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Review Article

Drug Delivery System in Pakistan: A Review

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Abstract:

Drug Delivery systems are the means by which drug molecules are delivered to sites of action within the body. There are several pharmaceutical dosage forms (delivery Systems) available in Pakistan that is being used in different health care centers. Both conventional and advance dosage forms are used now days depending upon the condition of the patient, the disease state and available resources. But unfortunately Pakistan is a way behind in the field of technology among the other developing and developed countries in the world. There are few private setups which are well equipped with high class technology that caters the need of advanced drug delivery system in Pakistan. Mostly advanced drug dosage forms are imported from the other countries, thus it costs Pakistan a lot. In the present study Drug Delivery Systems in Pakistan is thoroughly studied and represented according to the generations of drug delivery system.

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Drug Delivery systems are the means by which drug molecules are delivered to sites of action within the body.

There are several pharmaceutical dosage forms (delivery Systems) available in Pakistan that is being used in different health care centers. Both conventional and advance dosage forms are used now days depending upon the condition of the patient, the disease state and available resources.

Properties of a responsive drug delivery device are:

- Inert, mechanically strong, easy to implant and remove (Patient Compliance).
- Biocompatible
- Less expensive
- Control release profiles, especially for potent active substances.
- Safe from accidental release, easy to fabricate and sterilize and allow high drug loading.

1st Generation of Drug Delivery System:

The first generation drug delivery systems (pharmaceutical dosage forms) appeared toward the end of the 19th century and in the 20th century, and they have consistency and uniformity. These drug delivery systems (conventional dosage forms) include tablets, capsules, elixirs, syrups, suspensions, emulsions, and solutions and topical administration of ointments, lotions and creams, suppositories or injection of suspensions and solutions. Though these conventional drug delivery systems are still with us, the need for more efficient drug delivery systems was realized with time.[1] As the manufacturing of these dosage forms required less cost as compared to the other

dosage forms which were invented after these drug delivery systems, that's why in Pakistan mostly conventional dosage forms are in use.

There are several pharmaceutical dosage forms available in Pakistan that is being used in different health care centers. Both conventional and advance dosage forms are used now days depending upon the condition of the patient, the disease state and available resources. However, Pakistan's health care system is based on the conventional pharmaceutical dosage forms.

Following are the conventional dosage forms (or conventional drug delivery systems) with their some examples:

Tablets:

Tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, manufactured by compression. Tablet is the dosage form in which the amount of drug is incorporated which is given in the single dose. This is the most stable and compact dosage form of all the dosage forms are invented so far. Even in the further generations of drug delivery systems, the tablet form is manipulated to control the release of the active substance. There are different types of tablets according to the type of active substance(s), the intended use, and manufacturing process.

Some types along with their examples are as follows.

Brand Name	Type	Active Ingredient
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Panadol	Compressed Tablets	Paracetamol
Captopril	Compressed Tablets	Enalapril Maleate
Envepe	Multiple Compressed Tablets	Doxylamine Succinate + Pyridoxine
Brufen	Sugarcoated Tablets	Ibuprofen
Methycobal	Sugar Coated Tablet	Mecobalamine
Flagyl	Film Coated Tablet	Metronidazole
Unisom	Gelatin Coated Tablet	Diphenhydramine
Ascard	Enteric Coated Tablet	Aspirin
Qalsan-D	Chewable Tablet	Multivitamins.
Cecon	Chewable Tablet	Multivitamins
Angised	Sublingual Tablet	Glyceryltrinitrate
CAC 1000	Effervescent Tablets	Calcium + Vitamins C + B ₆ + D ₃
Ponstan Flash	Oral Dispersible Tablet	Mefenamic Acid
Canesten	Vaginal Tablet	Clotrimazole

Capsules:

Capsules are solid dosage forms in which medicinal agents and/or inert substances are enclosed in a small shell of gelatin. Gelatin capsule shells may be *hard* or *soft*, depending on their composition.[2]

Most filled capsules are intended to be swallowed whole. However, it is fairly common in hospitals and other health care facilities in Pakistan.

Some Examples are:

Brand Name	Type	Active Ingredient
Vibramycin	Hard Gelatin Capsule	Doxycycline
Amoxil	Hard Gelatin Capsule	Amoxycillin
Risek	Hard Gelatin Capsule	Omeprazole
Voren	Hard Gelatin Capsule	Diclofenac Sodium
Sunny D	Soft Gelatin Capsule	Cholecalciferol
EZmega	Soft Gelatin Capsule	Omega 3 Fish Oil

Syrups:

Syrup is a condiment that is thick, viscous liquid consisting primarily of a solution of sugar in water, containing large amount of sugar, medicinal active ingredients in it, and bitter taste can be masked.

Examples are:

Brand Name	Type	Active Ingredient
Acefyl	Syrup	Acefyllinepiperazine +

		Diphenhydramine.
Ulsanic	Syrup	Sucralfate
Rubifer	Syrup	Iron Polymaltose Complex

Elixirs:

Clear, sweetened hydro-alcoholic solution, intended for oral use and are usually flavored to enhance palatability. Elixirs are usually less sweet than syrups and also less viscous.

Example of medicated elixirs in Pakistan is:

Brand Name	Type	Active Ingredient
Phenobarbital Oral Solution	Elixir	Phenobarbital

Suspensions:

Suspensions may be defined as preparations containing finely divided drug particles distributed somewhat uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility.[2]

In Pakistan, some suspensions are available in ready-to-use form that is, already distributed through a liquid vehicle with or without stabilizers and other additives. Other preparations are available as dry powders intended for suspensions in liquid vehicles.

Examples are:

Brand Name	Type	Active Ingredient
Cefspan	Powder for oral suspension	Cefixime.
Malafantrine	Powder for oral Suspension	Artremether + Lumefantrine
Calpol	Suspension	Paracetamol

Emulsions:

An emulsion is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout a vehicle in which it is immiscible. Emulsification enables the preparation relatively stable and homogeneous mixtures of two immiscible liquids. It permits administration of a liquid drug in the form of minute globules rather than in bulk.[2] These emulsions can be oral or injectable.

Examples in Pakistan Market

Brand Name	Type	Active Ingredient
Propofol	Injectable Emulsion	Benzyl Alcohol

Topical Preparations:

Ointments, creams, and gels are semisolid dosage forms intended for topical application. They may be applied to the skin, placed on the surface of the eye, or used nasally, vaginally, or rectally. Most these preparations are used for the effects of the therapeutic agents they contain. Topical preparations are used for both local and systemic effects.[2]

Examples of Topical Preparations in Pakistan are:

Brand Name	Type	Active Ingredient
Betnovate	Cream and Ointment	Betamethasone
Synalar	Cream and Ointment	Fluocinoloneacetonide
Capsidol	Cream	Capsaicin
Genticin	Cream and Ointment	Gentamicin sulfate
Nascobal	Gel	Cyanocobalamin
Timoptic	Gel	Timolol Maleate
Tobrex	Ophthalmic Ointment	Tobramycin
Garamycin	Ophthalmic Ointment	Gentamicin sulfate
Tronolane	Rectal Cream	Pramoxine Hydrochloride
Canesten	Vaginal Cream	Clotrimazole
Betnovate	Topical Lotion	Betamethasone

Suppositories:

Suppositories are solid dosage form intended for insertion into body orifices where they melt, soften, or dissolve and exert local or systemic effects. Suppositories are commonly used rectally and vaginally.[2]

Examples from Pakistan are:

Brand Name	Type	Active Ingredient
Voltral	Rectal Suppositories	Diclofenac Sodium
Phenergan	Rectal Suppositories	Promethazine
Monistat 7	Vaginal Suppositories	Miconazole nitrate

Parenteral Route:

Drug in liquid form is given by routes other than the digestive tract e.g. Intramuscular (IM), Intravenous (IV), Subcutaneous (s/c), Intrathecal etc. Some examples of brands available in Pakistan:

Brand Name	Type	Active Ingredient
Spasfon	IM, and IV	Phloroglucinol + Trimethylphloroglucinol
Klaricid	IV	Clarithromycin
Oxidil	IM, and IV	Ceftriaxone Sodium

Flagyl Infusion	IV	Metronidazole
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2nd Generation of Drug Delivery System:

With the advancement in the biopharmaceutics, pharmacokinetics, and human physiology and their applications to drug formulation and development, various in drug molecules and dosage forms were introduced. These dosage forms were formed to protect the drugs against hostile conditions along the gastrointestinal tract, prolong their action if necessary, and improve bioavailability. The materials used in these formulations include polymers, waxes, plastics, and oils. They are described by various terms such as repeat action, prolonged action, extended release and time release. In this type of drug delivery system; repetitive, intermittent dosing of a drug occurs from one or more immediate release units incorporated into a single dosage form. The best example of this type drug delivery system is enteric coated tablets. Though these drug delivery systems provide some degree of control, but it is not complete.[3]

This drug delivery system does not generally permit a long term drug release. Further, they do not produce a uniform blood drug concentration as a function of time.[1, 3]

In Pakistan there are many Pharmaceutical companies are engaged in preparing these types of drug delivery systems.

Examples in Pakistan

Brand Name	Type	Active Ingredient
Tab. Lopirin	Enteric Coated	Aspirin
Tab. Naproxen	Enteric Coated	Naproxen Sodium
Tab. Erythrocin	Enteric Coated	Erythromycin
Tab. Zomig	Enteric Coated	Zolmitriptan, imported from UK.
Tab. Ziapine	Extended release	Quetiapine Fumarate
Tab. Xatral LP	Prolong release	Alfuzosin
Tab. NovoNorm	Extended release	Repaglinide
Tab. Sparaxin	Extended release	Sparfloxacin
Tab. Hytrin	Enteric Coated	Terazosin Hydrochloride
Cap. FefolVit	Enteric Coated	Iron + Vitamins
Cap. Risek	Enteric Coated	Omeprazole
Tab. Tramal Plus	Enteric Coated	Tramadol + Paracetamol
Tab. Danzen	Enteric Coated	Serratiopeptidase

3rd Generation Drug Delivery System

The main purpose of advances in the drug delivery system is to achieve spatial (Required small amount of drug that is delivered to specific organ or specific place where it is required to produce the desired therapeutic effect) and temporal (Required small amount of drug delivered to specific organ or specific place at a required rate for a required period of time) delivery of the drug. The third generation drug delivery system is also called '**Controlled Drug Delivery System**'. The Controlled drug delivery system refers to the precise control of the rate at which a drug dosage is released from a delivery system, ideally in a constant or near constant manner over a long period of time. In order to permit an accurate, reproducible, and predictable drug therapy, the third generation drug delivery systems (controlled drug delivery systems) were designed to provide drug release that is dependent on the properties of the device and the physiochemical characteristic of the drug and the delivery system and in dependent of the environmental factors existing at the site of administration (i.e., pH of fluids and the presence of enzymes in the body).[3]

The third generation drug delivery system moved beyond extension of the blood level within the therapeutic range, which is characteristic of the second generation drug delivery systems, to controlled drug release such that a constant blood drug level can be maintained for a long period of time. The drug formulation scientists believe that the most desirable situation is that 'the flatter the plasma drug concentration vs. time curves the better.' [3, 4]

The design of the vast majority of the third generation drug delivery systems involves the use of **polymers**. As there is an element of diffusion of drug molecules in most of the systems, polymers serve as permeable barriers that the drug must cross before reaching the body fluids.[4] Polymers are particularly suitable for this purpose because their properties can be manipulated easily and diffusion rates of drug molecules through polymers are orders of magnitude less than the diffusion rates of the same molecules through water. The betterment and advancement in the controlled drug delivery system is in continuous evolutionary process.[1]

In Pakistan there are very few Pharmaceutical companies which are manufacturing these types of advanced drug delivery systems. Some of the controlled release drug delivery products are also imported from the other countries to fulfill the needs of the patients, which make it more difficult for most of the people to use them. Some examples of the control release drug delivery systems in Pakistan market are as follows.

Brand Name	Type	Active Ingredient
Tab. Seroxat CR	Controlled Release	Paroxetine Hydrochloride
Tab. Dinemic SR	Sustained Release	Trimetazidine Dihydrochloride
Cap. Lescol XL	Extended Release	Fluvastatin
Tab. Pentasa	Sustained Release	Mesalazine
Tab. Everlong	Controlled Release	Dapoxetine
Cap. Eflexor XR	Extended Release	Venlafaxine
Tab. Lamictal CR	Controlled Release	Lamotrigine
Tab. Nolvadex CR	Controlled Release	Tamoxifen Citrate

4th Generation Drug Delivery System

The third generation drug delivery systems have no control over the fate of the drug once it enters the body. Within the advent of highly potent drugs such as peptides, proteins, and low molecular weight anticancer drugs with narrow therapeutic indices, efforts were geared towards drug delivery systems that could exercise control on the time of availability and the localization of the drug in the body. In fourth generation drug delivery system drug is delivered from the dosage form when and where required. Various drug delivery systems belong to this generation: targetable, modulated, pulsatile and self-regulated, or feedback controlled drug delivery systems.[1]

This mode of delivery involves specific delivery of the active compound (drug) to its site of action and keeping it there until it is inactivated or detoxified. Drug targeting increases the therapeutic potential and reduces the side effects of the drug. Targeted (site-specific) delivery systems by the parenteral route are, at present, in different stages of development, and the most of them consist of the following components:

- An active moiety for the therapeutic effect,
- A carrier for protection and changing the disposition of the drug, and
- A homing device for the selection of the selection of the assigned target (site specificity)

The systems are suitable for anticancer drugs and highly potent recombinant peptides and proteins in which site-specific delivery is needed to reduce side effects.

Commercial targetable drug products have reached the clinic in the field of immunotherapy. It is believed that new immunotherapies, such as liposomes, monoclonal antibodies, antisense compounds, vaccines, and angiogenesis inhibitors, revolutionizing and will revolutionize the treatment process in the near future. [1]

Most commonly used targetable dosage form is using in the international market is Liposomes. Example is 'Doxorubicin Liposomal Preparation'. [5]

In Pakistan the only targeted drug delivery system (4th generation drug delivery system) is 'Amphotericin B Liposomal Parenteral Preparation'. [5] Another Advanced drug delivery system related to the targeted drug delivery system which was introduced in the Pakistan is 'Transdermal Patch'. A transdermal patch is used to deliver a specific dose of medication through the skin and into bloodstream. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation. Transdermal delivery provides controlled, constant administration of the drug, and allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation. TDDS offers many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused from temporary overdose. It is convenient, especially notable in patches which require only once weekly application. Such a simple dosing regimen aids in patient adherence to drug therapy. [6]

Few examples of Transdermal patches which are available in the Pakistan are:

Brand Name	Type	Active Ingredient
Deponit NT10	Transdermal Patch	GlycerylTrinitrate
Kefen Tech Patch	Transdermal Patch	Ketoprofen
Fentanyl	Transdermal Patch	Fentanyl
Quick Fix Patch	Transdermal Patch	Natural Capsicum Extract
Salonpas	Transdermal Patch	Methyl Salicylate, Levomenthol

'Inhalers' are the another type of the targeted drug delivery system, it delivers the drug in the mist form directly on the bronchioles to dilate them in the emergency condition of asthmatic attack. In Pakistan there are many brands of inhalers; both metered dose and dry powder inhalers, in the market. Inhalers are also manufactured by some reputable companies in Pakistan e.g., Getz Pharma (Karachi).

Few Examples are given below

Brand Name	Type	Active Ingredient
Xaltide	Metered Dose Inhaler	Salbutamol + Beclomethasonedipropionate

Ventoline	Metered Dose Inhaler	Salbutamol
Fostair	Dry Powder Inhaler	Beclomethasonedipropionate + formoterol
TiovairRotacaps	Dry Powder Inhaler	Tiotropium Bromide

Conclusion:

Pakistan is a way behind in the field of technology among the other developing and developed countries in the world. There are few private setups which are well equipped with high class technology that caters the need of advanced drug delivery system in Pakistan. Mostly advanced drug dosage forms are imported from the other countries. Commonly conventional drug delivery system is used in Pakistan for the medicine. For example tablets, capsules, syrups, suspensions, injections etc. Although advancement in the drug delivery system is in continuous process in Pakistan, but this process is very slow due to the lack of latest equipment and assistance and also lack of governmental support. There is also lack of technology advancement and research opportunities for health professional at national level. In Pakistan there is also a poor accessibility and affordability to advanced health care devices. The government of Pakistan should capitalize in producing professionally trained human resource, who can manufacture the advanced dosage forms in the country and government should also take effective financial as well as professional part in research and development programs. So that, Pakistan's Pharmaceutical Industry can also meets the international standards and make the required dosage form in the reach of every individual.

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