ISSN 2229-3566
Review Article

IJRAP
www.ijrap.net

NEW DRUG DELIVERY SYSTEM

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Received on: 16/08/11 Revised on: 10/09/11 Accepted on: 15/10/11

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ABSTRACT
Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety, and improved patient compliance. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the development of new drug delivery systems. Today, drug delivery companies are engaged in the development of multiple platform technologies for controlled release, delivery of large molecules, liposome, taste-masking, oral fast- dispersing dosage forms, technology for in- soluble drugs, and delivery of drugs through intranasal, pulmonary, transdermal, vaginal, colon, and transmucosal routes
Keywords: liposome, controlled drug delivery**,** Crohn's disease, scintigraphic study, transdermal drug delivery

INTRODUCTION

Development of new drug molecule is expensive and time consuming. Improving safety efficacy ratio of "old" drugs has been attempted using different methods such as individualizing drug therapy, dose titration and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, targeted delivery are other very attractive methods and have been pursued very vigorously. This article reviews the work done in our country on drug delivery system. It is interesting to note that considerable work and many publications from USA, Europe are authored by Indian researchers.

Controlled rate, slow delivery and targeted delivery are some of the focus systems that are being pursued very vigorously in light of patients' needs and also to succeed in today's competitive business world. In the area of targeted delivery, the colonic region of the GI tract is the one that has been embraced by scientists and is being extensively investigated over the past two decades. Targeted delivery to the colon is being explored not only for local colonic pathologies, thus avoiding systemic effects of drugs or inconvenient and painful trans-colonic administration of drugs, but also for systemic delivery of drugs like proteins and peptides, which are otherwise degraded and/or poorly absorbed in the stomach and small intestine but may be better absorbed from the more benign environment of the colon. This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis. Furthermore, there is urgent need for delivery to the colon of drugs that are reported to be absorbable in the colon, such as steroids, which would increase efficiency and enable reduction of the required effective dose. The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), colitis, Crohn's disease and colon disease, where it is necessary to attain a high concentration of the active agent, may be efficiently achieved by colon-specific delivery. The necessity and advantages of a colon-specific drug delivery system (CDDS) have also been extensively reviewed elsewhere in the literature.

Transdermal drug delivery system

The literature on transdermal delivery of drugs has been revised[1]. The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period of time, decrease side effects, decrease gastrointestinal effect that occur due to local contact with gastric mucosa and improved compliance. The release pattern from TDDS is studied by *in vitro (ex vivo*) models using artificial membranes or animal or cadaveric skin. The hairless guinea pig and Brattleboro rat appear to be good models for investigating skin/transdermal drug delivery systems, in vivo. Rao and Diwan[2] developed ethylcellulose polyvinylpyrrolidone (PVP) film containing diltiazem hydrochoride and indomethacin. The influence of initial drug concentration, film composition, and film thickness on the *in vitro* drug release rate as well as drug permeation through rat abdominal skin were studied using paddle over skin method and full thickness rat abdominal skin using a modified Franz diffusion cell. The release rate increased linearly with increasing drug concentration and PVP fraction in the film but was independent of film thickness, followed a diffusion controlled model but a burst effect was observed initially at high concentration. The *in vitro* skin permeation profile showed increased flux values with increased drug and PVP concentration in the film. Authors concluded that films composed of ethylcellulose: PVP: diltiazem (8:2:2) or indomethacin (8:2:3) with suitable adhesive layer and backing membrane could be developed for therapeutic purpose. The same group studied[3] permeability of cellulose acetate (CA) free films casted from chloroform solution containing different plasticizers viz. dibutyl pthalate (DBP), polyethylene glycol (PEG) and propylene glycol (PG). Permeability characteristics of free films were studied using the drugs such as diltiazem hydrochloride (DLT) and indomethacin. The order of permeability of plasticized films with plasticizers is PEG>PG>DBP. Diffusion of drugs through the free films of CA was extended over a longer period of time at a controlled rate and thus, these can be used as rate controlling membranes for the development of a transdermal drug delivery system. In an attempt to develop TDDS for pulsatile delivery of testosterone (T) Misra et al[4] developed two formulations, one consisting of T and a polymer blend dissolved in isopropanol administered by dispensing the solution on skin to cast a film in situ and another one an adhesive dispersion patch. *In vitro* release from the patch was evaluated using a flow through cell interfaced with a HPLC pump and UV detector. Single dose pharmacokinetics was evaluated in castrated Wistar rats and bonnet monkeys immunized against gonadotropin releasing hormones to deplete endogenous T. The two formulations resulted in a burst and sustained phase of drug release.

Membrane permeation controlled TDDS for nifedipine using collagen (from calf fetus skin) and chitosan membranes has been developed[5]. Alginate gel was used to increase stability of nifedipine in the system. Transdermal devices were prepared by adhesive sealing technique. In vitro release studies were carried out using modified Franz diffusion cells. Drug release was found to depend on the type of membranes used to control the drug delivery. In another study[6] Chitosan membranes with different permeability to

propranolol hydrochloride were obtained by controlled cross-linking with glutaraldehyde to regulate the drug release in the devices. Chitosan gel was used as the drug reservoir. The ability of these devices to deliver the drug while supported on rabbit pinna skin was tested by conducting in vitro studies in modified Franz diffusion cells. The drug release profiles showed that the drug delivery is completely controlled by the devices. The rate of drug release was found to be dependent on the type of membrane used.

Krishna et al[7] formulated a carboxymethylcellulose sodium based TDD for propranolol and evaluated it for in vitro and in vivo performance. In vitro studies using excised hair free rat skin model in a modified Franz diffusion cell resulted in 66.54% permeation at the end of 24 hr in a zero order permeation profile. Skin irritation studies in rats evaluated for flare and wheal with respect to a formalin control indicated that drug containing patch invoked only a mild response over a 7 day period. Bhat et al[8] prepared betamethasone dipropionate ointment and studied the effect of permeation enhancers such as surfactants, B cyclodextrin, bile salt, iontophoresis, sonophoresis and hyperthermia, using Sigma dialysis membrane and rat skin. Histamine wheal suppression technique was used to assess permeation. It was seen that in vivo 0.2% Span 20 and 0.1% sodium lauryl sulphate and 0.45% sodium chloride promoted permeation of drug; sonophoresis and iontophoresis enhanced permeation through rat skin.

Iontophoresis involves transport of ionic (charged) molecule into a tissue by passage of a direct electric current through an electrolyte solution containing ionic molecule to be delivered using an appropriate electrode polarity, and enhancement of transport of high molecular weight peptides and nonelectrolytes due to the indirect effect of electric current i.e. coupled flow of water (ion to hydrokinesis). The relative conductivity of skin is proportional to its water content; stratum cornium is the major barrier for permeation of ionic compounds. Conventional direct current (dc) iontophoresis inevitably develops a skin polarization potential which reduces the efficacy of iontophoretic transdermal delivery. It may also cause irritation and burns. A prolonged iontophoretic delivery therefore cannot be used. These limitations can be overcome by using depolarizing or pulsatile current. Nanda et al[9] showed that iontophoresis caused a significant increase in transdermal permeation of propranolol hydrochloride in vitro through skin. They also studied[10] the effect of pulsed dc wave form on transdermal delivery of propranolol hydrochloride in rats having normal blood pressure and in those made hypertensive with in fusion of noradrenaline. Unlike after passive diffusion, propranolol, delivered in vivo into rat by iontophoresis, was detected in blood and it blocked response to isoprenaline and decreased the rise in mean arterial pressure due to noradrenaline. Transdermal (TD) films of terbutaline hydrochloride were formulated[11] using hydroxypropyl methyl cellulose as monolithic matrix, for evaluation of pharmacokinetic and pharmacodynamic parameters. The skin irritation study revealed no signs of erythema or edema in rabbits. TD formulation was more effective than oral dosage form as evident from the pharmacodynamic studies carried out on guinea pig, using histamine aerosol induced bronchospasm model. Bioadhesive drug delivery system was prepared[12] using polymer carboxy methyl cellulose, polyvinyl pyrrolidone, sodium alginate, hydroxy propyl cellulose, hyroxymethyl cellulose, 100 cps, K4M, carbopol 93%. The adhesion strength of the polymer was assessed by a shear stress detachment method. The bio-adhesion strength was measured using a modified Martii Marvola method. Hydroxypropylmethyl cellulose K4M and 100 cps tablets exhibited maximum bio-adhension. X-ray studies in rabbits confirmed the bio-adhesion. Tablets had adhesion of more that 7 hours. Transdermal films to terbutaline sulphate were formulated[13] as monolithic matrices using cellulose polymers like hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (CMC), PEG 400 and propyleneglycol were used as enhancer in various ratios. In vitro diffusion studies were carried out across isolated stratum corneum of fresh human cadaver skin using a polycarbonate feeding bottle modified as a diffusion cell. The release of drug from formulation followed zero order kinetics. The transdermal permeability across human skin was enhanced with the increasing plasticiser concentration. The release rate was greater in case of HPMC films, which may be due to low viscosity and greater hydrophilicity of the polymer than CMC. PEG 400 was found to be better permeation enhancer compared to propylene glycol. The drug permeability was not enhanced when % w/w of plasticizer was doubled from 20 to 40. Combination of plasticizers resulted in significant increase in permeability. Tatapudy and Madan[14] described preparation of benzolyl peroxide microcapsules. Benzoyl peroxide is used for treatment of acne but it explodes in micronized drug state and is a known skin irritant. Microencapsulation would result in slow release for prolonged period thus avoiding toxic effect.

Liposomal and targetted drug delivery system

Liposomes are concentric bilayered structures made of amphipathic phospholipids and epending on the number of bilayer, liposomes are classified as multilamellar (MLV), small unilamellar (SUVs) or large unilamellar (LUVs). They range in size from 0.025µ - 10µ in diameter. The size and morphology of liposomes are regulated by the method of preparation and composition. Liposomes are used for delivery of drugs, vaccines and genes for a variety of disorders.

Infectious diseases

Bacchawat and coworkers developed liposomal amphotericin and investigated it in animal models of fungal infection and leishmaniasis. Kshirsagar and coworkers[15], [16] modified the formulation, developed a "Patient Worthy" sterile pyrogen free liposomal amphotericin preparation and investigated it in patients with systemic fungal infections and leishmaniasis. It was found to be safe producing significantly less adverse effects compared to plain amphotericin in patients with systemic fungal infection, did not produce nephrotoxicity and could be given to patients with renal damage. It was effective in patients resistant to fluconazole and plain amphotericin. Unlike Ambisome (USA) which needs to be used in dose of 3 mg/kg/ day this is effective at 1 mg/kg/day dose. The same group studied different dosage regimens of liposomal amphotericin using Aspergillus murine model[17]. It was found that liposomal amphotericin was more effective than equal dose of free amphotericin B given after fungal spore challenge. A large single dose of liposomal amphotericin was more effective, whether given before or after spore challenge, than given as two divided doses. It was investigated[18] in patients with visceral leishmaniasis and found to be effective in patients who had not responded to antimony, pentamidine and amphotericin. Because of its safety, it can be given at 3 mg/kg/day dose thus reducing total duration of treatment. It was successfully used in a child suffering from visceral leishmaniasis[19]. This is the first liposomal preparation developed outside of USA, which has been used in patients. In an attempt to improve efficacy and reduce toxicity further, liposomes with grafted ligand have been developed. Pentamidine isethionate and its methoxy derivative were encapsulated in sugar grafted liposomes and tested against experimental leishmaniasis in vivo [20]. It was seen that sugar grafted liposomes specially the mannose grafted ones were potent in comparison to normal liposome encapsulated drug or free drug.

Anticancer drugs

Mukhopadhyay[21] developed conjugate of antineoplastic drug daunomycin (DNM) with maleylated bovine serum albumin. It was taken up with high efficiency by multi drug resistant variant JD100 of the murine macrophage tumor cell line J774A.1 through the scavenger receptors resulting in cessation of DNA synthesis. A thermosensitive liposomal taxol formulation (heat mediated targeted drug delivery) in murine melanoma was developed and studied by

another group of workers[22]. Cremophor which is used as excipient due to the low aqueous solubility of taxol has toxic side effects. Temperature sensitive liposomes encapsulating taxol were prepared using egg phosphatidylcholine and cholesterol in combination with ethanol. The liposomes have a phase transition temperature of 43°C. A significant reduction in tumor volume was noted in tumour bearing mice treated with a combination of hyperthermia and theromosensitive liposome encapsulated taxol, compared to animals treated with free taxol with or without hyperthermia in B16F 10 murine melanoma transplanted into C57BI/6 mice. Sharma et al[23] also investigated the use of polyvinyl pyrrolidone nanoparticles containing taxol prepared by reverse micro-emulsion method. The size of nanoparticle was found to be 50-60 nm. The antitumor effect of taxol was evaluated in B16F10 murine melanoma transplanted in C57 B 1/6 mice. In vivo efficacy of taxol containing nanoparticles as measured by reduction in tumor volume and increased survival time was significantly greater than that of an equivalent concentration of free taxol.

Lung specific drug delivery

In Chandigarh lung specific liposomes was developed and investigated in animal models of tuberculosis[24]. Liposomes tagged with O-stearlylamylopectin (O-SAP) resulted in increased affinity towards lung tissue of mice. Liposomes containing egg phosphatidylcholine cholesterol dicetylphosphate, O-SAP, monosialo-ganglioside (GMI)/DSPE PEG 2000 were found to be more stable in serum. These liposomes accumulated more in lungs than in reticulo endothelial system of normal and tuberculosis mice. Liposomes were stable in vivo and released contents slowly. INH and rifampicin encapsulated in liposomes were less toxic to peritoneal macrophages and also in vivo as compared to free drug.

Targeting to brain

Jain et al[25] developed dopamine hydrochloride bearing positively charged small liposomes by sonicating multilamellar vesicles and studied their physical attributes and drug leakage and release pattern. In vivo performance was assessed by periodic measurement of chlorpromazine induced catatonia in Sprague Dawley rats and was compared with plain dopamine hydrochloride, dopamine and levodopa carbidopa. The studies showed that dopamine can be effectively delivered into the brain and its degradation in circulation can be prevented by incorporating it into liposomes.

Transdermal delivery

Bioadhesive liposomes bearing levonorgestrel as controlled drug delivery system has been studied[26]. Mesophasic proliposomal system for levonorgestral was prepared[27]. The vesicles were mostly unilamellar and some were multilamellar. Release was of zero order kinetics. Alcohol as compared to oils had greater effect on transdermal flux. In vivo studies showed that a significant lag phase was observed before the therapeutic levels were reached indicating the requirement for a loading dose. This proliposomes system was found to be superior to PEG based ointment system. Liposomal reservoir system bearing local anesthetic benzocaine was developed[28] for controlled and localized delivery via topical route. The liposomal suspension was incorporated into an ointment and gel base. The systems delivered the drug at a controlled rate ever 24 hr compared to plain ointment which had a rapidly decreased release rate. The drug delivery across human cadaver skin was very slow. In vivo studies showed a longer duration of action in the case of liposomal formulation.

Miscellaneous

Nabar[29] studied the effect of size and charge of liposome in the bio-distribution of 99m TC-DTPA encapsulated in liposome after intravenous injection in rats. They observed that multilamellar vesicles (MLV) were taken up to a greater extent as compared to SUVs in liver spleen and lungs. Positively charged MLVs than negative or neutral ones, were taken up more in liver, positively charged SUVs were taken up more in kidneys and neutral MLVs were taken up more in lungs than charged ones. An attempt was made[30] to improve stability of liposome by coupling the drug with the lipid bilayer using a cross linking agent. Soya phosphatidylcholine (SPC) containing liposomes were prepared by calcium induced fusion method. Positively charged stearylamine was introduced in the bilayer. The liposomes were coupled to entrapped ibuprofen by EDAC (1-ethyl 3-(3-dimethyl aminopropyl) carbodiimide HCI) and the coupling was confirmed by UV spectrum. It was observed that EDAC in SPC containing stearylamine liposomes retarded the release of ibuprofen significantly.

In albino rats, the various factors affecting systemic absorption of nasally applied gentamycin sulphate using in situ nasal perfusion technique was studied[31] Tween 80 which is a surfactant increases permeation by altering membrane structure and permeability. In this study Tween 80 upto 1% W/V concentrations, increased permeability. Betacyclodextrin at 0.25% W/V concentration, another permeability enhancer was found to significantly increase permeability initially but was found to plateau off later on. However both these permeability enhancer were found to decrease stability and potency of gentamycin.

Other controlled drug delivery systems

Extended release, slow release and sustained release preparation have been developed by pharmaceutical industry and pharmacy departments and investigated in vitro for release pattern and in vivo for bio-equivalence.

Oral

There is a great need in oral delivery of protein and peptide drugs, suitable devices for delivering the therapeutic agent incorporated microspheres selectively in the intestine. Gelatin capsules were coated with various concentrations of sodium alginate and cross-linked with appropriate concentrations of calcium chloride and tested in vitro for resistance to gastric and intestinal medium. Gelatin capsules coated with 20% w/v of the polymer, which gave the most promising result in vitro, were evaluated in human volunteers for their in vivo gastro intestinal tract behaviour. The radiographical studies show that while the un-coated gelatin capsules disintegrated in the stomach within 15 min of ingestion, the alginate coated gelatin capsules remained intact as long as they were retained in the stomach (up to 3 h) and then migrated to the ileocecal region of the intestine and disintegrated[32] Vanarase and Nagarsenkar[33] prepared pellets of 1mm and 1.65 mm size of prochlorperazine maleate using a modern pelletization technique. The pellets were coated with ethylcellulose and evaluated for in vitro release, using USP dissolution apparatus. They noted that release of PCPM can be reduced with increasing amount of ethylcellulose. Rangaiah et al prepared and studied[34] the sustained release tablets of theophylline using Eudragit RLPM, RSPM and HPMC. Bioavailability studies in volunteers showed that HPMC and Eudragit formulation produced sustained plasma concentration of the drug. Another group[35] formulated sustained release capsules of nifedipine containing an initial rapidly available loading dose in the form of solid dispersion and a sustained release part as micro particles coated with polyvinyl acetate (m.wt 45000) film using a modified Wurster coating apparatus. The products provided release of initial therapeutic dose of drug in less than 45 min and sustained release over 11-12 hours. The same group developed[36] a diffusion cell for the determination of drug release from a topical aerosol formulation.

Parenteral

Kushwaha[37] used a blend of synthetic polymer polyvinyl alcohol and natural macromolecule gum Arabica and found that duration and release of drug depends on the amount of drug loaded in the matrix and solubility of the drug in the matrix and the release medium. The advantage of this system is that the release kinetics of the drug from

the system can be tailored by adjusting the plasticizer, homopolymer and cross linker composition. Chitosan microspheres of 45-300 micros were used for controlled delivery of progesterone[38]. In vitro and in vivo release was tested. It was seen that highly cross linked spheres released only 35% of incorporated steroids in 40 days compared to 70% from lightly cross linked spheres. Determination of in vivo bioavailability of the steroid from microsphre formulation by intramuscular injection in rabbits showed that a plasma concentration of 1-2 ng/ml was maintained upto 5 months without a high burst effect. The data suggests that cross linked chitosan microspheres would be an interesting system for long term delivery of steroids. Cross linked dextran beads were developed as a carrier for development of a single contact vaccine delivery system[39]. There has been extensive research on drug delivery by biodegradable polymeric devices since bioresorbable surgical sutures entered the market two decades ago. Among the different classes of biodegradable polymers, the thermoplastic aliphatic poly (esters) such as poly (lactide) (PLA), poly (glycolide) (PGA), and especially the copolymer of lactide and glycolide referred to as poly (lactide-co-glycolide) (PLGA) have generated tremendous interest because of their excellent bio-compatibility, biodegradability, and mechanical strength[40]. They are easy to formulate into various devices for carrying a variety of drug classes such as vaccines, peptides, proteins and micromolecules. Most importantly, they have been approved by the United States Food and Drug Administration (FDA) for drug delivery. Dhiman and Khuller[41] found that mice immunized with microparticles of poly (DL-lactide-co-glycolide) (DLPLG) as delivery vehicles for 71-KDa cell wall associated protein of mycobacterium tuberculosis H37 Ra, exhibited significantly higher T cell stimulation and cytokine release in comparison to 71-KDa emulsified in Freund's incomplete adjuvant (FIA) as well as BCG vaccinated group. Further the protective effect of 71KDa- PLG was compared with 71KDa FIA on the basis of survival rates and viable bacilli load in different organs at 30 days post challenge and median lethal dose (LCD50) of M. tuberculosis H37Rv. 71KDa PLG was more effective when challenge was given 16 week after immunization. Further 71KaDa- PLG immunized group exhibited a significantly higher clearance of bacterial load from the lungs and livers in comparison to the 71KDa FIA immunized group. Poly (lactide-co-glycolide) (PLG) was used[42] to deliver diclofenac in the form of microspheres and in situ gel-forming systems, subcutaneously. The pharmacokinetic and pharmacodynamics studies in the adjuvant - induced arthritic rats showed that micro spheres produced steady therapeutic levels of the drug in the plasma for about 16 days following a single subcutaneous injection. The in situ gel-forming provided significantly higher maximum plasma concentration and inhibition of inflammation was maintained for about 10 days.

Dental product

Somayaji et al[43] used an ethylcellulose strip as delivery medium for tetracycline and metronidazole to reduce sub-gingival microorganisms in periodontal pockets. Patients were given supragingival scaling and then divided into 5 groups, depending on the length of time the medication was in place. Sites were marked for tetracycline, metronidazole, and placebo. Sites were wiped and isolated, and baseline microbiology samples were taken for gram staining and culture methods. After treatment, subgingival microbiological samples were taken again. The ethyl cellulose strips were removed and analyzed for any remaining drug. Results showed that tetracycline and metronidazole could both be applied locally to periodontal sites using ethyl cellulose strips and markedly suppress the subgingival bacteria over a period of several days. The tetracycline showed a faster release; however, the metronidazole required a lesser concentration to achieve complete reduction of the subgingival flora. A saliva activated bio-adhesive drug delivery system was developed[44] for lidocaine hydrochloride and compared its effect with topical gel preparation in dentistry. It was found that DDS adhered to gingival within a minute and produced peak effect in 15 minutes and produced greater depth of anesthesia than the marketed topical gel.

Colon specific drug delivery

Specific targeting of drugs to the colon is recognized to have several therapeutic advantages. Drugs, which are destroyed by the stomach acid and / or metabolized by pancreatic enzymes, are slightly affected in the colon, and sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis. Treatment of colonic diseases such as ulcerative colitis, colorectal cancer and Crohn's disease is more effective with direct delivery of drugs to the affected area. Likewise, colonic delivery of vermicides and colonic diagnostic agents require smaller doses. Prasad et al[45] developed a colon specific oral tablet using guar gum as carrier. Drug release studies under conditions mimicking mouth to colon transit have showed that guar gum protects the drug from being released completely in the physiological environment of stomach and small intestine. Guar gum at pH 6.8 is susceptible to colonic bacterial enzyme action, with drug release. Pre-treatment of rats orally with aqueous dispersion of guar gum for 3 days, induced enzyme specifically acting on guar gum. Thereby increasing drug release. The result indicates usefulness of guar gum as a potential carrier for colon specific drug delivery. A novel colon specific drug delivery system based on a polysaccharide, guar gum was evaluated[46] in healthy human male volunteers, with gamma scintigraphic study using technetium 99m-DTPA as tracer. It was seen that some amount of tracer present on the surface of the tablets was released in stomach and small intestine and the bulk of the tracer present in the tablet mass was delivered to the colon. The colonic arrival time of the tablets was 2-4 hr. On entering the colon, the tablets were found to degrade.

Methacryloyloxy azobenzene and hydrogel was prepared by copolymerizing with hydroxyethyl methacrylate[47]. In vitro release studies of the incorporated 5-flurouracil was carried out in simulated gastric and intestinal fluids. In vitro release profile in hte presence of azoreductase in the culture of intestinal flora followed a zero order pattern.

CONCLUSION

Pharmaceutical development of drug delivery system is being pursued enthusiastically in many laboratories in India. These are being investigated in vitro for release pattern and in some cases in vivo in animals for pharmacokinetics but less frequently for efficacy. There is a paucity of data on clinical studies and utility of the DDS in patients. It is necessary that pharmacologists should be involved in the investigation of pharmacokinetics and pharmacodynamics of DDS if the products have reached their meaningful out come - the clinical use.

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