
Advance Delivery System Dosage Form for Analgesic, Their Rationale, and Specialty

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Additional information is available at the end of the chapter

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Abstract

Drugs including analgesics need a delivery system to deliver it to the site of action upon administration. Delivery can be achieved using various types of dosage forms including tablets, capsules, creams, ointments, liquids, aerosols, injections, and suppositories. Conventional drug delivery systems provide immediate release of the analgesics without controlling the rate of release. A number of doses must be given daily in order to achieve and maintain effective plasma concentrations. Frequent administration causes fluctuations in plasma levels of the drug. The drug plasma levels could fall below the minimum effective concentration and can also exceed the minimum toxic concentration. The purposes behind controlling the drug delivery for analgesic are to achieve more effective therapies while eliminating the potential for both under and overdosing. The need for fewer administrations for “no pain” maintenance and with optimal use of the drug in question is to avoid adverse effect, and to increased patient compliance. Modified-release analgesics have enabled patients to better maintain pain control by convenient dosing intervals and sustained blood concentrations. The differences between available modified-release products are half-life, cost, and formulation and drug-release properties.

Keywords: analgesic, pain management, modified drug delivery system, specialty product and polymer

1. Introduction

Analgesics are medicines that relieve pain or in other words they are drugs that are used to provide pain relief. When we browse the topic on analgesics we will also come across

the term narcotic as first analgesics as they were narcotics, and their derivatives and analogs were chemically based on the morphine molecule [1]. Additionally, analgesics may include nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol (acetaminophen). Practically, the term may also include others like tricyclic antidepressants and substances such as gabapentin, although they are not commonly classified as analgesics [1]. It should be well differentiated that usually analgesics give symptomatic relief, but have no effect on the body condition, although NSAIDs are beneficial in both reducing pain and inflammation.

2. Pain

Why god created pain? To the author, the answer to this question explains the term “productive pain” which has been described in literatures as a warning on the occurring of injury in the body. This pain will guide the person to seek treatment, and this pain will also facilitate diagnosis. “Nonproductive” pain by definition serves no purpose either as a warning or diagnostic tool. It is important for us to understand pain pathophysiology for management purpose.

Pain syndromes may be different, but their sensory pathways are the same. It starts from the affected organ and the message flow to the brain for interpretation. The pharmacological path of analgesics’ action is by working at the level of the nerves, they work by either blocking the signal originating from the peripheral nervous system, or can work centrally by distorting the interpretation by the central nervous system.

Practitioners’ selection of an appropriate analgesic is first based on the type of pain and severity and then the knowledge of risk and extra benefit and indirectly considering existing risk-benefit of a particular drug. The decision will also depend on the knowledge on the classes of drugs, and their adverse effect. Text books have divided pain into two classes, acute and chronic. In selecting the analgesic to be used, severity and predicted survival of patient must also be considered as a selection criteria [2].

2.1. Acute pain

Acute pain duration is self-limiting and this includes postoperative pain, pain of injury, and childbirth. This type of pain is foreseen to be short in duration so the treatment using narcotic pain killer is considered to be safe as there will not be long-term addiction problem on using narcotics. Using NSAIDs will also be beneficial as it allows fluctuation of dose but with limiting concern on the risk of ulcers. For both categories of painkillers, their doses may be adjusted based on observation of healing rate, changing doses from high to low doses, and from narcotic analgesics to nonnarcotics as required. In severe pain, it is the rule of thumb that patients should not be subject to the return of pain so painkiller needs to be dosed adequately to ensure that pain is at least tolerable to avoid the occurrence of anxiety, usually after the return of pain [3]. Generally, in pain management, painkiller

should never be dosed on as needed basis, but should be administered often enough to assure effective plasma level (this could be warranted with the use of a sustained release preparation).

2.2. Chronic pain

Chronic pain is defined as pain lasting over 3 months and severe enough to have effect on body function. This condition is more difficult to treat, as the expected side effects of the drug are more difficult to manage because of the long-term exposure to the drug. There will be addiction potential for those who are on narcotic analgesics which can exacerbate to respiratory depression and constipation. For those using NSAIDs, the risk of gastric ulcers is evident. Drugs with narcotic agonist-antagonist properties such as buprenorphine, nalbuphine, pentazocine, or the COX-2 inhibitors, such as celecoxib and rofecoxib, which reduces the common side effect, are still not recommended for long-term management of severe pain. Usually, practitioners following the guidelines for chronic pain management will recommend a combination of drug therapy to suite the lifestyle and other treatment modalities [2]. Modification of the delivery system of the drug for the purpose of long-term treatment is also beneficial [4].

3. Group of analgesic drug

3.1. Narcotic analgesics

Narcotic analgesics are all derived from opium. They include morphine, codeine, and a number of semisynthetics including meperidine (Demerol), propoxyphene (Darvon) tramadol, and a few others. Different narcotic analgesics may vary in their potency, but all of them are effective in the treatment of visceral pain. Generally, their adverse effects are very much dose-related as they are all addictive in nature [5]. These category of drug are regulated by the authorities as they are open for abuse, usually they are controlled under the nation's laws.

3.2. NSAIDs

NSAIDs are available as effective analgesics even at low doses where there is no antiinflammatory effect. They are in the form of various chemical types although they have demonstrated similar pharmacological effect in reducing pain. They may even possess similar side effects. They are mostly provided in the form of oral dosage although some may be in the form of injection [6].

Paracetamol, or acetaminophen as Americans call it, is a nonnarcotic analgesic with no antiinflammatory properties. It is the most popular analgesic which is appropriate for mild to moderate pain. It is well tolerated in normal recommended doses but it may have significant liver toxicity at high doses. Clinically, paracetamol has been considered the first choice for mild pain as it is considered to be very safe at therapeutic doses.

4. Various dosage form of analgesic and their mode of actions and limitations

4.1. Conventional dosage forms of analgesics

Conventional dosage forms of analgesic are the same as any conventional dosage form of general pharmaceuticals. Dosage which is synonymous with unit doses, means pharmaceutical drug products in the form found commercially in the market with a specific mixture of active ingredients and inactive excipients in specific form or configuration. Dosage forms come in several types, depending on the route of administration. The general forms include liquid, solid, and semisolid forms. Specifically, conventional dosage forms are solutions or suspensions for injection, pill, tablet, capsule, and syrup. Clearly, the administrative route of the drug is dependent on the dosage form of the substance. An oral solid dosage form is the solid form of a dose of a chemical compound used as a drug or medication intended for oral consumption. More than one dosage forms may exist for a single particular drug. This is due to the fact that different clinical conditions may need different routes of administration [8]. For example, where there is a condition of nausea or vomiting, it may be difficult to use an oral dosage form. Such condition may warrant an alternative route such as injection or rectal route. Dedicated specific route may be a requirement for certain kinds of drugs, as there may be issues with various factors like chemical stability or pharmacokinetics. A good example is the analgesic paracetamol, it exist in a number of dosage form, that is, tablet, capsule, syrup, suppository, and injection (**Table 1**).

	Type of pain killer in the market	Common dosage form available
1.	Paracetamol (acetaminophen)	Tablets, solution, suspension, suppository, injection
2.	Paracetamol with codiene	Tablets, solution, suspension
3.	Celecoxib	Capsules
4.	Diclofenac	Tablets, capsules, gel (local application)
5.	Fentanyl	Tablets, capsules, *transdermal patch
6.	Hydrocodone	Tablets, elixer
7.	Hydrocodone with paracetamol	Tablets, elixer
8.	Hydromorphone	Tablets, injection, suppositories, liquid
9.	Ibuprofen	Tablets, solution, suspension
10.	Meloxicam	Tablets, oral suspension
11.	Methadone	Tablets, oral solution, oral concentrate, injection
12.	**Methylprednisolone	Tablets, injection
13.	Milnacipran	Tablets, injection

	Type of pain killer in the market	Common dosage form available
14.	Morphine	Tablets, injection
15.	Naproxen	Tablets, *delayed-release enteric coated tablets, suspension
16.	Oxycodone	Tablets, oral concentrate, oral solution
17.	Oxycodone with paracetamol	Tablets
18.	**Prednisone	Tablets, solution
19.	Sumatriptan	Injection, tablets, *nasal spray

*Analgesic specialty products.

**Steroids as adjuvant to analgesic, OK.

Table 1. Some of the analgesic and their dosage form available in the market.

5. Various new dosage forms, making their way to the market

5.1. Research in the development of new delivery system with existing analgesic

Development of modified release painkiller is a popular research. This type of research looks into the development of techniques and evaluation of the modified forms used in the management of chronic pain in comparison with existing dosage form [7]. The realization on the importance of pain management and the treatment of pain has initiated more research in this area among healthcare researchers. Modified-release products have enabled patients to better maintain pain control due to convenient dosing intervals and sustained blood concentrations. With the above statements, it is evidenced that development of modified release is very much needed for pain management drug, so as to be very effective and to prolong the effect for more effective pain management [7].

All drugs need a delivery system to deliver it to the site of action upon administration. Delivery of the drugs can be achieved using various types of dosage forms including tablets, capsules, creams, ointments, liquids, aerosols, injections, and suppositories. These conventional drug delivery systems provide immediate release of the drug without controlling the rate or drug release. A number of doses given daily in order to achieve and maintain therapeutic level to achieve effective plasma concentrations cause fluctuations in plasma levels of the drug [8–10] and drug plasma levels could fall below the minimum effective concentration and can also exceed the minimum toxic concentration (**Figure 1**).

5.2. The various types of modified release preparation possible for analgesics delivery

The purpose behind controlling the drug delivery for analgesic are to achieve more effective therapies while eliminating the potential for both under- and overdosing of analgesic.

Maintenance of analgesic levels within a desired range to combat pain is indirectly combatting stress to the patient. The need for fewer administrations of analgesic or optimal use of

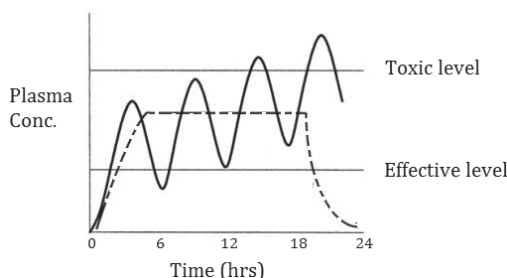


Figure 1. The conventional four times daily oral doses of diclofenac sodium (25 mg) plasma level compared to a daily doses sustained release formulation (100 mg) plasma level.

analgesic toward “no pain” maintenance is to avoid adverse side effect and indirectly to increase patient compliance in their pain management [8].

5.2.1. The polymeric delivery system: polymers in controlled drug delivery

The use of various polymers in controlled drug delivery is very popular among formulation researchers. These polymers can be natural or synthetic in nature. Different polymer is combined with a drug in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period or it may be cyclic over a long period or it may be triggered by the environment or other external events [9].

Polymer can be used to encapsulate drug molecules for the purpose of sustaining the release and extending the availability of the drug so that dosage administration frequency can be reduced while maintaining the plasma level steady state. A good example would be the sustenance of release preparation of diclofenac sodium for oral administration [8].

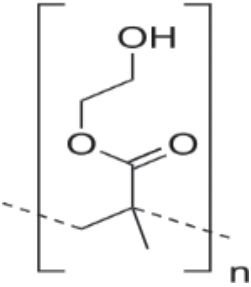
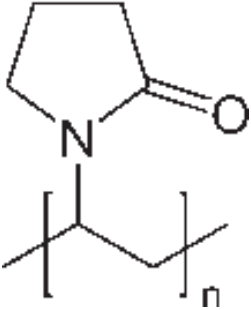
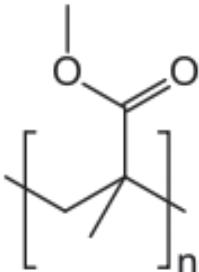
Polymer can also be used in protecting the drug from the environment in order to target the delivery of the drug to certain side of the body. A very simple targeting is the delivery of weak base drug to the small intestine where most of this type of drug is acid labile. So the polymer is used as a protective shield. This can be a pH-sensitive polymer where in acidic environment it is very stable and will disintegrate in basic environment.

Characteristics of polymer may be engineered to the advantage in the development of a drug delivery system. A mucoadhesive polymer which can stick to the mucosa can be used to encapsulate drug and attach to the mucosa and sustain the release of the drug it encapsulates. A biodegradable polymer can be used to encapsulate drug for slow release as the polymer degrades. A pH-sensitive polymer can be used to target the release of drug either in acidic or basic environment. Combining all these characteristic, a researcher can even deliver a drug which currently can only be delivered by parenteral route, using the enthrall route. Logically, the drug can have an outer encapsulation with a pH-sensitive polymer which can save it from the acidic environment in the stomach and can have a mucoadhesive polymer inner encapsulation for it to stick to the small intestine lining and to release the drug direct across the membrane into the blood.

The vast uses of polymer in the gastrointestinal, enthrall, or oral drug delivery system do not limit the same polymer to be used in other route of dosage administration. Several polymers in the form of nano size particles are used to deliver drug as an intravenous dosage form [11]. Researchers are also looking into various polymers which can act as a depot for big dose administration of drug through implantation in the subcutaneous area for cases of difficult patient compliance such as delivery of antipsychotics and cancer drugs.

Some of the synthetic materials that are currently being used or studied for controlled drug delivery are as depicted in **Table 2**.

Polymer are sometimes crudely extracted from natural resources be it from animals or from plants. Such natural materials are depicted in **Table 3**.

Polymer	Polymer structure
Poly(2-hydroxy ethyl methacrylate). ($C_6H_{10}O_3$) _n	
Poly(N-vinyl pyrrolidone). (C_6H_9NO) _n	
Poly(methyl methacrylate). ($C_5O_2H_8$) _n	

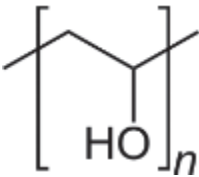
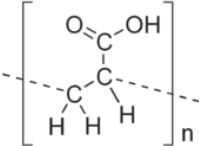
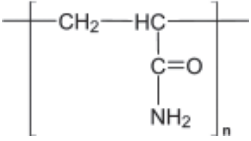
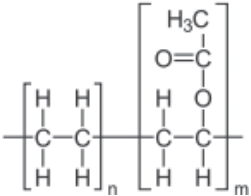
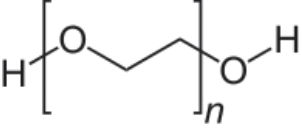
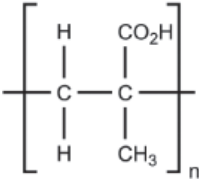
Polymer	Polymer structure
Poly(vinyl alcohol). (C ₂ H ₄ O) _x	
Poly(acrylic acid). (C ₃ H ₄ O ₂) _n	
Polyacrylamide. (C ₃ H ₅ NO) _n	
Poly(ethylene-co-vinyl acetate). (C ₂ H ₄) _n (C ₄ H ₆ O ₂) _m	
Poly(ethylene glycol). C _{2n} H _{4n+2} O _{n+1}	
Poly(methacrylic acid). (C ₄ H ₆ O ₂) _n	

Table 2. Example of synthetic polymer available in the market.

5.3. Controlled-release mechanisms in the case of using polymer as a drug delivery system

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system [12]. We can easily understand this mechanism through **Figures 2–8**.


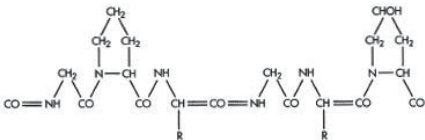
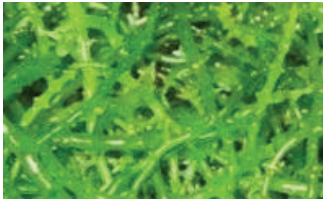
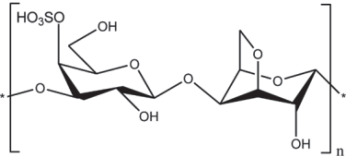

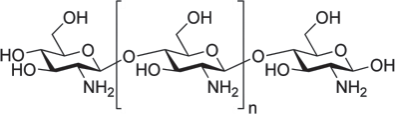

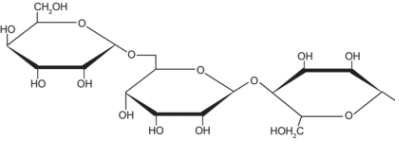

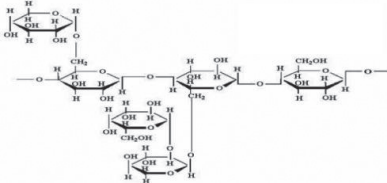

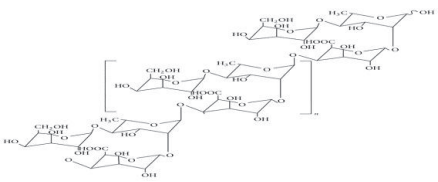
Material	Illustration	Structure (if available)
Gelatin		
Carrageenan		
Chitosan		
Arabic gum		
Tamarind seed gum		
<i>Hibiscus esculentus</i> gum		

Table 3. Example of natural polymer used in drug delivery research.

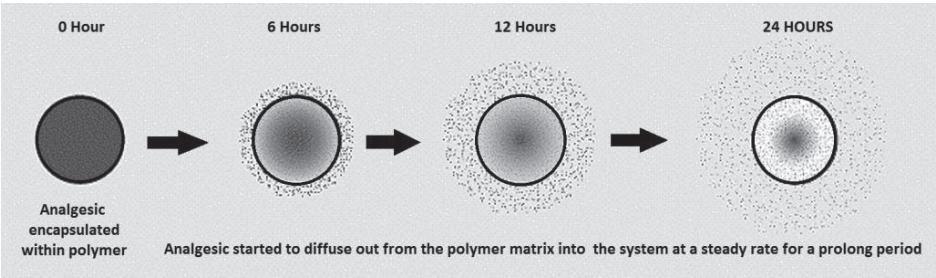


Figure 2. Analgesic diffusing out from a matrix of polymer in a sustain release model.

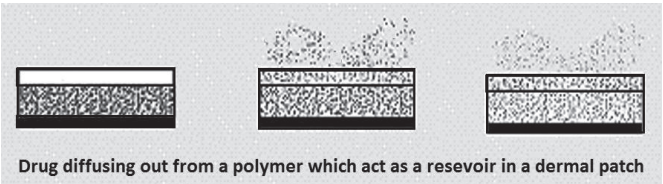


Figure 3. A dermal patch model illustrating the diffusion analgesic from a dermal path polymer matrix.

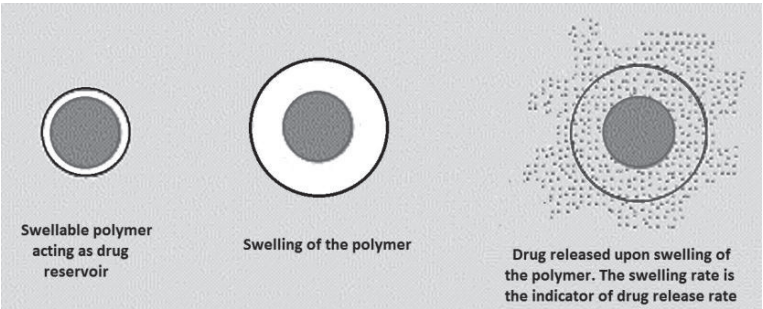


Figure 4. Analgesic delivery system by swelling of polymer acting as drug reservoir.

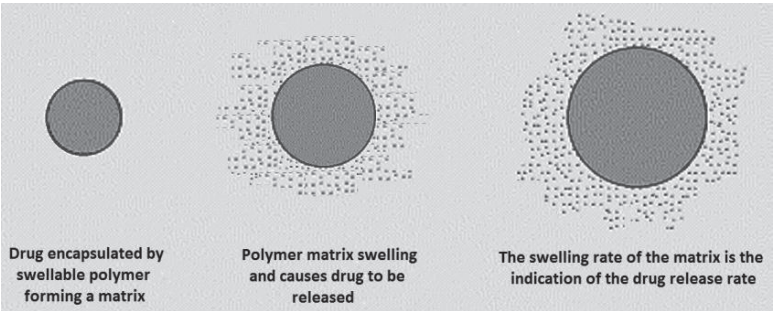


Figure 5. Analgesic delivery system by swelling of the polymer matrix encapsulating the drug.

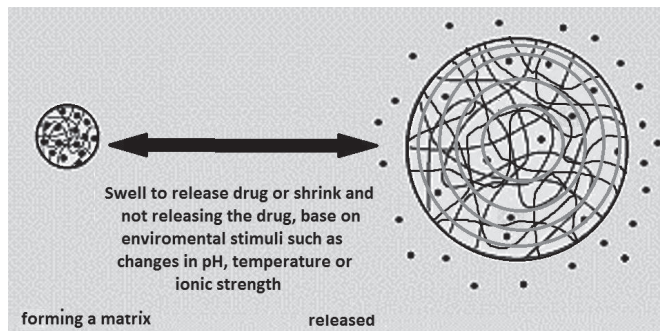


Figure 6. Drug delivery from environmental sensitive release system.

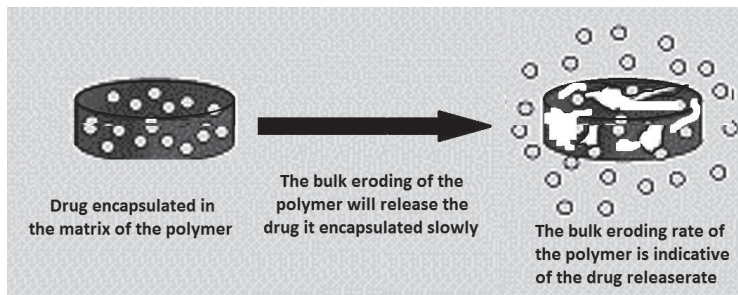


Figure 7. Bulk eroding biodegradable polymeric delivery system.

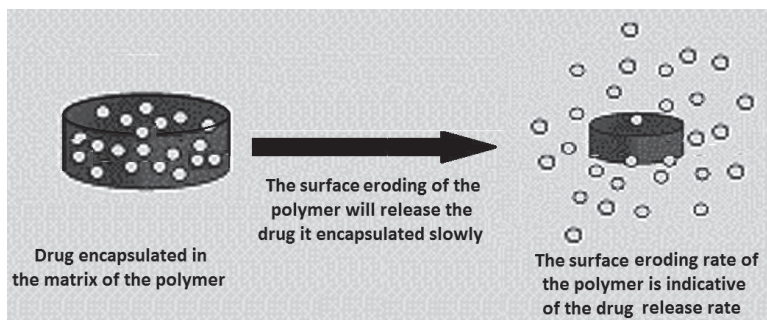


Figure 8. Surface eroding biodegradable polymeric delivery system.

6. Transdermal drug delivery

Transdermal delivery patch usually consists of a reservoir of drug on a protective backing layer, a rate-limiting release membrane, and an adhesive layer to attach the patch to the skin. The physicochemical of the drug suitable for transdermal delivery includes low molecular

weight (<500 daltons), big molecules will have difficulty in penetrating the stratum corneum of the skin, high potency drug, water solubility (to facilitate movement of the drug out of the reservoir and to allow passage through the epidermal and dermal layers of the skin), and lipid solubility (to permit penetration of the stratum corneum of the skin). Fentanyl, a synthetic opioid agonist, is delivered by transdermal patch. For transdermal drug delivery, the penetration of the drug through the skin constitutes an additional series of diffusional and active transport steps [13].

The skin functions to maintain homeostasis of the body through temperature regulation, protection of underlying tissues, control water loss, rich sensory receptors, synthesizing of certain body chemicals, and excretion of wastes by sweating. The skin is made up of an outer epidermis and a dermis, followed by underlying tissue of subcutaneous layer (**Figure 9**). The epidermis is made up of stratified squamous epithelium and lacks blood vessels and it forms good barrier to protect the underlying tissue and blood capillaries. This becomes an important issue in the development of transdermal dosage forms so as to deliver the drug across the stratified layers [14].

Drug in the transdermal dosage form are generally poorly absorbed, but in the positive manner this will form a dosage form with a very controlled depot effect. It is an ideal dosage form for analgesics but the common problem is that the drug may cause focal irritation. Currently, in the market transdermal drug delivery for systemic effects is limited to very few drugs, those having low molecular weights and high lipophilicity. Transdermal drug delivery system may be optimized for controlled release of the drug for a steady plasma profile. This will reduced systemic side effects and may also improve efficacy of the analgesic drug. It is user-friendly, convenient, painless, and offer prolong dosing and all this will contribute to improved compliance [15]. Examples of such dosage forms available in the market are the morphine and sufentanil patches.

Normally, transdermal system in a patch form is made up of an outer covering which forms the barrier, a drug reservoir, a control membrane to control the release of the drug, a contact adhesive applied to some or all parts of the system to make it stick to the skin surface, and a covering protective layer that is removed before the patch is applied (**Figure 10a**). The drug reservoir is sometimes replaced with a matrix of polymer where the drug is encapsulated (**Figure 10b**).

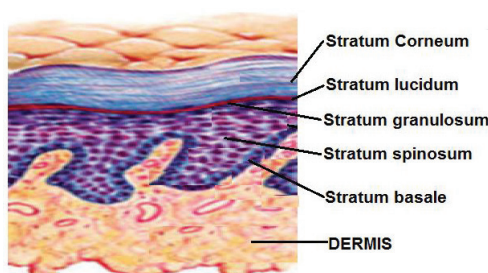


Figure 9. The barriers in epidermis which limit the penetration drug through the skin.

Researchers can be creative in the development of transdermal delivery system for analgesics. The followings are a few creative ideas on delivery of drug using various dermal patches with each having its own technique of engineering.

6.1. Iontophoresis

An active state of transdermal technologies uses low voltage electrical current to drive charged drugs through the skin. This will enable charged particles of drugs to move across the stratum corneum. Each iontophoresis patch is a device consisting of a housing which contains the battery and related electronics, two polymeric reservoirs for anode and cathode, and skin adhesive. Only one of the polymeric reservoirs contains the drug. The other may contain only pharmacologically inactive ingredients. **Figure 11** depicts the iontophoresis system. The choices on whether the anode or the cathode contains the drug are dependent on the drug charge.

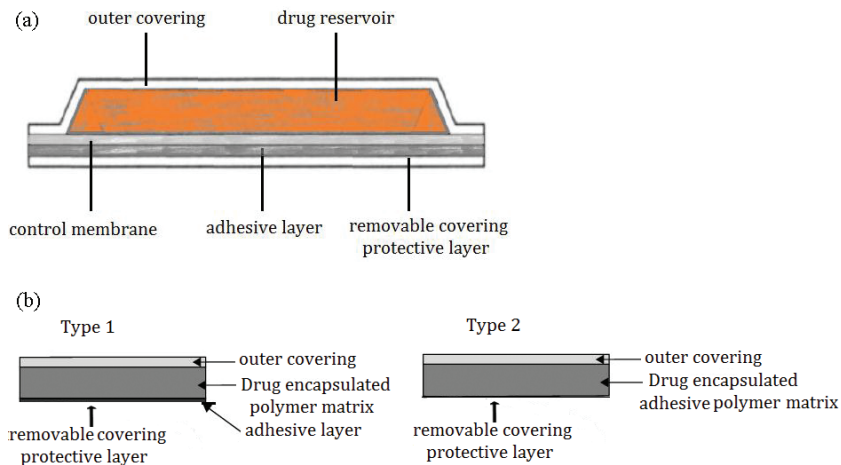


Figure 10. (a) The structure of a reservoir dermal patch. (b) Two types of structures for matrix dermal patch.

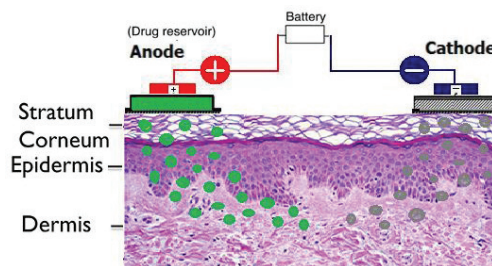


Figure 11. Iontophoresis patch illustration.

The technique of iontophoresis has the potential to be expanded to deliver proteins and peptides. The current can be literally switched on and off and modified, also iontophoretic delivery enables rapid onset and offset, and drug delivery is highly controllable and programmable.

6.2. Electroporation

This transdermal drug delivery technique uses short electrical pulses of high voltage to create transient aqueous pores in the skin, in a variety of forms, temporarily to disrupt the stratum corneum and to allow drug in the reservoir or the polymeric matrix to cross the stratum corneum and then penetrate the blood vessel (**Figure 12**).

6.3. Sonophoresis

This transdermal drug delivery technique uses low-frequency ultrasonic energy (15-second burst of ultrasound at 55 kHz) to disrupt the stratum corneum and to allow drug in the reservoir or the polymeric matrix to cross the stratum corneum and then penetrate the blood vessel. Similar to the electroporation effect, the sound waves create cavitation bubbles in the tissue that disrupt the lipid bilayers of the cells of the stratum corneum creating microchannels. The ultrasound poration can increase the transport properties of the stratum corneum by 100-fold. **Figure 13** illustrates the effect of sonophoresis.

6.4. Microneedle dermal patch

This transdermal patch technique makes use of microneedles, which are microscopic, just a few hundred microns in size. They can pierce the skin in a minimally invasive manner

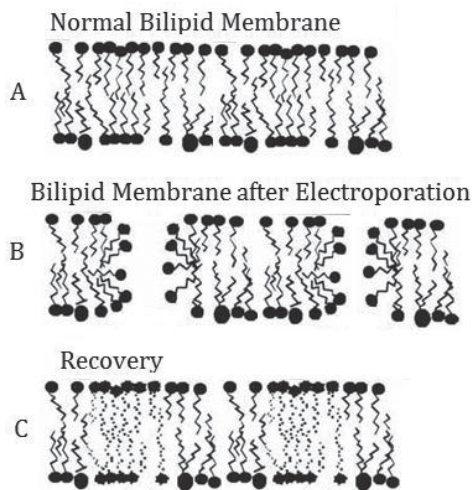


Figure 12. Temporary disruption of the bilipid membrane after electroporation. A: Normal arrangement of the bilipid membrane B: Bilipid membrane after electroporation C: Recovery of the Bilipid membrane after an interval.

without causing pain or injury [16]. A lot of research in the literature shows that this piercing effect increases transdermal flux of large molecular weight compounds by many folds. There are two ways of utilizing the microneedles, one of the ways in which drug delivery is achieved is to coat the drug onto microneedle shafts and insert them into the skin where they deposit the drug. The second way is upon piercing skin they create microconduits across stratum corneum and this will provide a direct route for transport of drugs into the skin from the patch reservoir (Figure 14).

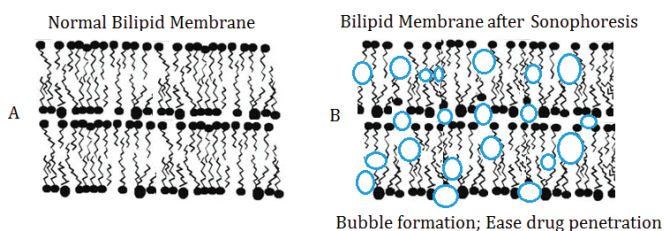


Figure 13. Bubble formation after sonoporesis process, forming channel for drug penetration. A: Normal arrangement of the bilipid membrane B: Formation of bubbles in Bilipid membrane after sonoporesis.

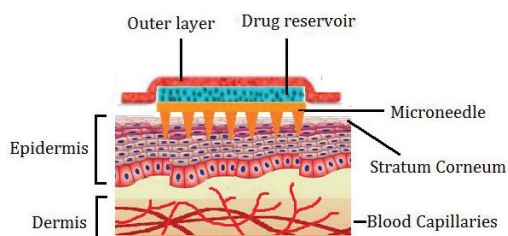


Figure 14. Illustration of microneedle transdermal patch with drug reservoir.

7. Nanoparticle delivery systems

Nanoparticle systems as drug carriers may also play a very important role in the delivery of analgesics. The advantages of nanoparticles used as drug carriers include fast action of the nano formulation, high product stability, good loading capacity, both hydrophilic and hydrophobic substances can be given together in the same formulation, and various routes of administration can be utilized [11]. Analgesics in nanoparticulate systems would be transported and released in a controlled manner at the target area, depending on the environmental conditions. Analgesic nanoparticulate can have the following advantages: reducing the dose of the drug, some specialty formulation may allow analgesic drugs that normally do not cross the blood brain barrier to penetrate into the brain where this can reduce the peripheral side effects by lowering the amount needed to act directly on the central nervous system. The development of the analgesic-loaded nanoparticulate systems

may represent a future challenge to achieve promising agents for regional drug delivery in pain management strategy.

Nanoparticles can also be solid or soft colloidal matrix-like polymeric particles or lipids. They can be drug carrier system such as liposomes. Other drug delivery systems are based on using nanoparticles composed of biodegradable polymers, this has been explained in the earlier subsection on polymeric drug delivery system [17]. These microparticles may consist of polymeric nanospheres in an oily reservoir or aqueous medium. It was shown in research that a numbers of analgesic drugs such as ibuprofen, flurbiprofen, and acetyl salicylic acid have been successfully delivered by entrapping in nanoparticles [18].

8. Multiphase liposomal drug delivery system

Liposome is a drug delivery system suitable for various routes of drug administration, i.e., oral, rectal, parenteral, and particularly local administration to the skin, eye, and mucous membranes [19]. Liposomes are microscopic phospholipid-bilayered vesicles and they have the advantage in which they can be used to entrap both hydrophilic and lipophilic drug for delivery. **Figure 15** illustrates the formation of liposome for drug delivery. Liposomes are generally administered by intravenous route but they are also developed for transdermal or subcutaneous implantation.

8.1. The concept of LipoSpray

Using the liposomal concept “LipoSpray” is an innovative idea in delivering an analgesic in the form of liposomal suspension. The suspension is sprayed into the mouth and under the tongue. Liposomes penetrate the mucosal tissue of the mouth, and the drug is released from the liposome into the bloodstream, distributing the drug throughout the body in minutes.

This path bypasses the gastrointestinal (GI) track and bypasses the first-pass effect of the liver. The analgesic in question would have a fast effect in pain management.

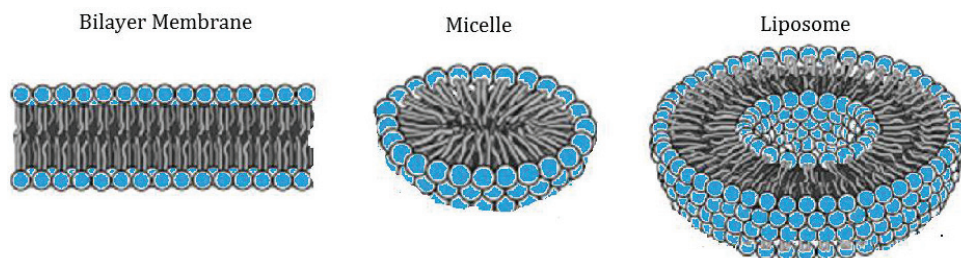


Figure 15. Various morphology of the polar and nonpolar arrangements in liposome and its formation.

9. Basic research methodology in development of new drug delivery systems in delivering analgesics

This subchapter illustrates an example of research steps in the development of a drug delivery system using nano technology. The steps illustrated in this section may be applicable to certain extent in research toward the development of an analgesic drug special delivery system. The techniques are not exhaustive and are just an example to guide the researchers.

9.1. Getting the delivery material (e.g., polymerization reaction to get the polymer)

At the beginning of the investigation, efforts should focus on the preparation of a polymeric system. There are two different types of polymerization reactions: addition polymerization and condensation polymerization. Addition polymerization involves the use of a radical generating initiator which triggers polymerization reaction of monomers. Condensation polymerization involves reaction of monomers containing reactive functional groups to form a polymer.

The FTIR and ^1H NMR spectra need to be used to confirm the formation of the desired polymer. Further attempts to synthesize larger amount of the polymer for characterization studies need to be done.

One important characterization is the determination of molecular weight. Gel permeation chromatography (GPC) can be used to analyze molecular weight of the polymer. A solution of 1 mg/1 ml of the polymer in tetrahydrofuran needs to be prepared and analyzed by GPC.

9.2. Determination of polymer stability

Another important criterion is to determine the *in vitro* degradation of the polymer so as to ensure its stability as required. The *in vitro* degradation study can be carried out through preparing polymeric devices and placing them in phosphate buffer solution for different periods of time, and analyzing their wet and dry weight loss [20].

Scanning electron micrographs of sample need to be taken by scanning electron microscope (SEM) to observe the erosion characteristics of the polymer. SEM is a technique for the preparation of high resolution images from surface of different compounds. Electrons are used for imaging in scanning electron microscopes.

The differential scanning calorimetry (DSC) is also a requirement in the determination of the thermal stability of the polymeric system [21].

9.3. Cytotoxicity issues

If the polymer being optimized is a new polymer then it is important to establish the cytotoxicity of the synthesized polymer to evaluate whether the polymer is appropriate for application in drug delivery systems or not. In other words, the synthesized polymer should be nontoxic to normal body cells and tissues, and cause minimum side effects at the site of action. There are different types of tests and assays for the evaluation of cytotoxicity of

polymers, as well as drugs. Cell-based assays are the most widely used methods for assessing cell toxicity effects of different polymers or drugs on a particular cell line.

9.4. Preparation of drug-loaded polymeric system

Thin film hydration method can be one of the methods for the preparation of the drug-loaded polymeric system. An example is by using a solution of 2 mg/ml of polymer in ethanol (10 ml) and mixed with a solution of 5 mg/ml model drug in ethanol (1 ml). After stirring for 15 minutes at room temperature, the solvent needs to be evaporated by rotary evaporator. The precipitant is then mixed with 20 ml distilled water. The mixture is then centrifuged at 6000 rpm for 10 minutes. The supernatant is then taken for further analysis for entrapment characteristics of the drug in the polymer.

9.5. Determination of entrapment efficiency

In order to obtain the entrapment efficiency, the concentration of the free drug is to be determined upon preparation of the entrapment, 1 ml of the supernatant is taken and diluted with 3 ml water, and the concentration of the drug is determined by high performance liquid chromatography (HPLC). Entrapment efficiency is calculated by the following equation:

$$EE(\%) = \frac{\text{total drug} - \text{free drug}}{\text{total drug}} \times 100 \quad (1)$$

9.6. Determination of polydispersity

The polydispersity index (PDI) is a reflection of the heterogeneity and a measure of the distribution of molecular mass in a given polymer sample. PDI is calculated as the weight average molecular weight, divided by the number of average molecular weight. It indicates the distribution of individual molecular masses in a batch of polymers. PDI value of 1 reflects that the polymer is of the same size and indicates uniformity of the chain length. The following equation denotes the PDI:

$$PDI = M_w/M_n \quad (2)$$

where M_w is the weight average molecular weight and M_n is the number average molecular weight.

9.7. Determination of size, size distribution, and zeta potential of nanoparticles

Scanning electron microscopy (SEM) and dynamic light scattering (DLS) can be used to determine the size of nanoparticle. DLS is used for determining the size distribution and zeta potential of nanoparticles as well. Dynamic light scattering, which is also known as photon correlation spectroscopy, is one of the most widely used methods for the determination of size, size distribution, and zeta potential of nanoparticles. This instrument works through radiation of a light beam into a particulate system with Brownian motion.

9.8. Determination of the thermal characteristic of the delivery system

Differential scanning calorimetry (DSC) technique is the most common thermal analysis equipment used in the determination of material in the delivery system. This primary

technique directly assesses the uptake of heat energy during the fluctuation of temperature in order to specify any connection among temperature and physical properties of samples. Calorimetry is a suitable thermal analysis technique for qualifying the purity, the melting point, and the polymorphic forms of samples [21].

9.9. *In vitro* drug release study

Drug release from the polymeric system shall be studied to prove good delivery as stipulated. Commonly, the *in vitro* dissolution of the drug from the formulation is done following the available compendium method where standard dissolution apparatus are recommended. Other methods include using dialysis method where the formulation prepared is placed in the dialysis bag. The dialysis bags are then placed in a bath shaker at the temperature of 37°C and rotated at the rate of 100 rpm. Samples were collected at different time intervals and analyzed.

9.10. *In vivo* animal study

This is one of the stages for preclinical study on the new formulation which can also be a new type of polymer or material used [19]. The safety and efficacy of this formulation need to be established. Before starting the study, the animal ethic committee needs to be consulted to get approval to start the study. Most of the studies are to prove that the pharmacokinetics of the drug delivered is appropriate as stipulated. The ADME (Absorption, Distribution, Metabolism, and Excretion) of the drug delivered by the system is important at this stage, especially the absorption and distribution.

For the technique in determining the absorption and the distribution of the active in a formulation, a researcher may in his or her study use optical *in vivo* imaging technique for monitoring the distribution of the drug in question the proposed delivery system in comparison with the conventional dosage form available. This technique is able to image the whole body of small animals and body cells. This technique includes both fluorescence *in vivo* imaging and fluorescence microscopy, and a low-light camera and proper filters were also used to collect fluorescence excitation and emission light from samples. In fluorescence microscopy, the objects of imaging are cells, slides, or culture dishes, while the whole body of small animals is pictured with optical *in vivo* imaging system. However, *in vivo* imaging is technically a more challenging process, as the animal tissues are opaque or/and thick, therefore, they absorb scatters photons and generate strong autofluorescence. Furthermore, it is essential to apply an appropriate imaging probe, which provides biologically stable distribution and preferential accumulation at the intended target site. Loading near-infrared (NIR) fluorophores with drug delivery agents would be a great opportunity to follow medicine distribution with optical *in vivo* imaging system without using specific conjugated antibodies. Near-infrared excitable fluorescent agents (NIR) provided deep tissue penetration and low tissue autofluorescence.

Researcher performing the animal study should also take the opportunity to do plasma level drug monitoring, urine metabolite level, and histological studies on heart, lungs, kidneys, spleen, and the liver.

9.11. The human bioavailability study

This is a regulatory requirement as to prove that the new system will make the drug available as the conventional system. It indirectly also determines if the drug pharmacokinetic parameters in human are the same as for the original available formulation. This is different from bioequivalence, which is used to evaluate the predictable *in vivo* biological equivalence of two proprietary preparations of a drug. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities after administration in the same dose are similar to such a degree that their effects, with respect to both efficacy and safety.

Bioavailability measures the extent of a drug reaching the systemic circulation and is therefore available for action at the expected site. For most drugs that are taken orally, the drug is released in the gastrointestinal (GI) tract and arrives at their site of action via the systemic circulation. Plasma concentrations of the drug or its metabolite would provide a marker for the concentration at the site of action and a valid measure of bioavailability. The researcher needs to build a plasma blood concentration time curve to prove the release of the drug from the preparation and its absorption from the GI tract, but also other factors including presystemic metabolism, distribution, and elimination. Bioavailability is proven through the area under the blood drug concentration versus time curve (AUC), the maximum blood concentration (C_{\max}) and the time to reach maximum concentration (T_{\max}). Clearly, bioavailability studies of the new delivery systems compared to the conventional ones need to be done so as to be assured that the new delivery system is not inferior compared to the existing systems.

10. Concluding statements

Drug delivery system represents a vast, vital area of research and development of new analgesic product. It is pertinent for analgesic as pain management needs the painkiller to be fast in action, prolong action, and reduce adverse or side effect. So development of specialty product using advance drug release system is the answer to the betterment of pain management and the research on this area is not exhaustive. In this chapter, we have discussed the available conventional dosage forms and gave examples. We also based our discussions on ideas in research and development of various advance new delivery system such as polymeric delivery system, sustain release system, transdermal delivery system, and liposome.

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References

- [1] Mark HB et al, editors. The Merck Manual of Medical Information. 2nd Home ed. Whitehouse Station, NJ: Merck; 2003
- [2] Kehlet H. Postoperative pain. In: Wilmore DW, Brennan M, Harken A, et al, editors. Care of the Surgical Patient. New York: Scientific American Inc; 1988. pp. 121-133
- [3] Ventafridda V, Stjernsward J. Pain control and the World Health Organization analgesic ladder. The Journal of America Medical Association. 1996;**275**(11):835-836
- [4] Bansal SS, Joshi A, Bansal AK. New dosage formulations for targeted delivery of cyclooxygenase-2 inhibitors: Focus on use in the elderly. Drugs & Aging. 2007;**24**(6):441-451
- [5] Khan MI, Walsh D, Brito-Dellán N. Opioid and adjuvant analgesics: Compared and contrasted. The America Journal of Hospice Palliative Care. 2011;**28**(5):378-383
- [6] Jenkins CA, Bruera E. Nonsteroidal anti-inflammatory drugs as adjuvant analgesics in cancer patients. Palliative Medicine. 1999;**13**(3):183-196
- [7] Hersh EV. New formulations of old analgesics. Clinical Therapeutics. 2015;**38**:424-425
- [8] Marzo A, Dal Bo L, Verga F, Monti NC, Abbondati G, Tettamanti RA, Crivelli F, Uhr MR, Ismaili S. Pharmacokinetics of diclofenac after oral administration of its potassium salt in sachet and tablet formulations. Arznei-Forsch/Drug Research. 2000;**50**(1):43-47
- [9] Kim T, Kim J, Kim S. Extended release formulation of morphine for subcutaneous administration. Cancer Chemotherapy and Pharmacology. 1993;**33**:187-190
- [10] Lötsch J, Kettenmann B, Renner B, Drover D, Brune K, Geisslinger G, Kobal G. Population pharmacokinetics of fast release oral diclofenac in healthy volunteers: Relation to pharmacodynamics in an experimental pain model. Pharmaceutical Research. 2000;**17**(1):77-84
- [11] D'Souza, S. A review of in vitro drug release test methods for nano-sized dosage forms. Advances in Pharmaceutics. 2014; Vol. **2014**:1–12
- [12] Rowe, Raymond C; Sheskey, Paul J; Owen, Siân C; American Pharmacists Association. 5th ed. / edited by Raymond C. Rowe, Paul J. Sheskey, Siân C. Owen. London ; Chicago: Washington, DC : Pharmaceutical Press ; American Pharmacists Association, 2006.
- [13] Keleb E, Sharma RK, Mosa EB, Aljahwi AZ. Transdermal drug delivery system - design and evaluation. International Journal of Advances in Pharmaceutical Sciences. 2010;**1**:201-211
- [14] Tortara GS, Grabowski SK. Principles of Anatomy and Physiology. 9th ed. New York, Chichester: Wiley; 2000. pp. 140-194
- [15] Barry B. Transdermal drug delivery. Aulton ME (2002) 'Pharmaceutics' The Science of Dosage Form Design, 2nd ed., Churchill Livingstone, Spain, pp. 499-533
- [16] Kumar JA, Pullakandam N, Prabu SL, Gopal V. Transdermal drug delivery system: An overview. International Journal of Pharmaceutical Sciences Review and Research. 2010;**3**(2):49-54

- [17] Peniche C, Arguelles-Monal W, Peniche H. et al. Chitosan: An attractive biocompatible polymer for microencapsulation. *Macromolecular Bioscience*. 2003;**3**:511-520
- [18] Gupta M, Majumdar DK. Effect of concentration, pH and preservatives on *in vitro* trans-corneal permeation of ibuprofen and flurbiprofen from non-buffered aqueous drops. *Indian Journal of Experimental Biology*. 1997;**35**:844-849
- [19] Smith LJ, Valenzuela JR, Krugner-Higby LA. et al. A single dose of liposome encapsulated hydromorphone provides extended analgesia in a rat model of neuropathic pain. *Comparative Medicine*. December, 2006;**56**(6):487-492
- [20] Crompton TR. *Polymer Reference Book*. 1st ed. Smithers Rapra Publishing, USA; 2006
- [21] Gill P, Moghadam TT, Ranjbar B. Differential scanning calorimetry techniques: Applications in biology and nanoscience. *Journal of Biomolecular Techniques*. 2010;**21**(4):167