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# COMPLEX DRUG DELIVERY SYSTEMS

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**ABSTRACT:** The majority of current drug delivery systems are existed as water-insoluble drug delivery systems but rarely water-soluble drug delivery systems. Low aqueous solubility is a common problem in pharmaceutical development. About 40% of commercialized drugs and as many as 90% of drugs in the discovery are low aqueous soluble. When given through traditional dosage forms, such drugs fail to be soluble and have limited bioavailability, so they tend to show limited therapeutic effect and often fail. Various methods to solubilize drugs usually involve a combination of pH modifiers, salt forms, co-solvent systems, surfactants, or complexation. A complex drug system is generally a complex system incorporated with API and compatible excipients to produce the desired effect. Complex drug systems are simply referred to as uncommon products that were not typical tablets. However, with the rise of insoluble API biologics, complex drug systems are quickly gaining importance. Most used complexes include phosphor lipid complex, chitosan complex, cyclodextrins complex, phosphatidylcholine complex. Complex drug systems are employed in various areas for treating various clinical conditions like insulin complexes for antidiabetic treatment, platinum complexes for anticancer treatment, cyclodextrins complexes for schizophrenia. They are developed by solubilization & bioavailability enhancement techniques, drug-eluting systems, sterile products, highly potent API or controlled substances.

**INTRODUCTION:** Drug delivery is the technique of regulating a drug to achieve a therapeutic effect in people. Drug substances such as fuse liposomes, proliposomes, microspheres, gels, cyclodextrins, prodrugs among others, have significant advantages over conventional dosage forms [1]. There might be a consistent, controlled, or focused drug delivery with this kind of system.

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As per clinical application, various drugs are being controlled through different conventional drug delivery dose structures such as solutions, lotions, mixtures, creams, gels, balms, powders, suppositories, suspensions, injectables, pills, immediate-release capsules, and tablets, *etc*. to treat unique infections. Development of new devices

with improved potential incorporate oral controlled delivery, fast dispersing dose structures, liposomes, taste-markers, transdermal patches, and site-specific delivery systems [2]. A newly emerging approach was developed based on the combination of phosphor lipid complexation and micelle techniques to enhance the oral antidiabetic effect of repaglinide (RG), Repaglinide-phospholipid complex (RG-PLC) was prepared by the solvent-evaporation method [3]. The concept of employing electrospun nanofibers as a matrix and improving hydrophobic compounds' solubility by combining drug/CD-IC and versatile electrospinning process [4]. Platinum (IV) complex has the striking advantage of the functional modification of the axial ligands for improved physicochemical properties and pharmacokinetic profiles. Many promising achievements were obtained in the field of Pt (IV) complex-based nano delivery systems. However, the limitations such as safety of the nanocarriers and scale-up production may impede Pt (IV) complex-based nanomedicines translation into clinical studies for stimuli-triggered drug release, ligand-mediated targeting, and combinational drug therapy [5]. The article focuses on the classification, ability of various complexes to enhance drug release at targeted sites and their applications**.** Complex Drug Systems have become so prevalent that the FDA has defined them with the following categories as mentioned in **Table 1.**

**TABLE 1: FDA CLASSIFICATION OF COMPLEX SYSTEMS**

| Classification | Examples |
|---|---|
| Complex Active Ingredients | Peptides, polymeric compounds |
| Complex formulations | liposomes, colloids. |
| Complex routes of delivery | Locally acting drugs, ophthalmological products such as suspensions, emulsions, or gels. |
| Complex dosage forms | Implantable, transdermal, metered-dose inhalers, extended-release injectable |
| Complex drug-device combination products | Auto-injectors[6]. |

**Complex Active Ingredients API:** Every drug product contains API, irrespective of its route and dosage form. Newer drugs are difficult to obtain frequently by simple approaches, as traditional solid oral dosage forms. This usually causes problems related to the bioavailability of dosage forms, particularly for BCS-II oral drugs. In 2017, there were 63 drug product grants to 505(b) (2) regulatory pathways, an all-time high. This route of approval has become of significant importance over the last decade and usually involves innovative dosage forms or drug delivery methods that are considered complex. These results in increased compliance, improve patient outcomes and provide additional economic opportunities for their sponsors, but they are considered as complex Drug Systems due to the following criteria

- Challenges in scale-up
- Less defined regulatory pathway
- Complex formulation and excipients
- Complicated characterizations
- No standard *in-vitro* drug release assay
- Few models correlating *in-vitro* drug release with *in-vivo* pharmacokinetic [7].

**Complex Dosage Forms:** Any non-oral complex dose structure has regularly at least two discrete matters inside the formulation. There are various methods available to increase the solubility of drugs and improve their delivery, including particle size reduction, micronization and nano milling, and amorphous solid dispersions, namely hot melt extrusion or spray drying processes. Encapsulation methods include Solid lipid Particles, liposomes, and reverse cubic phase particles.

**Complex Drug Devices:** In this type, the drug constituent part is pre-stacked in a device, in which the device configuration influences drug delivery to the site of absorption. Drug-eluting systems (DES) are combinations of drugs and polymer wherein the polymer acts as a vehicle to deliver the drug. There are two categories of drug-eluting systems **Table 2.**

**TABLE 2: TYPES OF DRUG-ELUTING SYSTEMS**

| Biodegradable DES (bio absorbable) | Bio durable drug-eluting devices |
|---|---|
| Use biocompatible materials such as Poly Lactic-co-Glycolic Acid (PLGA) to deliver drugs that decompose in the body over time. | Use biocompatible materials like silicone, polyethylene-vinyl acetate, and thermoplastic polyurethane (TPU) to deliver drugs. Bio durable drug-eluting devices can be designed as a matrix, reservoir, or osmotic systems to deliver drugs via diffusion or osmosis [8]. |

**Complex Transdermal Systems:** These are commonly intended to convey an API through the skin for systemic activity. The saturation of an API through the skin is constrained by changing drug concentration and preparation composition [9]. A bilayer drug in adhesive TDDS configuration may permit improved permeation of the drug release by fluctuating layer thicknesses and drug spatial circulation over each layer [10]. **Table 3.** illustrates the previous research work done by various researchers using a specific complex and the API and excipients used to develop an intended complex drug delivery system.

**TABLE 3: PAST WORK DONE ON THE COMPLEX DRUG DELIVERY SYSTEM**

| S. no. | Drug Name | Excipients used | Complex | Reference |
|---|---|---|---|---|
| 1 | Amphotericin B | 4-arm-PEG$_{10,000}$-MAL Amphotericin B (AmB) Coumarin-6 (C6) 1,1′-Dioctadecyl-3,3,3′,3′-tetramethylindotricarbo cyanine iodide (DiR). Rabbit anti-SPARC antibody | micro-to-nano (MTN) albumin Complex | 11 |
| 2 | Doxycycline Hydrochloride | Transcutol Hp, Poloxamer 188 And Cremophor Rh40 Peceol, Labrasol, Labrafac Lipophile Wl1349 | Polysaccharide | 12 |
| 3 | amlodipine besylate | β-Cyclodextrin, Peg- Kolliphor Ps20, Polysorbate 20 (Ps20), And Kolliphor P188, Poloxamer 188. | β-Cyclodextrin Inclusion complexes | 13 |
| 4 | Thiram | HPMC β-CyclodextrinThiram, Dimethyl Sulfoxide, Triethylamine, Sodium Chloride | hydroxypropyl-*C* inclusion complex | 14 |
| 5 | Folic acid | Lignin, Ethanol, Sodium Hydroxide, Sulfuric Acid. Sodium Dodecyl Benzenesulfonate, 3-Chloro-2 Hydroxypropyltrimethylammonium Chloride, | Platinum Complex | 15 |
| 6 | 5 – Fluro Uracil | Berberine, Ethanol, Formic Acid, Methanol & Acetonitrile. | Hydrogel Complex | 16 |
| 7 | Boron Nitride | Boron Nitride, Poloxamer 188 (P188), Poly (Ethylene Glycol), Poly (Propylene Glycol), Poly (Ethylene Glycol), Dichloromethane, Ethyl Alcohol | Nanocarriers | 17 |
| 8 | Eudragit® | SpioNanoparticles, Phosphate-Buffered Saline (Pbs), Nitric Acid, HCL | Interpolyelectrolyte complexes | 18 |
| 9 | Domperidone | Domperidone, Sodium Polystyrene Sulfonate, Dodecyl Trimethyl Ammonium Bromide | Domperidone resinate complex | 19 |
| 10 | Tetracycline | Tetracycline, anionic beta-cyclodextrin complex, Sulfisoxazole, Ethanol, Acetonitrile, Methanol, | anionic beta-cyclodextrin complex | 20 |
| 11 | Ruthenium | Polyethylene Glycol,Poly (Glutamic Acid), Poly(L-Lysine), Methoxylpoly(Ethylene Glycol). | polypyridyl complexes | 21 |
| 10 | ferulic acid | Cyclodextrins, Cellulose, Sulphuric Acid, Glycidyltrimethyl Ammonium Chloride, B-Cyclodextrin | cyclodextrin inclusion complex | 22 |
| 13 | 5-fluorouracil | Chitosan, Acetone, Ether, Methanol, Ethanol, Pyridine, Dmso | Chitosanaptamer complex | 23 |
| 14 | Insulin | Insulin, phosphatidylcholine, Deoxynucleotidyl Transferase, Poly (ADP-Ribose) Polymerase. | phosphatidylcholine complex | 24 |
| 15 | Ibuprofen | Ibuprofen, Sulfisoxazole, Ethanol, Acetonitrile, Methanol, Lysozyme | Polyelectrolyte–surfactant–complex | 25 |
| 16 | Supramolecules (DNA) | Chitosan, phosphatidylcholine, Deoxynucleotidyl Transferase, Poly (ADP-Ribose) Polymerase | Chitosan Complex | 26 |
| 17 | Chitosan-N-acetylcysteine | Chitosan, acetylcysteineTriethylamine, Tetrahydrofuran, Dichloromethane | HP-β-CD inclusion complex | 27 |
| 18 | carboxymethyl starch (CMS) and chitosan (Cs) | Capryol 90, Labrafac Cc, Labrasol, Lauroglycol, Oleic Acid, Tween 80, Tween 20, Span 20, Propylene Glycol, Peg 400 And Peg 200 | polyelectrolyte complex | 28 |
| 19 | Domperidone | Domperidone, Simvastatin, Filipin, 1, 6-Diphenyl-1, 3, 5-Hexatriene, Nile Red, Verapamil, Fetal Bovine Serum | resinate complex | 29 |

| | | | | |
|---|---|---|---|---|
| 20 | chitosan | Calcium hydride, PEG, Methyl Ether, Tetrahydrofuran, Fluorescein Isothiocyanate | polyelectrolyte complexes | 30 |
| 21 | Metronidazole | Metronidazole, Hydroxypropyl-β-Cyclodextrin, Monomethyl Ether, Γ-Benzyl-L-Glutamate-N-Carboxyanhydride (Blg-Nca) Dimethylformamide | Hydroxypropyl-β-Cyclodextrin inclusion complex | 31 |
| 22 | paclitaxel | Paclitaxel, Sodium Hydroxide, Glacial Acetic Acid, Sodium Acetate, Sodium Starch Glycolate (SSG), Potassium Dihydrogen Phosphate, Magnesium Stearate, Talc | phospholipid complex | 32 |
| 23 | Curcumin | Acetone, Paraformaldehyde, Xylene, Toluene, Ether, Ethanol, P-Tert-Butylphenol, Phenol, Sodium Hydroxide, Barium Carbonate, Aluminum Trichloride, Concentrated H2so4 &Hcl, Phosphate Buffered Saline pH 7.4 | lecithin complex | 33 |
| 24 | indomethacin | High Amylose Starch (HylonVii), Lecithin, Glyceryl Tristearate, Carboxymethylcellulose, Ethyl Cellulose, Mesalamine | phospholipid complex | 34 |
| 25 | Doxorubicin hydrochloride | 6-Deoxy-6-[(2-Aminoethyl) Amino]-B-Cyclodextrin, Folic Acid, N-Hydroxysuccinimide, Carboxymethylcellulose, Xanthan, Pectin, Alginate | DOX-MSN-ZnO-PLL-PLL(DMA) | 35 |
| 26 | iridium | Polyethylene Glycol, Poly (Glutamic Acid), Poly(L-Lysine), Methoxylpoly(Ethylene Glycol). | polypyridyl complexes | 36 |
| 27 | benznidazole | Polyethylene Glycol, Poly (Glutamic Acid), Cellulose, Sulphuric Acid, Glycidyltrimethyl Ammonium Chloride, B-Cyclodextrin | polymethacrylate interpolyelectrolyte complexes | 37 |
| 2 | clindamycin phosphate | Polyethylene Glycol, Poly (Glutamic Acid), Poly(L-Lysine), Methoxylpoly(Ethylene Glycol), Acetone, Ether, Methanol, Ethanol, Pyridine, Dmso. | polyelectrolyte complex | 38 |
| 8 | Atenolol | Atenolol, β-cyclodextrin,Deoxynucleotidyl Transferase, Poly (ADP-Ribose) Polymerase | β-cyclodextrin | 39 |
| 29 | Lidocaine | Lidocaine, β-cyclodextrinRibonuclease A, Trypsin, Thrombin, N-Hydroxysuccinimide, Lysozyme. | β-cyclodextrin | 40 |
| 30 | chlorthalidone | Soluplus, chlorthalidone, sodium lauryl sulfate Methoxylpoly(Ethylene Glycol) | Soluplus-sodium lauryl sulfate complex | 41 |
| 31 | Titanium Dioxide | ruthenium, Cellulose, $TiO_2$, Sulphuric Acid, Glycidyltrimethyl Ammonium Chloride, | ruthenium complex | 42 |
| 32 | methotrexate &cyclophosphamide | methotrexate &cyclophosphamide, N-Hydroxysuccinimide, Dicyclohexyl Carbodiimide, Acetone, Ether, Methanol, Ethanol, Pyridine, Dmso | Interpolymer complex | 43 |
| 33 | Indomethacin-Eudragit® | Indomethacin, Eudragit, Deoxynucleotidyl Transferase, Poly (ADP-Ribose) Polymerase. | Interpolyelectrolyte complexes | 44 |
| 34 | hyaluronan | Poly-4-Phenylene Tetraiodide (PFEP), Sodium Hyaluronate, Hyaluronidase, Ribonuclease A, Trypsin, Thrombin, N-Hydroxysuccinimide, Lysozyme. | polysaccharide complexes | 45 |
| 35 | Rhenacarborane | Polyethylene Glycol, Poly (Glutamic Acid), Poly(L-Lysine), rhenacarborane Methoxylpoly(Ethylene Glycol) | rhenacarborane complexes | 46 |
| 36 | Breviscapine | Polyethylene Glycol, Poly (Glutamic Acid), Poly(L-Lysine), Cellulose, Sulphuric Acid | Polyelectrolyte-ionic complexes | 47 |
| 37 | Oxaprozin | Oxaprozin, N-Hydroxysuccinimide, Dicyclohexyl Carbodiimide, Acetone, Ether, Methanol, Ethanol, Pyridine, Dmso | hydrogels and nickel complex | 48 |
| 38 | folic acid | Cyclodextrins, Folic AcidCellulose, Sulphuric Acid, Glycidyltrimethyl Ammonium Chloride, B-Cyclodextrin | cyclodextrin complex | 49 |

Marketed products of the complex drug delivery systems were represented in **Table 4.**

**TABLE 4: MARKETED COMPLEX DRUG PRODUCTS**

| | |
|---|---|
| Ozurdex® | NuvaRing® |
| Zuplenz® | Narcan® |
| Avycaz® | Bendeka™ |
| Omnitrope® | Yosprala™ |
| Lupron Depot®, | Xuriden™ |

**CONCLUSION:** The literature search unquestionably ratifies the progressively increasing popularity of complex drug systems in designing formulations.

A variable number of complexes were seen in the drug industry, where they are applied much more frequently. Only a min fraction of industrial studies were reported and most investigations remain as only in-house information.

The supervision and control of new complex system development help in product improvement.

**TABLE 5: APPLICATIONS OF COMPLEX DRUG DELIVERY**

| S. no. | Complex | Application |
|---|---|---|
| 1 | Hydrogel PEG PA-PEG | Tissue engineering. Live cell biosensor. Glucose biosensor [50] |
| 2 | PLGA/PVA complex gel | Temperature-sensitive polymer system for drug delivery [51] |
| 3 | polyelectrolyte complex | Carrier for colon-specific drug delivery [52] |
| 4 | cyclodextrin-naproxen inclusion complex | Enhanced solubility and permeation of poorly water-soluble drugs[53.] |
| 5 | lidocaine (LC) and β cyclodextrin (β-CD) inclusion complex | Improve the drug safety and enhance the penetration and release of the drug[54]. |
| 6 | morin-phospholipid complex | Enhance oral bioavailability+42 |
| 7 | Rosin Cyclodextrin Complexes | AS film-forming materials to achieve controlled drug release. Matrix-forming material to achieve sustained drug release. AS for taste masking agents in oral drug delivery [55] |
| 8 | Chitosan Complex | Enhances the residence time of the system and consequently the bioavailability of the drug [56] |
| 9 | Polyelectrolyte Complex | Controlled Loading and Improved Release performance for Bone Therapeutics |
| 10 | lignin-based complex micelles | Used for pH drug dependence [57] |

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