-especially as the complexity of the delivery systems is increased and as several processes (release, dissolution, permeability, clearance) play a role in shaping the clinical profile [12]. In addition, variability is driven by the interplay between drug physicochemical properties and the function and variability of excipients (interactions between drug and excipient, excipient functionality difference) [13], but also by variability in patient and gastrointestinal tract (e.g., pH, GI tract transit, luminal fluids, food effects, special populations), which can significantly modify the oral absorption and pharmacokinetics even of the same product [14].

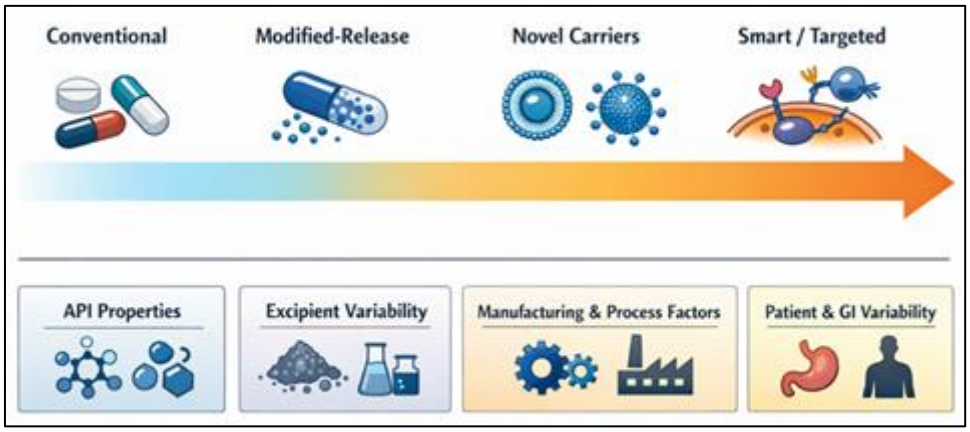

Figure 1 Evolution of Drug Delivery Systems in Industrial Pharmacy: from traditional dosage forms to smart and targeted drug delivery systems

3. Basic Pharmaceutical Mechanisms of Advanced Drug Delivery Systems

3.1. Formulation Architecture and Carrier Based Control of Drug Release

Advanced drug delivery systems (DDS) are based on architecture - the controlled assembly of binomials such as drug, excipients and carrier materials in space - in order to determine the way and extent in which the active pharmaceutical ingredient (API) will hydrate, dissolve, diffuse and ultimately become available for absorption. In polymeric matrix systems release is often controlled by some combination of diffusion through a hydrated polymer network, swelling of polymers (which increases the mesh size and permeability) and matrix erosion or degradation (which progressively changes the amount of resistance to structural components as well as convert diffusion-limited release to erosion dominated release). In parallel the designs and implementation of semi-permeable barriers and internal osmogen counterpart's setup osmotic gradients to drive water influx and generates near zero order release where there is no substantial change in mechanical integrity and membrane permeability. At the micro and nanoscale level, the surface area to volume ratio, porosity and tortuosity of particulate systems (e.g. polymeric microspheres, nanoparticles and printed micro-geometries) influence the burst release vs sustained phases and drug-income polymer miscibility and solid state (crystalline vs amorphous dispersion within a carrier) influence the initial "front-end" release behavior. Beyond polymers, lipid-based carriers (self-emulsifying systems, lipid micro/nanoparticles) can promote a change in the sequence of events (release-antigen absorption) by correlating drug solubilization and dispersion in gastro-intestinal (GI) fluids, or hydrogel and network systems can be engineered to result in water-triggered swelling, pH-dependent ionization, or enzymatically-mediated relaxation of the network system - all of which translate into different release kinetics. Importantly, "architecture" is not only a variable of the design of a lab; it is intimately related to manufacturability (e.g., reproducible pore structure as well as layer thickness and polarity of the geometry), as deviations in microstructure don't have to be as great as they can disproportionately change release profiles at scale. For industrial pharmaceutics, the mechanistic worth of formulation architecture thus takes up to be its potency for the conversion of molecular properties into predicted macroscopic performance - provided that the architecture can be manufactured and maintained consistently from one batch to another and within shelf-life [15].

3.2. Controlled and Modified Mechanisms of Release

Modified-release (MR) platforms are aimed at controlling time-dependent exposure - decreasing peak-trough fluctuation, maintaining therapeutic concentrations, and decreasing dosing frequency. Mechanistically, MR is often achieved by barrier formation (polymeric coating), matrix controlled release or multiarticulate designs which release drug into multiple sub-units in an attempt to minimize variability and provide programming of a lag time or pulsatile profiles. Film coating is still a focal industrial approach as it can separate the API core from the release-controlling layer: coating polymer type (enteric vs insoluble vs swellable), plasticizer concentration, coating thickness and curing conditions determine permeability, mechanical integrity and susceptibility to composition of the GI fluid. The reason in MR performance why often times the process parameters such as spray rate or inlet temperature, pan speed/fluidization dynamics, and atomization efficiency play important roles in the coating uniformity and microdefects that can cause a dose dump out or wider dissolution variability. From an industrial point of view, the question of MR success is not so much about hitting an "ideal" in-vitro curve once, and then worrying about building the same micro-barrier structure again and again, down the scales, and in trains of equipment. Even if the principle of formulation is simple (diffusion through a polymer film), there are other layers of complexity added by industrial reality: inter- and intra-batch coating variation and variation of raw material attributes, and also the need to closely control residual solvent, moisture and mechanical stress introduced in downstream handling and packaging. Critically, MR mechanisms need to be robust to differences across physiological variation between patients (fed/fasted state, GI transit time, local pH range, bile salt composition), which may pose a problem for enteric and pH-dependent designs. Therefore, industrial-clinical bridge for MR systems is realized in the form of developing mechanistic margins: coating systems and matrix designs that allow to cope with realistic process variability, physiological variability, without lecting small deviations in the form of clinically meaningful exposure deviations. In this regard, MR is an engineered compromise - between mechanistic control being too rigid, and manufacturability and real-world robustness [16].

3.3. Biopharmaceutic Barriers and Absorption Enhancement Strategies

Many advanced DDS are designed specifically to overcome biopharmaceutic barriers - poor aqueous solubility, limited dissolution rate, low permeability and pre-systemic loss. Mechanistically, absorption enhancement strategies typically work at one (or more) of three levels: (i) increasing the thermodynamic activity of the drug at the level of the absorption surface (solubility/dissolution enhancement), (ii) increasing effective residence time at the mucosa (mucoadhesion,

controlled local release) and/or (iii) facilitating the transport across epithelial membranes (paracellular modulation, transcellular uptake or transporter interaction). Amorphous solid dispersions (ASDs) are a good example of the first approach because by stabilizing an API in the amorphous high energy state within a polymer matrix, ASDs can create supersaturation in GI fluids that increases the concentration gradient driving absorption - provided recrystallization can be controlled through polymer selection, drug-polymer interactions and moisture management. However, the very same thermodynamic "advantage" which allows supersaturation is concerned, also establishes the stability hazard from ASDs, which are susceptible to humidity-induced phase separation and crystallization, and whose performance can be significantly affected by storage and processing. In parallel, chemical and functional absorption enhancers - including surfactants, fatty acids, and bile salt mimetics, as well as other excipients - can transiently change the properties of the membrane, loosen up tight junctions, or make the membrane more fluid; thereby enhancing epithelial transport. Yet this mechanistic leverage has accompanying safety and variability issues since the modulation of the barrier is too potent or too long lasting, the risk for irritation could be increased, local immunity might be interfered with and the potential exposure is too vague in sensitive population. Industrially, the hindrance is to provide a suitable "enhancement window" that is under control, reproducible at the level of manufacture and also very precise provenances to physiology (diet, bile salts, microbiome, disease states). Therefore, absorption-enhancing DDS should be tested according to not only the peak bioavailability enhancement, but also the predictability of exposure, the reversibility of the barrier effects and the stability of the formulation state that allows the mechanism to occur. (e.g. maintenance of ASD amorphicity or excipient performance through shelf-life) [17,18].

3.4. Targeting Strategies and Stimuli-Responsive Behavior

Targeted and "smart" DDS tries to bypass time-control and go for site-control and condition-control. Mechanistically it is possible to target drugs by either passively (by taking advantage of biodistribution tendencies such as increased permeability and retention in certain tumors) or by active targeting (by using ligands, antibodies, peptides, or small molecules connected to the surfaces of delivery vectors to bind to receptors overexpressed within a target tissue). Stimuli-responsive systems provide one additional level, in which the design of the carriers is such that it undergoes a change in behaviour when stimulated by pH, temperature, enzymes, redox state, ionic strength or external stimulus (light, magnetic field, ultrasound). The pharmaceutic logic is attractive - release the API where and when it is needed only but the mechanism is demanding. First, the ligand density, orientation and surface chemistry should be tightly controlled, as variations in one or more of these factors can change one's opsonization, clearance and binding efficiency. Second, there is a need to calibrate stimulus thresholds to real biological ranges, otherwise the carrier will either trigger prematurely (by releasing an off target trigger) or not trigger at all. Third is the industrial penalty (complexity), such as multi-step syntheses, narrow quality attributes for (for example) particle size distribution, zeta potential and ligand conjugation efficiency sensitivity to shear/temperature in scale up.. In addition, stimuli-responsive polymers and networks are often based on reversable transitions (e.g. swelling-deswelling, sol-gel switching, bond cleavage transition), which can be impacted by variability of their excipients and exposure to environmental parameters during storage. From the standpoint of industrial-clinical development, smart DDS are thus best thought of as mechanism-rich but trait-sensitive products: Smart DDS can potentially deliver a fair amount of therapeutic precision, provided their triggering and targeting mechanisms are reproducible on scale as well as robust against heterogeneity of biological targets. As a result, mechanistic evaluation must generally incorporate a combination of structure--function evaluation with the capability for verifying manufacturability requirements (process reproducibility, in-process controls, validated analytical methodologies that can provide evidence of significant changes in "smart" behavior) [15,17].

3.5. Stability, Degradation and Product Lifecycle Issues

Advanced formulations are often more sensitive to environmental and time-dependent change than conventional dosage forms so that stability is a very important and central determinant of real-world performance. For polymeric and carrier-based DDS, degradation can be a feature (e.g. biodegradable matrices) but degrade instead become a risk, when it happens during storage or it been uncontrolled. Mechanisms are the hydrolysis of polymer backbones, oxidation of lipids or surfactants, plasticization of polymers by moisture (changing permeability and release), aggregation of the colloidal carrier and solid-state transformations such as recrystallisation of ASD. These changes can alter partisanship liberation kinetics, reduce bioavailability, or introduce risk for dose dumping - turning another aspect or else an regulatory mechanism in a far way else to a inconsistent product. In the field of industrial pharmacy, stability is also a lifecycles issue: formulation and process changes (supplier changes, equipment upgrades, site transfers) may cause subtle changes in microstructure, residual solvent/moisture levels or coating integrity - all of which may make a difference in release. Film coating illustrates this interface, coatings may be used not only for MR behavior, but for the protection of moisture and mechanical robustness of the coating but also for stability will depend on the choice of polymer, curing and the formation of defects under stress. Similarly, ASDs indicate stability-performance tradeoff in that although the amorphous state offers advantages of supersaturation and absorption gains, eliminating degradation of the amorphous state over the course of the shelf-life requires carefully selected polymers, packaging strategy, and

controls on the exposure to humidities and temperatures. Practically, this is one reason why "advanced DDS" development treats stability more and more like a mechanistic of the yet unknown, rather than a late-stage checklist item - because the clinical mechanism (controlled release, enhanced absorption, targeting, etc.) can be lost if there is a drift in the formulation's intended structural state. Lifecycle planning thus combines analytics (stability-indicating), packaging engineering and manufacturing controls aimed at maintaining the critical architecture of the formulation from the release of the batch until end-of-shelf-life and through post-approval changes [16,17].

Table 1 Key pharmaceutic mechanisms of advanced drug delivery systems and their predicted effects on therapeutic performance and industrial complexity

Mechanism (examples)	Key levers	Therapeutic effect (likely)	Industrial complexity (likely)
Matrix-controlled release (polymer matrices, hydrogels) [19]	Polymer type, crosslinking, swelling/erosion	Sustained exposure; smoother PK	Sensitive to microstructure; release variability risk
Coating-controlled MR (enteric/SR coatings) [20]	Polymer, thickness, curing, coating uniformity	Delayed/sustained release; less dosing	Scale-up/CPP control critical; defect risk
Osmotic systems (osmotic pumps) [21]	Membrane, orifice, osmogen	Near zero-order release (possible)	Specialized steps; strict integrity testing
Supersaturation-based (ASDs) [22]	Polymer miscibility, Tg, moisture control	Higher bioavailability (poorly soluble APIs)	Stability (recrystallization) is main bottleneck
Lipid-based solubilization (SEDDS/SMEDDS) [23]	Lipid/surfactant mix, droplet size	Better absorption (lipophilic drugs)	Raw material variability; digestion-dependent behavior
Permeation enhancement (enhancers) [24]	Enhancer type/dose, exposure time	Increased permeability/bioavailability	Safety & inter-patient variability concerns
Active targeting (ligand-coated carriers) [25]	Ligand density, surface chemistry, size/charge	More site-selective delivery (context-dependent)	High characterization burden; reproducibility challenges
Nanocarrier scale-up (PLGA nanoparticles) [26]	Size/PDI, loading, residuals, aggregation	Protection + controlled release	Scale-up and QC are major bottlenecks
Stimuli-responsive (pH/redox/enzyme) [27]	Trigger chemistry, threshold, kinetics	On-demand/condition release	Highest complexity; validation and stability challenges

4. Industrial Manufacturing, Scale-Up, and Regulatory Translation

The transition from laboratory-scale formulation to industrial production is a frequent bottleneck for advanced drug delivery systems (DDS) Due to the fact that many complex platforms are highly sensitive to minor variations of raw materials and unit operations, the variability of key quality attribute and performance arises [28]. Regulatory translation hence requires placing ever more emphasis on creating structured developmental frameworks and open control strategies linking formulation design with manufacturable product quality [29]. Within this context, reiterated obstacles persist in translational reviews including inadequate definition of critical quality attributes (CQAs), poor standardization of analytical techniques to characterize heterogeneity and poor comparability strategies in scaling-up and lifecycle changes [30]. Regulatory agencies therefore impose the stringent requirement for characterization, stability information and performance validation-and as the complexity of DDS increases, these demands become more burdensome [31].

From an industrial engineering point of view scale-up is often not a simple 'linear' increase in the size of a batch. For example, manufacturing reviews of solid lipid nanoparticle (SLN) production include the importance of the scalable routes (e.g., high-pressure homogenization and so forth) that can enable the manufacture of a commercial product only if particle size distribution, loading, aggregation, residuals, and stability can be controlled within validated process windows [32]. Increasingly, both continuous and hybrid manufacturing strategies are being discussed as enabling possible to improve control over their production process and explain the reduction of batch-to-batch variability of the nanoparticles produced, although integration of upstream/downstream operations and regulatory alignment, remain non-trivial [33]. Overall, wider assessments of the readiness of nanomedicine remain vivid anterior to the complexity and dynamic thought of the effectual law - anchoring a fresh need for early scientific advice, platform suitable analytics strategies and for keeping robust control strategies for product quality all over the lifecycle [34].

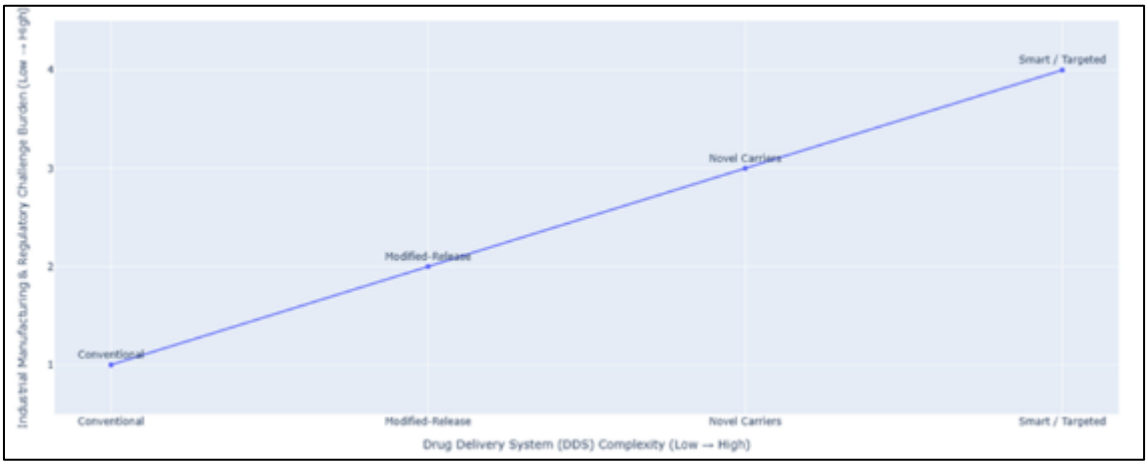

Figure 2 Relationship between drug delivery system complexity and industrial manufacturing and regulatory challenges

5. Advanced Drug Delivery Systems and Therapeutic Outcomes

Advanced drug delivery systems (DDS) can often be justified based on the potential to enhance therapeutic outcomes such as optimized WG/c pharmacokinetic and immunologic alterations (PK), minimized systemic toxicity, enhancing convenience, or enhancing site-of-action exposure. However, the true clinical impact of an advanced DDS is dependent on whether these technical advantages are translated into clinical benefits, in terms of better outcomes for patients and health systems - and this under conditions of real-world use where dosing behaviours, comorbidities and constraints of access determine real-world outcomes. One of the main reasons for "underperformance" in practice is the lack of automatic resolution of the dominant causes of treatment failure, especially non-adherence and treatment burden, by improved formulation performance. Next generation DDS can have significant impact on reducing barriers to adherence by reducing dosing frequency, increasing tolerability, allowing for alternative routes of administration, or offering more acceptable user experiences, but their benefit is only realized if these variants are well suited to the adherence barrier that predominates in a given disease setting (e.g., forgetfulness vs adverse effects vs complex administration) [35].

Clinical benefit is also limited by translation gaps: a DDS may do well in controlled in vitro tests (or even in animal models), but fail to produce appropriate commensurate benefit in humans because of heterogeneity in physiology, endpoint choice and product design/clinical applications. A "top-down" translational mindset has therefore been promoted for complex platforms (notably nanomedicines) in which end-user needs are seriously considered early, feasibility and trial design and clinically thought-through endpoints are considered rather than relying on mechanistic promise alone [36].

Integrated evaluation frameworks are going to be needed more and more to determine whether an advanced DDS is truly outcome-improving. These frameworks facilitate networking between (i) PK/biopharmaceutic gains (e.g. exposure control, reduced variability); (ii) clinical endpoints for efficacy and safety; (iii) patient relevant endpoints (convenience, acceptability, quality of life); and (iv) constraints for implementation (training, supply chain, stability and usability of the devices) Review of authorized medicinal products shows the opportunities of formulation/DDS selection in enhancing benefit--risk by modifying PK (including route of delivery and long-acting formulation), but also reveal that enhancement should be demonstrated in clinically relevant situations, as well as sustained throughout the product lifecycle [37].

Therapeutic "success" has to be interpreted in relation to cost and accessibility Complex DDS can contribute to increased manufacturing and quality burdens that can lead to increased prices and limited availability, even with clinical sound technology. Systematic assessments of advanced DDS balance adoption as often constrained by biological barriers and manufacturing complexity and cost, supporting that outcome claims be coupled with a feasibility and value argument (e.g. reduced visits to hospital, improved persistence, or less complications) [38].

6. Impact on Patient Compliance and Quality of Life

Advanced drug delivery systems (DDS) can improve patient compliance primarily by reducing regimen burden (e.g., less frequent dosing), ease of use, and tolerability - factors which have a direct impact on how consistent patients can be when following therapy in the real world, Beyond "release control," adherence is often based on the experienced usability of the product: is it swallowable, does it taste good, does it come in the dose appropriate for the medication, does it have discomfort levels during injection, does it require device steps, is packaging legible and readable, and is the usability in daily routines practical (relating to work and travel, training in privacy and in presence of family, or caregivers)? A patient-centric drug product design approach therefore does not consider dosage form selection, packaging, and administration modality as adherence-less, post-marketing considerations [39].

Quality of life (QoL) benefits may follow from DDS decreasing the fluctuation of symptoms or the adverse effects or treatment disruptions of a disease - particularly for chronic diseases in which continued pharmacologic coverage and predictable exposure can result in improved function and fewer daily restrictions. However, these are not automatically attained benefits - one can still have a "superior" DDS with adverse effects on adherence (increasing complexity and requiring special handling, necessary refrigeration and training, etc.) or burden on patients (requiring mandatory clinic visits, an anxiety response to injections or stigma). Because of this, the incorporation of patient needs in modern patient-centric development has increasingly occurred within and as part of the Quality Target Product Profile (QTPP) and includes formulation/device decisions based on the feasibility of Chemistry, Manufacturing, and Controls (CMC) and combination-product requirements throughout the lifecycle [40].

A major shortcoming in the field is that the patient-centered endpoints are not consistently captured. In an analysis of systematic reviews concentrating on outcomes used to assess medication-adherence-enhancing interventions, patient-reported outcomes were measured in a minority of studies and health-related QoL was assessed for a limited proportion - indicating a continued evidence gap between "adherence improvement" claims and benefit experienced by the patient [41]. Regulatory practice is also changing: according to an analysis of European Public Assessment Reports (EPARs) for medicines reviewed by the European Medicines Agency between 2017-2022, evidence of patient-reported outcomes has been seen in a substantial but not universal proportion of patient assessments, reinforcing the idea that QoL and patient experience is gaining increasing relevance but not necessarily decision importance in drug approvals [42].

The benefit of cost and access can counter the benefit of adherence and improved QoL. Even if long-acting or advanced platforms have high acceptability, implementation barriers, such as prior authorizations, procurement logistical challenges and costs incurred at the clinic level, may prevent equitable uptake - meaning that "better DDS" may be functionally unavailable to patients who could benefit most [43].

6.1. Future Directions

Future research in advanced drug delivery systems (DDS) should go beyond "better formulations" instead of linking to somehow end-to-end evidence chains (formulation architecture --> in vivo exposure --> clinical response --> manufacturability & lifecycle control). A priority is broader implementation of model-informed drug development workflows -- specifically physiologically based pharmacokinetic (PBPK) development approaches -- to sponsor model the hypotheses of release/absorption into quantitative predictions in subsets of the population (food effects, GI variability, organ impairment) and to enable rational decisions regarding dosage form earlier in the drug development process [44].

From an industrial feasibility point of view the field will rely more on digitized manufacturing control strategies, which can manage greater formulation complexity without a loss of reproducibility. This includes wider use of process analytical technology (PAT) and monitoring of Intermediate quality attributes using data in order to support the continuous verification of the process and validate the robust scale-up decision making [45]. In parallel, increasing real-time release testing (RTRT) as allowed by scientific justification can reduce release timelines and reduce reliance on end product testing when models for the sensors are validated and well correlated with crucial quality attributes [46]. Regulatory translation will also change in the form of increased alignment with modern guidance on analytical procedure development and lifecycle management. Implementing science and risk approaches (including multivariate

procedures where appropriate) may help make methods more robust and allow for more predictable pathways for change after approval [47,48].

Finally, to ensure that DDS innovation results in meaningful health impact, more studies should include frameworks for real-world evidence (RWE) to assess adherence, persistence, safety signals and comparative effectiveness after launch - with particular attention to costly 'smart' platforms where access and use conditions play a strong role in determining outcomes [49].

7. Conclusion

Advanced drug delivery systems (DDS) have evolved from conventional dosage forms towards modified-release, carrier-based and smart/targeted systems with a view to engineering drug exposure for improved efficacy, safety and convenience of treatment. However, throughout the DDS spectrum, the same mechanism features that provide the performance increases- (controlled release architectures, supersaturation-based absorption enhancement, permeation modulation and targeting/triggering functions) simultaneously amplify the risk of development through heightened sensitivity to variability and stability drift risk as well as manufacturing complexity. As highlighted in this review, translation success is therefore not defined by the attainment of an "ideal" in-vitro profile per se but by demonstrating an end-to-end evidence chain relating formulation architecture and key quality attributes to predictable in-vivo exposure and clinically meaningful benefit and being scalable and controllable throughout product lifecycle. From the point of view of an industrial pharmacy, the main need is to combine the pharmaceutic mechanism with manufacturability: and how to define robust CQAs/CPPs, to standardize the characterization of heterogeneous products, to define control strategies, to always maintain the intended microstructure and performance during scale-up, transfer of technology, packaging and post-approval changes. In parallel, the clinical value proposition of advanced DDS should be backed up with patient-centric endpoints and, where applicable, the only real-world evidence of adherence, persistence, safety, and comparative effectiveness, particularly for complex and expensive "smart" platforms whose real-world impact may be limited by access and implementation constraints. Collectively, these considerations support the need for integrated frameworks, spanning from formulation design to industrial control to regulatory expectations to therapeutic outcomes, which help to maximize the likelihood of successful clinical and commercial translation.

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