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CURRENT STATUS AND FUTURE DIRECTIONS OF NEW DRUG DELIVERY TECHNOLOGIES

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ABSTRACT
New drug delivery systems based products have significantly increased in the past few years, and this growth is expected to continue in the near future. Today a large number of companies are busy developing protein- and peptide-based drugs. Large molecules that degrade rapidly in the blood stream so these biopharmaceuticals (proteins, peptides, carbohydrates, oligo-nucleotides, and nucleic acids in the form of DNA) present drug delivery challenges. Moreover, they have a limited ability to cross cell membranes and generally cannot be delivered orally. Such molecules will be much more difficult to deliver via conventional routes, and injections may be the only means of delivery (at least as of today). This review is an update on some of the existing drug delivery technologies for oral controlled-release, delivery of large molecules, liposomes, taste masking, fast-dispersing dosage forms, and technology for insoluble drugs, nasal, pulmonary, vaginal, and rectal routes.
KEYWORDS New drug delivery systems, biopharmaceuticals, oligo-nucleotides, liposomes, fast-dispersing dosage forms

INTRODUCTION

New drug delivery systems based products have significantly increased in the past few years, and this growth is expected to continue in the near future. Today a large number of companies are busy developing protein- and peptide-based drugs. Recent advances in the field of genomics have accelerated research of biopharmaceuticals but present challenges to drug delivery scientists because of their unique nature and difficulty in delivery through conventional routes so future research will focus on the delivery of these complex molecules through different routes, including oral, nasal, pulmonary, vaginal, rectal, etc. This review is an update on some of the existing drug delivery technologies for oral controlled-release, delivery of large molecules, liposomes, taste masking, fast-dispersing dosage forms, and technology for insoluble drugs, nasal, pulmonary, vaginal, and rectal routes. In the 21st century, the pharmaceutical industry focused on designing and developing new and better methods of drug delivery. There has been a significant increase in approvals of new drug delivery systems (NDDS) in the past couple of years, and this is expected to continue at an impressive rate in the near future[1].

Current status of Drug Delivery Technologies

Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety, and improved patient compliance. Pharmaceutical companies to engage in the development of new drug delivery systems because the need for delivering drugs to patients efficiently and with fewer side effects has prompted. Today, drug delivery companies are engaged in the development of multiple platform technologies for controlled release, delivery of large molecules, liposomes, taste-masking, oral fast dispersing dosage forms, technology for insoluble drugs, and delivery of drugs through intranasal, pulmonary, transdermal, vaginal, colon, and transmucosal routes[2].

(A) Oral controlled release[3,4]

The traditionally preferred route of drug administration is oral ingestion, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of the drug, grossly excessive doses for effective concentration at the target site, unpredictable and often sub- or supra-therapeutic plasma concentrations leading to marked side effects. An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period and maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. A number of techniques are used to achieve controlled release of drugs via the oral cavity. Some of these techniques are reviewed briefly as follows in Table 1.

Table 1. Oral controlled release techniques

S.No.	Oral controlled release techniques
1	**Macrocap** A controlled release pellet system, which is based on the coating of pellets containing pharmaceutical compounds with specialized polymers and plasticizers to control the rate and location of drug release in the gastrointestinal (GI) tract. The Macrocap system uses pH-activated or pH- independent diffusion, osmotic diffusion, or a combination of these mechanisms (control the delivery of drugs depending on the pH environment of the GI tract).
2	**Micropump** Micropump dosage form is composed of thousands of microparticles ranging in size between 200 and 400 mm and having a bioadhesive surface. Each microparticle contains a drug crystal or granule enclosed in a polymer coating that acts as a shell through which the drug can be released under the effect of osmotic pressure.
3	**MODAS (Multiporous oral drug absorption system)** The tablet consists of a core of active drug plus excipients and coated with a solution of insoluble polymers and soluble excipients. After ingestion, the fluid of the gastrointestinal tract dissolves the soluble excipients in the outer coating leaving just the insoluble polymer, thereby forming a network of tiny, narrow channels connecting fluid from the GI tract to the inner drug core of water-soluble drug. This fluid passes through these channels into the core, dissolves the drug and a resultant solution of drug diffuse out in a controlled manner to the outside.
4	**SCOT** or (**Single composition osmotic tablet system)** Based on osmotic principles and utilizes various osmotic modulating agents as well as polymer coatings to provide a zero-order release of a drug.
5	**Portab system** An osmotic core, typically containing a water-soluble drug. The core includes a water-soluble component and a continuous polymer coating. The purpose of the soluble agent is to expand the core and thereby create microporous channels through which the drug is released.
6	**Zer-Os tablet technology** An osmotic system developed specifically for the delivery of lipophilic compounds. The tablet consists mainly of a core of poorly water soluble drug, gel forming agents and standard excipients. The gel-forming agent, after coming in contact with water, forms a gel of an appropriate viscosity, and a suspension of a poorly water-soluble agent is formed and is pushed out of the orifice at a controlled rate.

7	**Ceform microsphere technology** These microspheres are perfectly spherical, diameter is typically 150 to 180 mm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres can be formulated for enhanced absorption (Ceform EA) or taste isolation (Ceform TI) and may be coated for controlled release (Ceform CR), provided with an enteric coating (Ceform EC), or combined into a fast/slow release combination (Ceform EA/CR).
8	**CONSURF (Constant surface area drug delivery shuttle)** These matrix tablet releases drug by the concurrent swelling and dissolution. A constant surface area is presented during the drug's transit through the GI tract.
9	**Contramid** The chemical cross-linking of a starch consisting mainly of amylose leads to Contramid. Once the Contramid dosage form is in the stomach, gastric fluids turn contramid's surface to gel and the resulting semipermeable membrane stabilizes rapidly. This membrane, which does not begin to break down until it reaches the colon, ensures that there is a regular release of the active ingredients contained in the dosage form.
10	**Dimatrix or Diffusion controlled matrix system** Consists of either bead made by extrusion-spheronization or by powder/ solution layering on nonpareil beads or in the form of a tablet matrix. The mechanism of release is by diffusion of dissolved drug molecules.
11	**Multipart or Multiparticle drug dispersing shuttle** Consists of a tablet that carries controlled release beads or pellets through the GI tract while maintaining their integrity and release properties. Release and distribution of the beads is triggered by super disintegration of the tablet.
12	**DPHS (Delayed pulsatile hydrogel system)** Hydrogel matrix products that are characterized by an initial zero-order release of drug followed by rapid release. This release profile is achieved by the blending of selected hydrogel polymers to achieve a delayed pulse.
13	**DUREDAS (Dual release drug absorption system)** These bilayered tablets are prepared by two separate direct-compression steps that combine an immediate-release granulate and a controlled-release hydrophilic matrix complex within one tablet. The controlled-release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix to expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner.
14	**Gastric retention system** Consists of a drug containing polymeric units that, if taken with a meal, remain in the stomach for an extended period of time to provide continuous, controlled delivery of an incorporated drug.
15	**Geomatrix** Geomatrix system is a multilayer tablet with a matrix core containing the active ingredient and one or more modulating layers (barriers) applied to the core during the tableting process. The function of these barriers is to delay the interaction of the core with the dissolution medium. 8 Geomatrix technologies are designed to meet a wide range of therapeutic objectives: Zero-order release provides a constant rate of drug release over a defined period of time; binary release is used to provide the controlled release of two different drugs in a single tablet; quick–slow release provides a quick burst of drug release followed by a constant rate of release over a defined period of time; slow–quick release provides an initial constant rate of release followed by a quick burst of drug release at a predetermined time; positioned release delivers the drug to a predetermined position in the digestive system before it begins to release the active drug compounds; accelerated release provides a constantly accelerating rate of drug release; delayed release provides a predetermined time lag before it begins releasing drug molecules; multiple pulse provides an initial quick burst of drug release followed by a predetermined period of no release.
16	**GMHS (Granulated modulating hydrogel system)** Incorporates hydrogel and binding polymers with the drug, which is formed into granules and then pressed into tablet form.
17	**IPDAS (Intestinal protective drug absorption system)** IPDAS, multiparticulate tablet, composed of numerous high-density controlled release beads. Each bead is manufactured by a two-step process that involves the initial production of a micromatrix of drug embedded in polymer and the subsequent coating of this micromatrix with time release coatings that are transformed into a rate-limiting semi permeable membrane in vivo. After ingestion, the tablet rapidly disintegrates and beads are dispersed into the stomach and subsequently pass into the duodenum and along the GI tract in a controlled and gradual manner, independent of the feeding state. Drug release from each bead occurs by a diffusion process through the micromatrix and subsequently through the pores in the rate controlling semipermeable membrane.
18	**Multipor technology** A tablet core of an active drug, which is surrounded by a water insoluble polymer membrane. The membrane consists of minute water-soluble particles that, after coming in contact with water, dissolve and form pores from which the drug is released.
19	**Pharmazome** or (**Microparticulate drug delivery technology**) Microparticle is a micromatrix of drug embedded uniformly throughout an insoluble polymer and is produced by either a spray drying or emulsion technique. This technology also can be used for taste masking because it acts as a means of physically preventing a drug from going into solution in the mouth and coming into direct contact with taste receptors.
20	**PPDS** or **(Pelletized pulsatile delivery system)** Pellets that are coated with specific polymers and agents to control the release rate of the microencapsulated drug. By varying the proportion and composition of the polymer mixtures, formulations can practically control the release rate of the drug and is designed for use with products that require a pulsed release of the drug.
21	**Peltab system** Polymer- coated drug pellets or drug crystals that are manufactured into tablets. In order to provide controlled release, a water-insoluble polymer is used to coat discrete drug pellets or crystals that then can resist the action of fluids in the GI tract. This technology incorporates a strong polymer coating enabling the coated pellets to be compressed into tablets without significant breakage.
22	**PRODAS** or (**Programmable oral drug absorption system)** A combination of multiparticulate and hydrophilic matrix tablet technologies and thus provides the benefits of both these drug delivery systems in one dosage form. These combinations may include immediate- release, delayed-release, and/or controlled- release.
23	**Reduced irritation system** Consists of an outer gelatin capsule that is designed to rapidly disintegrate upon ingestion to deliver multiple small spherical pellets. The spherical pellets are composed of an inert matrix of polymeric material in which the active ingredient is homogeneously dispersed in its solid state. Significantly reduce local gastrointestinal irritation from the effects of certain drugs.
24	**Ringcap** The Ringcap system utilizes bands of insoluble polymer on a matrix tablet. The manufacturing process involves compressing the drug into cylindrical matrix tablets that are subsequently film coated. Then, existing capsule- banding technology is used to apply two or more polymeric rings around the circumference of the matrix tablet. These bands lower the initial release of the drug by reducing the surface area exposed. As the matrix tablet erodes, new surface areas are created underneath and around the bands, thus increasing the rate of release.
25	**SODAS** or (**Spheroidal oral drug absorption system)** Multiparticulate drug-delivery technology and consists of controlled-release beads, an inert core onto which the drug is applied, followed by a number of layers of soluble and insoluble polymers combined with other excipients to produce the rate-controlling layer. Drug release from these beads occurs by a diffusion process. Within the GI tract, the soluble polymers dissolve, leaving pores within the outer membrane. Fluid then enters the core of the beads and

	dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the in vivo dissolution and absorption phases.
26	**SMHS** or (**Solubility modulating hydrogel system**) Hydrogel based dosage system that provides sustained release without the need to use special coatings or structures, both of which add to the cost of manufacturing. This technology avoids the initial burst effect commonly observed with other sustained- release hydrogel formulations. Used for the treatment of hypertension and angina.
27	**SPDS** or (**Stabilized pellet delivery system**) Designed specifically for unstable drugs and incorporates a pellet core of drug and protective polymer outer layer(s).
28	**SQZGel oral controlled-release system** An oral delivery system based on patented pH-sensitive hydrogels comprised of combinations of FDA-approved generally recognized as safe (GRAS) polymers. In response to internal or external pH levels, and by design, this system evenly releases a drug over an 8- to 20-hour period based on the delivery needs of the therapy.
29	**TIMERx** This technology is based on an agglomerated hydrophilic matrix. The matrix consists of two pharmaceutically acceptable polysaccharides, locust bean gum and xanthan gum. Interactions between these components in an aqueous environment form a tight gel with a slowly eroding core from which the drug is released at a controlled rate for an extended period of time. Slofedipine XL (nifedipine) and Cystrin CR (oxybutynin) are based on this technology and are marketed in Europe.
30	**Meter release** Polymer based drug delivery system that offers different release characteristics than KV/24 and is used for products that require a drug release rate of 8 to 12 hours.
31	**Symatrix** Microparticulate formulation that employs smaller particles and meter release. Symatrix encapsulates therapeutic agents that improve a drug's absorption in the body when precise release profiles are less important.
32	**Spheroid** Each particle has its own matrix as the rate-controlling mechanism for the release of its contents. These particles can be filled into hard gelatin capsules or can be compressed into tablets.
33	**Orasert** A solid oral dosage system that possesses bioadhesive and controlled release properties.
34	**Orasite** A controlled release muco-adhesive delivery system administered orally in solid or liquid form.
35	**Triglas technology** Mainly for water-insoluble drugs and is based upon formulating drug with appropriate additives to form a solid solution of drug that can be coated onto the carrier particles. These particles then can be made into tablets.
36	**Rhotard** Based on double-matrix technology that involves two granulation stages during the manufacturing process.

(B) Large-molecule delivery

This class of drugs is usually characterized by large size, fragile nature, short biological half life, and limited ability to cross cell membranes. These properties, along with the methods of administration of biopharmaceuticals, can limit their clinical applications to certain disease states that warrant the expense and inconvenience of frequent injection. At present, a large number of companies are working in this area, as evidenced by the increasing number of available technologies for delivering these compounds. Table 2 describe various large molecule delivery techniques.

Table 2. Large-molecule delivery techniques

S.N	Large-molecule delivery techniques
1	**BEODAS** or (**Bioerodable enhanced oral drug absorption system**) An oral microparticulate drug delivery technology designed for the delivery of macromolecules and is based on the entrapment of active pharmaceutical entities in a range of submicron sizes within biodegradable polymer matrices.
2	**Depofoam** Drug delivery system consists of microscopic spherical particles composed of nonconcentric chambers (depots) encapsulating the drug to be delivered. The individual chambers are separated by a bilayer lipid membrane made up of synthetic duplicates of lipids found naturally in the body, resulting in a material that is both biodegradable and biocompatible. Depofoam formulations maintain a drug in its therapeutic window for periods ranging from days to many weeks, allowing lower initial drug levels and significantly fewer doses. Depofoam technology is applicable across a variety of compounds, including small molecules, proteins, peptides, DNA, vaccines, products like Depocyt (cytarabine), Depomorphine (morphine sulfate), and Depoamikacin (amikacin).
3	**DUROS** These implants are miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body for up to one year. The cylinder protects therapeutic agents from degradation in the body and enables a drug to remain stable for extended periods of time.
4	**LOCDAS** or **(Localized drug absorption system)** oral drug delivery technology utilizes targeting ligands, that specifically bind to certain absorption sites located on the apical surface of the epithelium cells of the human GI tract. These ligands are attached to coated microparticles of protein and peptide drugs that serve to protect their contents from the hostile environment of the GI tract.
5	**Macromol systems** Enable polypeptides and proteins to be administered by the oral route rather than by injection.
6	**Oral mucosal vaccines** Administered by mouth and act by presenting the antigen to specialized cells within the intestine that pick up small particles via the peyer's patch and can process them into the immune system to stimulate a defensive response at mucosal sites.
7	**Medipad** Medipad is a low-cost, disposable, single-use system that combines unique microinfusion technology with an integral subcutaneous probe. An adhesive backing fixes the system discreetly against the user's chest or abdomen where it continuously dispenses drug for up to 48 hours. The Medipad technology can be tailored to a range of delivery volumes, delivery rates, and delivery profiles (bolus, extended bolus, continuous, or continuous plus bolus).
8	**Oral vaccines** The technology focuses on two different approaches for oral delivery of antigen through intestinal epithelial tissue. These are the production of micro- and nanoparticles of a defined size range containing antigens dispersed within a bioerodable polymer matrix and polymerized liposomal vesicles in which antigens are enclosed in a stable membrane. Both of these technologies protect antigens from the hostile environment of the GI tract and ensure that they are presented in an intact form to the mucosal surface for absorption.
9	**Prolease and Medisorb** Prolease is specifically designed for complex and fragile bioactive molecules such as proteins, and Medisorb is designed for traditional small molecules and

	peptides. Both technologies are microsphere based delivery systems composed of the desired bioactive molecule incorporated into a matrix of poly-(DL-lactide-coglycolide), a common biodegradable medical polymer. Microspheres are packaged in vials as a dry free-flowing powder. Before administration the microspheres are suspended in an aqueous vehicle and administered by subcutaneous or intramuscular injection. Release profiles can be adjusted by manipulation of formulation parameters and by control of the fabrication process.

(C) Transdermal and topical delivery

Transdermal drug delivery systems (TDDS) deliver drugs through the skin into the systemic circulation at a predetermined rate, thereby avoiding metabolism in the GI tract and liver so the amount of active ingredient required for transdermal delivery can be significantly less than that for oral systems. Use of penetration enhancers, prodrugs, iontophoresis, electroporation, sonophoresis, and reverse iontophoresis can increase the transdermal permeability of drugs because of their poor permeability across the skin. Some of the successful technologies in this field are as follows in Table 3.

Table 3. Transdermal and topical delivery techniques

S.No.	Transdermal and topical delivery techniques
1	**Dermaflex** A passive transdermal patch employing a hydrogel matrix in which a pharmaceutical compound is incorporated. Dermaflex regulates the availability and the absorption of pharmaceutical compounds in a manner that may allow controlled and efficient delivery.
2	**Dermasite** A semisolid site-release configuration for topical applications to the skin.
3	**D-trans** A transdermal system that provides rate-controlled administration of drugs through the skin. These systems resemble small adhesive bandages and can offer multiday or weekly dosing and improved patient compliance.
4	**E-trans** An electrotransport system that uses low-power electric current to control drug administration through intact skin. E-trans systems are being developed to provide continuous drug delivery as well as patient-controlled pulsatile delivery.
5	**Microsponge systems** Based on microscopic polymer-based microspheres that can bind, suspend, or entrap a wide variety of substances and incorporate them into a formulated product, such as gel, cream, liquid, or powder. Microsponge systems are used primarily as reservoirs for releasing active ingredients in an extended period of time and as receptacles for absorbing undesirable substances, such as excess skin oil.
6	**Polytrap systems** Designed to absorb skin oils and eliminate shine, provide a smooth and silky feel to product formulations, entrap and deliver various ingredients in personal care products, and convert liquids into powders.
7	**Theraderm-LRS (Liquid reservoir system)** Numerous drug formulations can be incorporated into a Theraderm-LRS patch because the system is not rate limiting to the administration of the drug and the drug reservoir is isolated physically from the adhesive within the system.
8	**Theraderm-MTX (Matrix system)** Based on an adhesive matrix patch design. The drug is incorporated into the adhesive, resulting in a light and flexible patch that conforms to the skin for maximum adhesion and comfort.
9	**Therapatch** A self-adhering patch that delivers medications topically into the skin for localized pain relief and therapeutic treatment.

(D) Liposomal delivery[5]

Liposomes are microparticulate lipoidal vesicular structures based on lipid bilayers surrounding aqueous compartments and have been used as a carrier for the improved delivery of a variety of drugs such as chemotherapeutic agents, imaging agents, antigens, genetic materials, immunomodulators, etc. Conventional liposomes are typically composed of only phospholipids (neutral and/or negatively charged) and/or cholesterol and characterized by a relatively short blood circulation time. To overcome this problem, long-circulating liposomes (stealth or sterically stabilized liposomes) have been developed. These stealth liposomes carry a polymer coating to obtain prolonged circulation times. Targeted liposomes (immunoliposomes) have specific antibodies or antibody fragments on their surface to enhance target site binding. Cationic liposomes are improving the delivery of genetic material. Various liposomal delivery techniques are described in Table 4.

Table 4. Liposomal delivery techniques

S.No.	Liposomal delivery techniques
1	**Novasome lipid vesicles** Organized lipid structures in which drugs or other materials may be encapsulated for delivery into the body topically or orally. Novasome lipid vesicles are made using amphiphiles, which include fatty alcohols and acids.
2	**Micellar nanoparticles** Water-miscible lipid structures that have different structural characteristics and are generally smaller than novasome lipid vesicles. Micellar nanoparticles are derived from amphiphile molecules.
3	**Proliposomes** This approach avoids many difficulties encountered with the manufacturing of liposomes by forming liposomes at the point of delivery, presenting opportunities for novel delivery systems designed for dermal, mucocutaneous, pulmonary, oral, and parenteral use.
4	**Stealth liposomes** Stable in plasma and avoid rapid removal from the bloodstream by attaching polyethylene glycol to the surface of the liposomes to form long-circulating liposomes. Stealth liposomes are large enough that typically they do not leak out of the bloodstream and into tissues through normal, healthy blood vessels, they continue to circulate intact until they reach tissues where new blood vessels form, such as tumors, sites of inflammation, and sites of injury.

(E) Taste masking

Oral pharmaceuticals often impart an unpleasant taste, primarily bitterness so desire for improved palatability in these products has prompted the development of numerous methods for taste masking, such as complexation of the drug with resins or cyclodextrins, use of microcapsules, particle coating etc. Various taste masking techniques are described in Table 5.

Table 5. Taste masking techniques

S.No.	Taste masking techniques
1	**Chewable tablets** A mild effervescent drug complex dispersed throughout a gum base. The drug is released from the dosage form as a result of physical disruption from chewing as well as chemical disruption from the interaction between the fluids in the oral cavity with the effervescent material.
2	**Flavortech** A liquid formulation technology designed to reduce the bad taste of therapeutic products.
3	**Micromask** A taste-masking technology that incorporates a dry-powder, microparticulate approach to reduce objectionable taste by sequestering the unpleasant drug agent in a specialized matrix.
4	**Liquette** A taste-masking technology that incorporates unpleasant tasting drugs into a hydrophilic and lipophilic polymer matrix to suppress the taste.
5	**Oraquick** A technology in which the bitter taste of a drug candidate is first enhanced by neutralizing its negative taste characteristics and then developed into a quick-dissolving tablet formulation.

(F) Oral fast-dispersing dosage forms[6]

An oral fast-dispersing dosage forms may be defined, a solid dosage form that dissolves or disintegrates rapidly in the oral cavity, resulting in a solution or suspension without the need for the administration of water. These are also known as fast dissolving, rapid-dissolve, rapid-melt, mouth-dissolving, and quick-disintegrating tablets. Some of the advantages of oral fast-dispersing dosage forms include administration to patients who have difficulty in swallowing, more rapid drug absorption, patient convenience, and compliance. These dosage forms are particularly helpful for pediatric and geriatric patients who have difficulty in swallowing (dysphagia) and also for traveling patients, for whom water may not be easily or readily accessible. Various oral fast dispersing dosage forms techniques are described in Table 6.

Table 6. Oral fast-dispersing dosage forms techniques

S.No.	Oral fast-dispersing dosage forms techniques
1	**EFVDAS** or (**Effervescent drug absorption system)** The granular contents of the sachets can be added to boiling water to produce pleasant-flavored solutions. In these cases the effervescence of the granulate mixture is modified to accommodate the use of heated water. Examples of products that Elan has developed include effervescent ibuprofen, paracetamol, cimetidine, naproxen, and a paracetamol and codeine combination product.
2	**Fast Melt** A highly porous, microfine matrix tablet. Once placed on the tongue, this matrix rapidly absorbs liquid and disintegrates. The combination of a mild effervescent base and drug processing ensures that the dosage form goes into solution in approximately 15 to 30 seconds. This is particularly advantageous in cases like migraine where a fast onset of clinical effect is required.
3	**Flashdose** Shear form technology to form a matrix known as floss. The floss is a fibrous material similar to cotton candy fibers and is commonly made from saccharides such as sucrose, dextrose, etc. The candy floss can then be milled and blended with active ingredients and other processing aids and subsequently compressed into fast-dissolving tablets.
4	**Flashtab** A combination of taste-masked multiparticulate active drug substances with specific excipients compressed into tablets. This oral dispersible tablet is placed in the mouth, where it disperses rapidly before the patient swallows. Some of the drugs that are marketed using this technology are acetaminophen (pediatric and adult), ketoprofen, and ibuprofen.
5	**Multiflash** A multi-unit tablet composed of coated micro granules and fast-disintegrating excipients. This multiparticulate tablet quickly disintegrates in the oesophagus after being swallowed with a minimum amount of water. This tablet avoids mucosal adhesion, and coated pellets can match various dissolution rates.
6	**Orasolv** The dispersion of active ingredient into a suitable polymer along with other excipients such as mannitol and magnesium oxide. The active agents and mannitol are added to the polymeric dispersion (ethyl cellulose, acrylates, etc.) under stirring, followed by the addition of magnesium oxide. The mixture is dried for one hour at 50ºC, delumped, and dried for another hour at the same temperature. The material is then screened (8-mesh) and dried for one hour at 60 ºC. The formed microcapsules, effervescent mixtures, and other standard excipients are mixed and compressed to form tablets.
7	**Wowtab** The formulation usually consists of a mixture of fast disintegrating but poorly compressible saccharides (e.g., mannitol, lactose, glucose, etc.) and a slowly disintegrating saccharide that shows good hardness upon compression (e.g., maltose, sorbitol, etc.). The mixture is compressed after undergoing a humidification and drying process resulting in tablets that show adequate hardness and rapid disintegration.
8	**Zydis** These formulations are combinations of water soluble matrix material along with the drug and some functional excipients that are formed in the blister pockets and freeze-dried to remove the water by sublimation. The resulting structures are very porous in nature and rapidly disintegrate or dissolve upon contact with water. Some of the drugs that are being marketed in the form of Zydis products are oxazepam, lorazepam, piroxicam, loperamide, and famotidine.
9	**LYOC and Quicksolv** Utilize freeze-drying technology to produce oral fast-dispersing tablets.

(G) Technology for insoluble drugs

Drug solubility may be the rate-limiting step in absorption (e.g., in drugs belonging to Class 2 or drugs having good permeability but poor solubility) and therefore may affect the bioavailability of the drug. More than 40% of potential drug products suffer from poor water solubility. A good deal of research has been done in this area, and currently a number of technologies are available to address the poor solubility of drugs in Table 7.

Table 7. Technology for insoluble drugs

S.No.	Technology for insoluble drugs
1	**INDAS or (Insoluble drug absorption system)** A drug to create a high-energy adsorbate that demonstrates enhanced solubility. This high-energy adsorbate is subsequently combined with other controlled absorption technologies to deliver the required plasma profile. The drug in question, usually crystalline in nature, is converted into an amorphous form by a combination of energy, excipients, and unique processing procedures. Once the drug is converted to the desirable physical form, an adsorption process utilizing a novel polymer cross-linked technology prevents recrystallization and stabilizes the resulting high-energy complex.
2	**Nanocrystal technology** A suspension of the insoluble drug in a stabilizing solution, consisting of stabilizers and other excipients, is used for the milling process to prevent aggregation of the resulting nanoparticles and also serves to increase the dissolution rate of the nanoparticles by acting as a surfactant within the GI tract. Once the Nanocrystal form of the insoluble drug has been transformed into a more physically stable form, it can be incorporated into other drug delivery systems such as oral controlled-release or highly concentrated parenteral solutions.
3	**Softgel** A soft gelatine capsule formulation that contains a high concentration of a hydrophobic drug in solution (or fine particles of drug in suspension) in a hydrophilic or lipophilic liquid to improve the solubility, stability, bioavailability, and rate of absorption of drug molecules.

(H) Colon-specific delivery[7]

Small intestine is the primary site for drug absorption and is therefore a preferred area of the GI tract to target with various controlled-release technologies due to the reduced proteolytic activity in the colon, which may be advantageous in targeting certain drugs such as proteins and peptides that are enzymatically degraded in the stomach or small intestine, and the topical treatment of carcinomas and inflammatory bowel diseases. In the past few years many colon-specific dosage forms have been developed, including prodrugs, cross-linked hydrogels, matrices, and coated dosage forms. Various colon specific delivery techniques are described in Table 8.

Table 8. Colon-specific delivery techniques

S.No.	Colon-specific delivery techniques
1	**Oros-CT** Based on the principles of osmotic pressure. Oros-CT can be a single osmotic unit or can be comprised of as many as five to six push-pull osmotic units filled in a hard gelatin capsule. Each bilayer tablet consists of an upper compartment (drug along with osmotic agents) and a lower compartment (polymeric osmotic agent), surrounded by a semipermeable membrane. An orifice is created in the membrane next to the drug layer. After coming into contact with the GI fluids, the gelatin capsule dissolves and the enteric coating prevents entry of water from the stomach. As the system enters into the small intestine, the enteric coating dissolves and water is imbibed into the core, thereby causing the push compartment to swell. At the same time, flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate that is precisely controlled by the rate of water transport across the semi permeable membrane.
2	**Pulsincap** Consists of a water-insoluble capsule body and a water soluble cap. The drug formulation is contained inside the capsule. The soluble cap dissolves in the intestine, thereby allowing the hydrogel plug to swell and expand. Ejection of the swollen plug occurs after a lag time that depends on the hydrogel plug, the length of the plug, and the fit ratio (plug diameter to body diameter).
3	**Colon specific systems** Uses microsponge systems to protect the active agent from the environment of the stomach and delivers the drug to the colon in a controlled fashion.

(I) Intranasal delivery

The nasal cavity can be used for the delivery of several compounds and offers rapid absorption into the systemic circulation, providing rapid onset of desired therapeutic effect, lower required dosages, fewer side effects, and improved patient compliance. Nasal dosage forms consist mainly of preparations containing dispersed or dissolved drugs placed in a container that is squeeze- or spray-activated. Alternatively, liquid solutions can be delivered using metered atomizing pumps or metered-dose pressurized nasal inhalers. Butorphanol, calcitonin, dihydroergotamine, sumatriptan, and desmopressin are some of the drugs marketed in the form of a nasal spray. Cromolyn sodium is available in a solution form. Budesonide and beclomethasone diproprionate are marketed in the form of metered-dose pressurized aerosols. Beclomethasone diproprionate available in the form of a metered-dose manual spray. Rinoflatore are some of the marketed insufflators for nasal administration of powders.

(J) Pulmonary delivery

Pulmonary delivery has been used primarily for the treatment of respiratory disease. This method is a noninvasive alternative to painful injections and can lead to the rapid onset of action and good bioavailability. Inhalation devices broadly fall into three categories: pressurized metered-dose inhalers (MDIs), nebulizers, and drug powder inhalers (DPIs). MDIs contain the drug as a solution or a suspension of fine particles in a liquefied propellant held under high pressure. The drug is emitted through an orifice from a metering valve. Nebulizers, on the other hand, do not require propellants and can generate large quantities of small droplets capable of penetrating into the lung. In DPIs, the drug is stored in a dry state, thereby ensuring long-term stability and sterility. Some of the single dose breath-driven DPIs that are currently marketed are Rotahaler, Flow caps and Cyclohaler. Diskhaler and Accuhaler are multidose factory-metered inhalers[8]. Various pulmonary techniques are described in table 9 .

Table 9. Pulmonary delivery techniques

S.No.	Pulmonary delivery techniques
1	**AERx system (Aerosol-generation technology)** The system aerosolizes liquid formulations that are prepackaged in unit-dose packets for inhalation. Each unit-dose packet consists of a small blister package that stores a liquid drug formulation and an aerosolization nozzle with a membrane incorporating an array of micro-machined holes. The actuator compresses the blister packet, thereby forcing open the sealed channel and extruding the liquid drug through the aerosolization nozzle.
2	**Spiros** An aerosol generator that uses electromechanical energy to disperse drug powder to form an aerosol for inhalation. The main components of the aerosol generator include the impeller, the motor, the breath-actuated switch, and the dosing chamber. When the switch is activated, the electric circuit is completed and the impeller rotates. The action of the impeller on the dry powder formulation supplies the energy to disperse the drug and provides a zero-velocity cloud of aerosolized drug for inhalation. The cloud of aerosolized drug is suspended in the dosing chamber and is delivered to the lungs only as the patient inhales.

(K) Vaginal / rectal delivery

The vagina as a favourable site for the local and systemic delivery of drugs due to the avoidance of the gut and hepatic first-pass metabolism, reduction in gastrointestinal and hepatic side effects, and local targeting of drugs to the reproductive organs. Vaginally administered agents and formulations are being developed mainly to provide dual prophylaxis for contraception and protection against microbial infections, including AIDS and other sexually transmitted diseases (Table 10).

Table 10. Vaginal / rectal delivery techniques

S.No.	Vaginal / rectal delivery techniques
1	**Hycore-V (Hydrogel polymer technology)** Hydrogel polymer technology to absorb fluid and swells without losing its physical form. As the hydrogel swells, the drug is released in a controlled manner. Drug release can be controlled over a period of a few hours to several days by varying the shape and the physical and chemical properties of the polymer. Hycore-V is delivered through the vagina in the form of a pessary.
2	**Hycore-R** Uses similar technology and delivers the drug through the rectum in the form of a suppository.
3	**Vagisite** A semisolid system intended for drug administration within the vaginal vault.
4	**Biosert** A bioadhesive controlled-release system that is a solid rectal or vaginal suppository at room temperature and, after insertion, becomes a bioadhesive long-acting cream.

(L) Site-specific drug delivery

One of the goals of effective drug delivery is to control and optimize the localized release of drug at the target site and rapidly clear the non targeted fraction. Some of the benefits of this type of delivery system are the delivery of a calculated amount of drug at the site of action and limited access to other organs. The amount of drug reaching the systemic circulation theoretically will be less, thereby resulting in fewer side effects. At present, a number of technologies are available for site-specific delivery. Various site specific drug delivery techniques are described in Table 11.

Table 11. Site-specific drug delivery techniques

S.No.	Site-specific drug delivery techniques
1	**Atrigel** Comprises biodegradable polymer formulations that are administered as flowable compositions (solutions, gels, pastes, and putties) that solidify in situ upon contact with body fluids to form biodegradable implants. The Atrigel system is designed to provide extended localized or systemic drug delivery in a single application without the need for surgical implantation or removal.
2	**Durasite** An eye drop formulation comprised of a cross-linked carboxyl-containing polymer that incorporates the drug to be delivered to the eye.
3	**Matrix delivery system** An aqueous-based protein system in which a chemotherapeutic drug is combined with a protein matrix and a vasoconstrictor to create an injectable gel. This gel enables targeted delivery of water-soluble drugs by direct injection into solid tumors and skin lesions. The Matrix delivery system localizes the release of the drug, maintaining high drug concentrations at the tumor or lesion site and increasing the duration of exposure of the targeted tissue to the therapeutic agent.
4	**Microsphere delivery system** Uses biodegradable polymers and a method that facilitates the microencapsulation of water-insoluble and water soluble compounds. Potential applications of this technology include the long-term controlled delivery of injectable compounds, the delivery of active agents to sites poorly accessible from systemic circulation, and site delivery of highly potent agents.
5	**Oligosphere injectable microspheres** Macromed's patented processing uses aqueous cosolvents providing a drug-friendly loading environment. Macromed's process also creates a homogenous drug/polymer matrix. This enables a constant release profile with little or no initial burst. Oligosphere is injected parenterally and is designed for drug release profiles of greater than one month.
6	**ReGel Injectable controlled-release system** These formulations are a liquid at or below room temperature and are injectable through a small 25- gauge needle. Upon injection as a liquid, the product quickly becomes a gel at body temperature, forming a depot that slowly degrades over a period of four to six weeks.
7	**Retinal delivery system** A device that provides controlled nonsurgical delivery of ophthalmic drugs to the retina and other tissues in the posterior chamber of the eye.

(M) Oral transmucosal delivery

Enable the delivery of many large-molecule drugs, including peptides and polysaccharides that cannot readily be delivered orally or transdermally. Oral transmucosal delivery systems are solid dosage forms that will adhere to various surfaces in the oral cavity and deliver drugs within a period of time. Table 12 describe various oral transmucosal delivery techniques.

Table 12. Oral transmucosal delivery techniques

S.No.	Oral transmucosal delivery techniques
1	**Bioadhesive delivery system** It consists of a polymer, polycarbophil, and an active ingredient. This system is based on the principle of bioadhesion, a process by which the polymer adheres to epithelial surfaces and to mucin, a naturally occurring secretion of the mucus membranes. The polymer remains attached to epithelial surfaces and the mucin and is discharged upon normal cell turnover or upon the detachment of the mucin from the mucus membranes, a physiological process that, depending on the area of the body, occurs every 12 to 72 h[9].

COMMERCIALLY MARKETED PRODUCTS

Table 13 shows various commercially marketed products with their uses.

Table 13. Commercially marketed products with their use

S.No.	Commercially marketed products	Uses of products
A	**ORAL OSMOTIC SYSTEMS**	
1	Acutrim	Appetite suppressant
2	Alpress LP	Hypertension
3	Calan SR	Hypertension
4	Cardura XL	Hypertension
5	Concerta	Attention Deficit, Hyperactivity disorder
6	Covera HS	Hypertension
7	Ditropan	Overactive bladder
8	DynaCirc CR	Hypertension
9	Efidac/24	Cold medication
10	Efidac 24 Chloropheniramine	Anti-allergic
11	Efidac 24 Pseudoephedrine/Brompheniramine	Anti-allergic and cold treatment
12	Glucotrol XL	Anti-diabetic
13	Minipress XL	Hypertension
14	Procardia XL	Hypertension /angina
15	Sudafed 24 hour	Nasal decongestant
16	Teczem	Hypertension
17	Tiamate	Hypertension
18	Volmax	Bronchospasm
B	**TRANDERMAL SYSTEMS**	
19	Alora	Postmenopausal syndrome
20	Androderm	Hypogonadism in males
21	Catapres-TTS	Hypertension
22	Climaderm	Postmenopausal syndrome
23	Climara	Postmenopausal syndrome
24	CombiPatch	Hormone replacement therapy
25	Deponit	Angina pectoris
26	Duragesic	Moderate/severe pain
27	Estraderm	Postmenopausal syndrome
28	Fematrix	Postmenopausal syndrome
29	FemPatch	Postmenopausal syndrome
30	Habitraol	Smoking cessation
31	Minitran	Angina pectoris
32	Nicoderm	Smoking cessation
33	Nicotrol	Smoking cessation
34	Nitrodisc	Angina pectoris
35	Nitro-dur	Angina pectoris
36	Nuvelle TS	Hormone replacement therapy
37	Prostep	Smoking cessation
38	Testoderm TTS	Hypogonadism in males
39	Transderm-Scop	Motion sickness
40	Transderm Nitro	Angina pectoris
41	Vivelle	Postmenopausal syndrome
C	**LIPOSOMAL/LIPID-BASED PRODUCTS**	
42	AmBisome	Systemic fungal infections
43	Abelcet	Systemic fungal infections
44	Amphotec	Systemic fungal infections
45	Doxil	Kaposi's sarcoma
46	DaunoXome	Kaposi's sarcoma

FUTURE DIRECTIONS AND CONCLUSION

As discussed in this article, many different delivery systems, including oral, transdermal, injection, implants, etc. are used for drugs can be delivered to a patient. Biotechnology companies are rapidly developing a large number of peptide- and protein-based drugs with the sequencing of the human genome. It is expected that protein- and peptide-based drugs will constitute more than half of the new drugs introduced into the market, and more than 80% of these protein drugs will be antibodies in the next 10 to 20 years. Because large molecules that degrade rapidly in the blood stream so these biopharmaceuticals (proteins, peptides, carbohydrates, oligo-nucleotides, and nucleic acids in the form of DNA) present drug delivery challenges. Moreover, they have a limited ability to cross cell membranes and generally cannot be delivered orally. Such molecules will be much more difficult to deliver via conventional routes, and injections may be the only means of delivery (at least as of today). The routes of administration will be dictated by the drug, disease state, and desired site of action. In conclusion, the market for drug delivery systems has come a long way and will continue to grow at an impressive rate. Today's drug delivery technologies enable the incorporation of drug molecules into new delivery systems and providing numerous therapeutic and commercial advantages. A large number of companies are involved in the development of new drug delivery systems, which is evident by an increased number of products in the market and the number of patents granted in the recent past.

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