Newer drug delivery systems in anesthesia

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Introduction

Drug delivery systems (DDSs) are developed to deliver the required amount of drugs effectively to appropriate target sites and maintain the desired drug levels. Research in newer DDS is being carried out in liposomes, nanoparticles, niosomes, transdermal drug delivery, implants, microencapsulation, and polymers.

Advantages of drug delivery system
1. Increases bioavailability
2. Can be used for long-term treatments of chronic illness
3. Sustained maintenance of plasma drug levels
4. Decreased adverse drug effects
5. Decrease in the total amount of drugs required thus reducing side effects
6. Improved patient compliance due to reduction in number and frequency of doses required

Alternate Route of Drug Delivery

Intranasal drug delivery
In addition to being convenient and painless, there is no reduction in bioavailability of drugs administered nasally. Direct deliveries to the cerebrospinal fluid due to nose-brain pathway reduce the onset time. Highly lipophilic drugs of low molecular weight easily cross the nasal mucosa. It does not require coupling with carrier nor any modification of therapeutic agent. To avoid runoff, 0.25–0.3 ml of concentrated drug per nostril is used. One of the limitations is that in patients with bloody nose or increased mucus production there may be decreased absorption. Intranasal drug takes about 3–5 min to be absorbed, and drug levels achieved rarely cause respiratory depression. However, sufentanil is an exception where toxic levels can reach very rapidly.

Abstract

A paradigm shift in drug delivery systems have been noted recently. The focus nowadays is to obtain maximum benefit with lower side effects. It is a monetary burden to launch newer molecules hence the industry is concentrating on improving the efficacy of existing molecules. Thus controlled release, target controlled infusion and closed loop infusion have entered the scene. Applying pharmacokinetic principles, instead of mathematically calculating drug dose could improve safety and maintain steady drug levels in the body. When computers are applied to an efficient operating system, it will only magnify the efficiency. Most of these technologies which were earlier limited to research only have entered clinical practice. This has made it mandatory for the practicing clinician to familiarize themselves with these technologies. Our focus in this review has been to discuss newer drug delivery systems available for anesthesia practice.

Keywords: Controlled released, newer drug delivery system, target control release

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Summary

7. There is less damage sustained by normal tissue due to targeted drug delivery
8. Reduction in cost by developing newer delivery systems for existing molecules.

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Pulmonary drug delivery system
Metered dose inhalers, nebulizers, and dry powder inhalers are used for pulmonary drug delivery.\cite{11} They offer several advantages including a larger surface area and closer proximity to blood flow.\cite{11,12} Lower doses can be used thus avoiding systemic toxicity. However, disadvantages include shorter duration and only 10–40% of the drugs delivered become available for systemic absorption, and to overcome this limitation, nanoparticles have been developed. There has been a constant endeavor to deliver opioids by inhalation route.\cite{13} Bioavailability of fentanyl when administered by this route has been found to be 20%,\cite{14,15} Iloprost, a newer prostacyclin analog used to treat pulmonary hypertension, has a very short half-life requiring frequent dosing regimens. Thus, to improve patient compliance an aerosolized controlled release formulation is an available alternative.\cite{10,16,17} The use of pulmonary DDS utilizing colloidal carrier systems has more physiological components.\cite{18} The drugs used to treat asthma and certain lung infections as well as inhaled insulin are also being developed with newer technology using carriers.\cite{19,20}

Buccal mucosal drug delivery system
In addition to ease of administration, it avoids the first pass effect and presystemic elimination.\cite{21,22} Toxicity or undesired side effects are significantly reduced. Drugs for chronic pain management and breakthrough pains including fentanyl (lozenges, tablets, and films)\cite{24} and buprenorphine hydrochloride (tablets) are available for delivery through this route. The buccal mucosa is less permeable with a large mobile surface which results in slower onset and is more suitable for sustained release preparations, whereas sublingual drug delivery has a more dramatic onset.\cite{25-27}

Intra-articular drug delivery
The size of the drug molecule has to be 3–5 µ. The residence time of drugs in intra-articular tissues may be prolonged by microspheres that are designed to improve their uptake by the synovium.\cite{28}

Controlled Release Drug Therapy
Drug impregnated lozenges, nasal and buccal aerosol sprays, and transdermal and transmucosal DDS are the various controlled release formulations available.

Transdermal drug delivery system
Fentanyl, clonidine, glyceryl trinitrate, lisuride, and buprenorphine are available as transdermal preparations. Advantage of this route is, it avoids first pass metabolism and large variations in plasma drug concentrations.\cite{29} Decreased gastrointestinal side effect improves compliance.\cite{3} Constant drug levels are maintained which avoids ups and downs in plasma concentration levels seen with oral and parenteral route.\cite{30} The stratum corneum is the greatest barrier to transport of drugs; hence, drugs need to be lipid soluble and have a low molecular weight.\cite{3,31,32} Factors such as drug permeability, molecular weight, total body clearance, and therapeutic plasma concentrations have to be taken into consideration when calculating transdermal doses.\cite{33} Reservoir patch and matrix patch are the two types of patches [Figure 1].\cite{33-35}

Fentanyl patches are of the matrix design from which a constant amount of drug is released per unit time. The diffusion occurs at a constant rate in the direction of the lower concentration. After application of patch, the skin under the systemic layer absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers.\cite{34,36} Plasma fentanyl concentrations gradually increase following initial application. A steady-state serum concentration is reached between 12 and 24 h and remains relatively constant, with some fluctuation, for the remainder of the 72 h application period.\cite{37} By the end of the second 72 h application, serum concentration remains nearly steady and is maintained during subsequent applications of a patch of the same size. The fentanyl patches are available to deliver the drug at a constant rate of 25, 50, 75, and 100 µg/h spread over a period of 72 h.\cite{38} The elimination half-life after patch removal is 13–22 h due to slow release of the fentanyl from skin depots. Thus, in cases of adverse effects, the patient needs to be monitored for a further period of 24 h after removal of the patch. The most frequent side effects observed are nausea, vomiting, and constipation. Less frequent ones include hypoventilation and rash at application site.\cite{39}

A newer patient-controlled fentanyl transdermal system, the size of a credit card has been designed, which has to be worn on the upper arm or the chest. Iontophoresis is utilized to deliver fixed drug boluses.\cite{40} There is no background infusion and also passive absorption of the drug is negligible.\cite{35,40,41} Ahmad et al. compared intravenous patient-controlled analgesia morphine with fentanyl iontophoretic transdermal system and found the latter to be associated with lesser analgesic gaps.\cite{42,43}
Although the transdermal delivery of drug is the most patient compliant mode of delivery only lipophilic, low molecular weight drugs can be delivered by this route.\cite{44,45} To overcome this shortcoming, second and third generation DDS has been developed. In the second generation, enhancers are incorporated into the DDS, to reversibly disrupt the stratum corneum and thus promote the transfer of lesser lipid soluble drugs. In case of hydrophilic drugs, active energy-dependent methods have been used to drive drug across. This can be achieved using eutectic mixtures of local anesthetics, controlled heat, magnetophoresis, iontophoresis,\cite{46,47} electroporation, or sonophoresis.\cite{48} Using iontophoresis dermal anesthesia with lignocaine can be achieved.\cite{49,50} The effect can be enhanced by adding adrenaline. Controlled release preparations of tramadol and buprenorphine are available. Beta blocker delivered in this way synchronized with continuous Holter monitoring is a novel application.\cite{51}

### Targeted Drug Delivery

Conventional DDS may cause reduction in potencies of drug before they reach the target tissues of the body due to partial degradation. Goal of all DDS is to deploy the active pharmaceutical compound to the particular targeted areas of the body. Past decade has witnessed the development of polymeric micelles, microspheres, etc., which effectively lower the systemic drug toxicity, enhance the ability of the drugs to target the specific sites, improve the absorption rates, and retard the biochemical degradation of the drug before reaching the target site.

#### Liposomes

Liposomes are nanovesicles encapsulated in phospholipid bilayer. They are biodegradable, nontoxic, and nonimmunogenic thus making them favorable carriers for drug delivery. Although major advances of liposomal drugs are in anticancer treatment, efficiency of anesthetic drugs can also be enhanced. Multimodal approach to postoperative pain management is the key to early recovery. One of the major limitations to the array of local anesthetics available is their relative short duration of action and the risk of systemic toxicity. Liposomal bupivacaine is an important advance in the delivery of local anesthetics formulations.\cite{52} Up to 96 h of therapeutically active concentration can be achieved after single administration with delay in peak plasma concentrations.\cite{53} However, phase 3 trials need to be conducted before they can be used in clinical practice for field blocks.\cite{54} Liposomal formulation of epidural morphine DepoDur can provide up to 2 days of analgesia.\cite{55,56} “This was also confirmed in a study by Viscusi et al. using extended release morphine.\cite{56} Liposomal encapsulated inhaled fentanyl having onset of action similar to intravenous preparation is also being developed\cite{57} Liposomal drugs though in clinical research since last 50 years have not made much strides in clinical practice due to the various hurdles faced in quality assurance and costs. Furthermore, clinical trials related to them are more complex than conventional molecules.\cite{58}

### Transient targeted thromboprophylaxis

Thromboprophylaxis in the immediate postoperative period has always remained a gray area. Bleeding in the postoperative period is a real danger and at the same time thrombosis risk is also highest during this period when the patient is immobile. The novel DDS for thromboprophylaxis includes flow sensitive nanoparticles which are coated with tissue plasminogen activator (tPA) which release it at the site of clot.\cite{59,63}

### Postoperative Pain Relief

Local anesthetic drugs can be delivered to the body by various routes.\cite{64} It can be delivered directly into the surgical incision or in the perineural\cite{65} tissues with benefits of improved analgesia, reduced consumption of opioids, and reduced hospital stay [Figure 2]. The concerns regarding wound infections are unwarranted. The drugs can be delivered either using patient-controlled syringe pumps or elastomeric pumps. Patient-controlled syringe pumps are electronic pumps which can deliver the prescribed amount of drug at specific intervals on demand. Elastomeric pumps are nonelectronic medication pumps.\cite{51} It consists of a balloon which deflates at a specified rate and this pushes the drug through the intravenous tubing and then into the catheter. It is available as variable or fixed rate module and can deliver the drug for 12 h to 7 days durations. The driving pressures in these pumps are from 260 to 520 mmHg, and the infusion rates can vary from

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**Figure 2:** Various routes of local anaesthetic delivery

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**Table:**

| Routes of Local Anaesthetic Delivery |
|-------------------------------------|
| *Epidural (PCEA)*                   |
| *Peripheral (PCRA)*                 |
| *Wound Catheters*                   |
| *Intranasal*                        |
| *Intra-Articular (IA)*              |
| *Intravesical (Bladder)*            |
| *Intra-Osseous*                     |
| *Intrpleural*                       |
The delivery rates are limited to the set values due to the presence of flow restrictors. The variable rate infusor can be adjusted to deliver 5, 7, or 12 ml/h drug, whereas the fixed infusors are designed to deliver 1.5, 2, 5, 7, and 12 ml/h of the drug volume. The infusor rate is most accurate when the temperature of the infusion can be maintained at 92°F or 33.3°C. Increase in temperature increases the infusor rate. To achieve this, infusor should be strapped to the torso. Furthermore, diluents used influence the rate of delivery which is most accurate when 5% dextrose is used. The drug should be filled to the prescribed nominal volume to maintain accuracy. The balloon reservoir and the Luer Lock connector should be adjusted to the same height to ensure delivery of the drug at the desired volume. Their advantages include small size, light weight, not dependent on electrical source. However, disadvantages include costs, inaccurate flow rates, and lack of flexibility with flow rates.

**Computer-controlled Local Anesthetic Delivery Devices**

Computer-controlled local anesthetic delivery devices (C-CLAD) forms important add-ons in dental anesthesia. Pulpal nerve block through the palatal approach can be performed using C-CLAD. The slow local anesthetic infusion rate using this device significantly reduces the discomfort and thus may find a niche in cosmetic and pediatric dentistry.

**Computerized Drug Delivery System**

Total intravenous anesthesia is becoming the norm due to rising environmental concerns and availability of newer shorter-acting anesthetic drugs. This is further aided with the advent of computerized DDS.

**Target-controlled infusion pumps (open-loop)**

In the routine practice in drug dose calculations, age, sex, or creatinine clearance is unaccounted for due to complex calculations. The distribution of the drug to the peripheral tissues must be taken into account and only after there is equilibrium with the peripheral tissue can clearance be taken for calculation.

Pharmacokinetic simulation of certain opioids has shown that initial boluses usually result in drug concentrations far in excess than that is in the therapeutic range, and subsequent boluses result in the drug concentration periodically falling in the subtherapeutic range. Ideally, the drug concentration should always be in the therapeutic range which can be achieved by continuous infusions. However, the currently available sophisticated infusion pumps fall short of the convenience and accuracy of volatile anesthetic agents the delivery of which is guided by the minimum alveolar concentration.

Development of infusion devices for intravenous drugs which are the prototype of the vaporizers would be desirable.

A step toward this goal is the development of target-controlled infusion (TCI) devices. In open-loop system, the plasma or the drug concentrations at the site of effect are calculated using a computer and the knowledge of the pharmacokinetic and the pharmacodynamic models of the drug. Conventional infusion pumps result in continuous drug uptake, whereas TCI pumps gradually decrease the rate of drug delivery based on the pharmacokinetics of the drug. In TCI, the anesthesiologist sets desired target concentration, and the computer calculates the infusion rate that is required to deliver the necessary target concentration [Figure 3].

Measurements obtained from clinical studies in various subgroups are used to first formulate the pharmacokinetic profile of the drug which is then fed into the computer system. The drug delivery in TCI pumps is based on bolus elimination and transfer principle. The initial bolus is given to reach the target concentration followed by infusion rate that replaces the amount of drug that is eliminated and the drug that is transferred to the peripheral tissue using an exponentially decreasing infusion rate. At present, only models for propofol, fentanyl, sufentanil, alfentanil, and remifentanil are available. Using pharmacokinetic data models for dexmedetomidine are also in the process of being developed.

Paedfusor TCI for pediatric use has shown promising results in cardiac surgery. Pediatric TCI models currently available can be used in healthy children over 3 years of age. However, further research is needed to develop a system for optimal drug delivery in children.

**Closed-loop systems**

The closed-loop systems have real-time monitoring of the patients’ variables such as muscle relaxation, hypnosis, analgesia, and a computer-controlled feedback mechanism which precisely delivers the drugs based on these parameters.

Muscle relaxation is monitored using peripheral nerve stimulator and recording the responses using accelerograph. Hypnosis

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**Figure 3:** Delivery of a drug via a computer controlled infusion pump
is monitored using the bispectral (BIS) monitor and a BIS index between 40 and 60 is generally advised as adequate hypnosis for general anaesthesia.[85-92] The most challenging parameter to monitor is the adequacy of analgesia as there are no objective parameters to verify. Since a surgical stimulus results in strong sympathetic activation, physical parameters such as heart rate and blood pressure can be used to monitor the level of analgesia.[93,94] Newer parameter, heart rate variability, has been used to quantify the degree of analgesia.[95] Hence, these patient parameters are fed to the computer which in turn using the inbuilt drug pharmacodynamic data adjusts the dose of intravenous drugs. Postoperative delivery of sedative doses of propofol after cardiac surgeries can also be delivered more precisely using closed-loop system.[88,96] With robotic surgery being the norm of the day, closed-loop anesthesia can be compared to pharmacological robot.[97] Teleanaesthesia is also not far away where not only the patient’s fitness will be done by distant preoperative assessment but also anesthesia will be provided at distant locations.[98]

**Pitfalls of drug delivery system**

1. Final drug product could turn out to be costly when high-end technology is being used
2. Toxicity of the various carriers
3. Lack of knowledge about the degradation products
4. Trained staff to administer personalized treatment and to use various DDS
5. Patient compliance may be affected due to complex devices.

**Conclusion**

DDS is a highly evolving field with the multidisciplinary involvement. The anesthesiologist in future will thus have a safer, simpler, and faster anesthetic practice with novel DDSs and monitoring equipment.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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