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Review Article

A Review on Smart Delivery of Drugs

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ABSTRACT

Drug delivery mention to approaches, formulations, technologies, and systems for deporting pharmaceuticals in the body by maintaining safety concern with therapeutic achievements. Drug delivery necessitates targeting site in the body, and makes the clear way for systemic pharmacokinetics. It is commonly troubled with the quantity and persistence time of drug in the system. Drug delivery is frequently accomplished through chemical formulation of drug alone, but also involves in drug vehicle combination products. Drug delivery is an idea where much emphasis should be given to dosage and route of delivery. It is important to explore the viability of the systems by scaling up from the laboratory to the production scale.

Key words: Drug delivery, sustained release, drug absorption, skin, brain, cancer.

INTRODUCTION

Drug delivery is a concept of safely transporting a pharmaceutical component in body to get its maximum therapeutic benefits. Quantity and the duration of drug presence both are managed through drug delivery system. The system uses different devices to achieve systemic pharmacokinetics to provide best therapeutic goal with minimum side effects. The main target of drug delivery system is to work with minimum drug loss and maximum exposer to target area of body. So drug must be stable in terms of physical and chemical environment and contamination free for safe delivery. The achievement of drug delivery system lies in reducing drug interaction and side effects along with target specific application. Optimization needed to finally formulate a drug to be delivered through smart approach (Figure 1).

Figure 1: Optimization needed to formulate medicine from drug

Drug Delivery: Drug delivery emphasises its efficacy and safety with the following:

- Release
- Absorption
- Distribution
- Elimination

Drug release is perused through dispersal, degradation, bulging. The accepted routes of administration allow for the preferred non-invasive oral, topical, transmucosal (nasal, buccal/sublingual, ocular, vaginal and rectal) and nasal routes. Drugs were introduced into the body, via injection or infusion called parenteral drug delivery. A specific route of administration was choosen depending on drug action, dose and nature of drugs. Intravenous, intramuscular, intradermal, subcutaneous, and intraperitoneal administration can be choosen for drug delivery. Intravenous delivery prefers aqueous drugs, but dispersed drug formulation can also be used to counteract embolism due to in smaller size i.e. near 100 nm. Drugs can be applied to skin with the use of gels, ointments, powder etc. The best application of drug delivery is target based, that means drug is only active in the affected site which increases therapeutic exposure with minimum drug loss and side effects. Drug dose must be lower than toxic dose but greater than minimal therapeutic dose to achieve safe drug delivery in the target site, and that is the therapeutic potency of drug delivery system where drug dose can be controlled.

The mucosal membrane is the best route to achieve drug delivery as it is the specialised site for absorption. But the most common drug delivery route is the oral one. Buccal and sublingual tablets are also effective to achieve maximum therapeutic benefits. For oral drug administration some key points must be considered:

- Gastric residence time for the drug varies from person to person and within same person in different environmental condition.
- Liquid dose of drug transit out faster than the solid drug dose.
- Fasted or the fed state of patient.

The varied pH in stomach (fasted to fed condition), small and large intestine may affect stability, ionization and finally absorption of drugs.

Drugs are transported to liver via portal vein through gastrointestinal mucosa. Drug activity can be minimized to regulate liver metabolic degradation. This hepatic first pass effect can be overcome by intravenous, vaginal, nasal, sublingual route where drug is dispersed in body prior to reaching liver.

Drug Release Profile:

- FDA approves different drug release profiles-
- **Immediate Release:** Release just after administration.
  - ❖ **Modified Release:** Release after some time of administration.
  - ❖ Delayed Release: Released after a point of initial administration.
  - ❖ **Prolonged Release:** Extended release with minimum dosing.

Immediate release

In oral dosing drug is released into gastrointestinal fluids. Drugs must be dissolved faster from powder, granules and tablets before reaching their target sites. Breakdown of capsule material is needed for release of drug content such as gelatine. So within hour drug can start its action. This action depends on concentration of drug. After drug administration drug is absorbed in body through proper channel and finally the excess drug is removed through body via urine and sweat with metabolic and excretory pathway. The main drawback of dosing system especially more than one maintains certain time interval, patients used to forget to take medicines. Even also they fill the urge to take the medication during maximum symptoms or discomfort arrives with disease. For example the medication of thyroid problem, blood sugar and pressure. To achieve therapeutic concentration of drug in plasma, drug concentration can be increased but this comes with greater side effects. So shelf life of a drug is important in immediate drug release kinetics.

Modified Release

- ❖ **Delayed Release:** Many oral drugs are degraded in low acidic environment of stomach and many drugs can cause stomach inflammation if take it in empty

stomach for long time even can cause ulceration such as non steroidal anti inflammatory pain killers. To overcome these problems delayed release profile is established where drug release is delayed until or unless the drug is transported to small intestine. Slow release can be achieved by using polymers which coats tablets and granules and make it safe from stomach acid and also protect the irritative nature of drug. The drug is released from the polymer coating when the drug is transporting from stomach to small intestine. The transition from low pH of stomach to high pH of small intestine triggers the drugs to be dissolved from the polymer coating essential for safe and desirable drug delivery.

- **Extended Release:** Prolonged time exposure of drug can be achieved by extended release profile, which lengthens the time period for slow release. Here drug dosing can be reduced to enhance the release for longer time. To achieve the therapeutic drug concentration in plasma for immediate and urgent treatment drug concentration were short. So overcome this frequent dosing is necessary. It is so annoying for patient to take several drug doses throughout the day for rest of the life for the treatment of chronic diseases. So sustained or controlled release profiles are designed to minimise the dosing with extended release.
- **Sustained Release:** Drug dosing can be minimised with sustained release profile. Biodegradable suitable polymers are used to coat tablets for better dissolution of drugs. So it would be good for patient if one time dosing can fulfill the days demand for drug.
- **Controlled Release:** Controlled release system is important because it can maintain consistent plasma concentration as compare to sustained release. Controlled release established its potency in terms of independent mode of action in biological target tissue. Various drug administration routes can be used for controlled release profile such as oral, transdermal, vaginal etc correlated to sustained release which is strict to oral dosing.

Drug absorption

Drug delivery influences release and absorption of drugs. Before transporting into systemic circulation drug must circumvent gastrointestinal epithelial barrier in oral dosing. Epithelial cells like blood vessels, oral columnar cells, villi, microvilli of small intestines and the buccal epithelium cells involved in drug absorption, secretion and protection. Mucus acts as barrier for drug transport, where drug is absorbed via epithelial lining. To be reached near epithelial lining for absorption drug must pass through mucus coating on epithelia. So mucus must be considered importantly because it is the challenge of drug delivery system. So it must be scrutinise the thickness of mucus membrane before a successful drug delivery. Mucus drug interaction should be acknowledged.

The mucus and epithelial barrier diminish the absorption of drugs. Absorption by:

- **Transcellular transport through cell:** This includes passive diffusion, carrier mediated transport, endocytosis and pore transport.
- **Paracellular transport between cells:** These include energy dependent efflux system.

Drug Delivery vehicle

Different carrier systems have already established their role as drug delivery vehicle such as nanoparticles, liposomes, dendrimers, micelles etc. Drug delivery vehicles are designed in such a way so that they can show their biodegradable property along with non toxic and non immunogenic nature which ultimately helps the delivery vehicle to transport drug to target site without undesired interruption by hosts defense mechanism.

- **Liposome:** Double layered amphipathic lipid vesicles i.e. liposomes are most common delivery vehicle which already established its role in current targeted

drug delivery research. Liposomes are formulated with biodegradable and biocompatible property so that toxicity, immunogenicity and hemolysis can be controlled while targeting. They are prepared to dodge renal clearance and chemical/enzymatic inactivation. Drugs can be stored safely in the inner core of liposome or in the hydrophobic shell depending upon the nature of the drug to be transported [Scott et al, 2008].

- **Micelle and Dendrimers:** Lipid micelle is one of the important vehicles for drug delivery; those are formulated from hydrophobic and hydrophilic units of lipid to maintain its amphipathic nature. The workability and size uniformity regulation is little with this delivery device. Generally micelles are used to transport drugs with low dissolve capacity.

  Dendrimers are small, spherical drug delivery vehicle prepared with biodegradable polymers having a core with branching structure make it tiny dense carrier of drugs [Pili et al, 2010].
- **Biodegradable particles:** Biodegradable nanoparticles targets over diseased area of body for maximum time due to its sustained release and degradative property minimises the chance of toxicity. Ligand based particles to endothelial selectin and ICAM-1 established its role to adhere inflamed [Homsi et al, 2007].

Polymers used in Drug delivery

Poly (esters): Poly (esters) is the best characterized and most widely studied biodegradable system. Poly (lactic acid), Poly (glycolic acid), and Their Copolymers Poly (esters) based on poly(lactic acid) (PLA), poly- (glycolic acid) (PGA), and their copolymers, poly(lactic acid-*co*-glycolic acid) (PLGA), are some of the best defined biomaterials with regard to design and performance. The motivation for designing poly (ortho esters) for drug delivery was the need to develop biodegradable polymers that inhibited drug release by diffusion mechanisms and allowed drug release only after the hydrolysis of polymer chains.

Pharmaceutical drug delivery

Brain Delivery

Most of the drugs can not be able to circumvent blood brain barrier to achieve its therapeutic efficiency [Brambilla et al, 2011]. So to target central nervous system and brain it is necessary to identify experimental way of to maximise drug biovailability which can overcome the problem of blood brain barrier [Banks and Kastin, 1985]. Due to small size of nanoparticles it is easy for them to be transported through capillaries and brain interstitial space. Nanoparticles tends to accumulate within cells allowing deficient drug delivery to target sites in the body [Bennewitz and Saltzman, 2009; Wilson, 2009].

Mucosal Drug Delivery

Most simple and common method of drug delivery is through oral route. Mucus barrier is the well known part that efficiently removes drugs by cilliary action and the GI tract also acts as a strong barrier for various challenges. However the drug may induce irritation and limit its application via mucosal route. Gold nanoparticles encapsulating anticancer drug showed its potency against microbial infection [Arias, 2008].

Pulmonary Drug Delivery

Deposition and accumulation of nanoparticles depends on the particle size in pulmonary delivery system [Reis et al, 2006]. But pulmonary mucus is the limiting factor that blocks the entry of nanoparticles. Literature describe how PSA-PEG (Poly-sebacic acid) nanoparticles can be targeted against cystic fibrosis patients by diffusing in sputum where mucus is the biggest threat and this increase the potency of delivery in mucosal surfaces [Tang et al, 2009].

Skin Drug Delivery

Topical and transdermal are the two common routes of delivery in skin. First pass metabolism and fluctuation of drug in blood plasma is the major problem of multiple oral dosing, that drawbacks can be

significantly replenished by the use of transdermal delivery. Initial burst and water evaporation leads to penetrate nanoparticles within human and pig skin *ex vivo* faster with high dose compare to conventional delivery by nano emulsion [Korting and Schäfer-Korting, 2010]. Follicle opening shows presence of tiny nanoparticles within the range of 20-200 nm in size [Larese et al, 2009].

Cancer Drug Delivery

Drug delivery and dose determination is the biggest challenge when the disease is cancer. The main target of this therapy would be targeting the cancer cell without harming the innocent neighbouring cell. Large body index, chemotherapy, drug resistance, low bioavailability, low absorption, little diffusion are the major drawback of delivering drug to target malignant site [Vlerken et al, 2008; Yang et al, 2009].

Toxicity Curative Drug Delivery

Arsenic, fluorides are the major environmental toxicant leads to many health hazards. Our report demonstrates the delivery of nanocapsulated antioxidant quercetin via oral route might be useful therapeutically to prevent arsenic induced hepatic and cerebral oxidative damage [Ghosh et al, 2009]. Combination of quercetin and meso-2,3-dimercaptosuccinic acid in a nanocapsulated drug delivery system is most effective in reducing the arsenic burden in liver and brain, protected liver from arsenic-induced fibrosis, safeguarded cells from ROS-induced damage, repairs mitochondrial dysfunction, and regulate oxidative signalling that mediate the cells to p53-dependent apoptosis in rat model [Ghosh et al, 2011]. Our previous report on combined therapy includes an antioxidant catechin hydrate and fluoride scavenger sodium metaborate in nanocapsulated drug delivery system could provide a complete protection against fluoride induced fluorosis [Samanta et al, 2016].

Promise of drug delivery

- The micro particle and nanoparticle approach that involves biodegradable polymers and is designed to uptake of intact drug loaded particles via the Peyer's patches in the small intestine could be useful for delivery of peptide drugs that cannot, in general, be given orally.
- Less expensive and most successful approach of drug delivery in which drug dosing can be minimised.

CONCLUSION

A drug development is dependent on dose and bioavailability. So these feathers should be optimized before marketing. The advent of drug delivery is to transport drug in target site with little toxicity as compared to free drugs. Safe administration of a drug is also important for drug delivery. This encompass that the drug in the formulation must be chemically, physically and microbiologically stable. Side effects should be as less as possible to achieve maximum benefit of drug delivery. The systems also required to improve the patient's condition with the therapy by the designing of target specific applications. Thus the pharmaceutical approach of the delivery systems requires being genuine, viable and working on target area of body by slow release to achieve sustained profile with maximum time exposure.

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REFERENCES

1. Scott RC, Crabbe D, Krynska B, Ansari R, Kiani MF. Aiming for the heart: targeted delivery of drugs to diseased cardiac tissue. Expert opinion on drug delivery. 2008; 5(4):459-70.
2. Pili R, Rosenthal MA, Mainwaring PN, Van Hazel G, Srinivas S, Dreicer R, Goel S, Leach J, Wong S, Clingan P. Phase II study on the addition of ASA404 (vadimezan; 5, 6-dimethylxanthenone-4-acetic acid) to

docetaxel in CRMPC. Clinical Cancer Research. 2010; 16(10):2906-14.
3. Homsi J, Simon GR, Garrett CR, Springett G, De Conti R, Chiappori AA, Munster PN, Burton MK, Stromatt S, Allievi C, Angiuli P. Phase I trial of poly-L-glutamate camptothecin (CT-2106) administered weekly in patients with advanced solid malignancies. Clinical Cancer Research. 2007; 13(19):5855-61.
4. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, Fehrenbacher L, Pajon ER, Wade JL, Robidoux A. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. Jama. 2006; 295(23):2727-41.
5. Brambilla D, Le Droumaguet B, Nicolas J, Hashemi SH, Wu LP, Moghimi SM, Couvreur P, Andrieux K. Nanotechnologies for Alzheimer's disease: diagnosis, therapy, and safety issues. Nanomedicine: Nanotechnology, Biology and Medicine. 2011; 7(5):521-40.
6. Banks WA, Kastin AJ. Aluminum alters the permeability of the blood-brain barrier to some non-peptides. Neuropharmacology. 1985; 24(5):407-12.
7. Bennewitz MF, Saltzman WM. Nanotechnology for delivery of drugs to the brain for epilepsy. Neurotherapeutics. 2009; 6(2):323-36.
8. Wilson B. Brain targeting PBCA nanoparticles and the blood-brain barrier. Nanomedicine. 2009; 4(5):499-502.
9. Arias JL. Novel strategies to improve the anticancer action of 5-fluorouracil by using drug delivery systems. Molecules. 2008; 13(10):2340-69.
10. Reis CP, Neufeld RJ, Ribeiro AJ, Veiga F. Nanoencapsulation II. Biomedical applications and current status of peptide and protein nanoparticulate delivery systems. Nanomedicine: Nanotechnology, Biology and Medicine. 2006; 2(2):53-65.
11. Tang BC, Dawson M, Lai SK, Wang YY, Suk JS, Yang M, Zeitlin P, Boyle MP, Fu J, Hanes J. Biodegradable polymer nanoparticles that rapidly penetrate the human mucus barrier. Proceedings of the National Academy of Sciences. 2009; 106(46):19268-73.
12. Korting HC, Schäfer-Korting M. Carriers in the topical treatment of skin disease. In Drug delivery 2010 (pp. 435-468). Springer Berlin Heidelberg.
13. Larese FF, D'Agostin F, Crosera M, Adami G, Renzi N, Bovenzi M, Maina G. Human skin penetration of silver nanoparticles through intact and damaged skin. Toxicology. 2009; 255(1):33-7.
14. van Vlerken LE, Duan Z, Little SR, Seiden MV, Amiji MM. Biodistribution and pharmacokinetic analysis of paclitaxel and ceramide administered in multifunctional polymer-blend nanoparticles in drug resistant breast cancer model. Molecular pharmaceutics. 2008; 5(4):516-26.
15. Yang R, Shim WS, Cui FD, Cheng G, Han X, Jin QR, Kim DD, Chung SJ, Shim CK. Enhanced electrostatic interaction between chitosan-modified PLGA nanoparticle and tumor. International Journal of Pharmaceutics. 2009; 371(1):142-7.
16. Ghosh A, Mandal AK, Sarkar S, Panda S, Das N. Nanoencapsulation of quercetin enhances its dietary efficacy in combating arsenic-induced oxidative damage in liver and brain of rats. Life sciences. 2009 Jan 16; 84(3):75-80.
17. Ghosh S, Dungdung SR, Chowdhury ST, Mandal AK, Sarkar S, Ghosh D, Das N. Encapsulation of the flavonoid quercetin with an arsenic chelator into nanocapsules enables the simultaneous delivery of hydrophobic and hydrophilic drugs with a synergistic effect against chronic arsenic accumulation and oxidative stress. Free Radical Biology and Medicine. 2011 Nov 15; 51(10):1893-902.
18. Samanta A, Chanda S, Bandyopadhyay B, Das N. Establishment of drug delivery system nanocapsulated with an antioxidant (+)-catechin hydrate and sodium meta borate chelator against sodium fluoride induced oxidative stress in rats. Journal of Trace Elements in Medicine and Biology. 2016 Jan 31; 33:54-67.

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