Chapter 2

REVIEW OF LITERATURE
## Chapter 2

### REVIEW OF LITERATURE

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2. REVIEW OF LITERATURE

Past works reported on the CDDS include matrix tablets, capsules, Pulsincap formulations, mini tablets, multi-particulate systems, hollow micro spheres, floating beads and polymers used for CDDS, etc. Few of the available reports were briefly reviewed.

2.1. Literature Survey on Matrix Tablets

SH Lakade, et al., (2008)\textsuperscript{83} formulated and evaluated the sustained release matrix tablet of anti-anginal drug, influence of the combination of hydrophobic and hydrophlic matrix form. The objective of the current study was to develop hydrophilic polymer (HPMC) and hydrophobic polymer (ethyl cellulose) based Nicorandil matrix sustained release tablet, which can release the drug up to 24 hours in a predetermined rate. The in–vitro release data was well fit to Peppas and Hixon Crowel release kinetics.

Sayed I. Adbel- Rahman, et al., (2009)\textsuperscript{84} prepared and compared the evaluation of sustained release metoclopramide hydrochloride (MCP) matrix tablets. MCP is mostly used to manage gastrointestinal disorders. MCP was incorporated in 12 formulae containing different polymers and/or different polymer ratios including hydroxypropylmethyl cellulose (HPMC), carboxymethylcellulose (CMC), and ethyl cellulose (EC). In addition, sodium starch glycolate (SSG) was added to some formulae in different amounts in order to soften and/or disintegrate the tablets. The tablets were prepared by using both direct compression and granulation techniques. The change-over
method was used to construct the dissolution profiles of the tablets. The drug release involved a combination of both diffusion and polymer-chain relaxation mechanisms.

Ibrahim EI-Bagory, et al., (2007)\textsuperscript{85} reported the formulation and in-vitro evaluation of theophylline matrix tablets prepared by direct compression. The deformation mechanism of pharmaceutical powders, which was used in formulating directly compressed matrix tablets, affects the characteristics of the formed tablets. Three polymers of different deformation mechanisms such as Kollidon SR (KL SR, plastic deformation), Ethylcellulose (EC, elastic deformation), and Carnauba wax (CW, brittle deformation) were tested on theophylline-compressed tablets at different compression forces. However, the tablets based on KL SR exhibited the highest hardness values compared to the other formulae, which are based on either blends of KL SR with CW, the very brittle deformed polymer.

Joshi N C, et al., (2010)\textsuperscript{86} formulated and evaluated the controlled release matrix tablets of Tramadol HCl by using different polymers viz. Eudragit RS-100, Ethylcellulose, Carbopol 934P, and Polyvinyl Pyrolidone K-90. The tablets were prepared through wet granulation method. The tablets were evaluated for thickness, weight variation, hardness, friability, drug content, and \textit{in-vitro} dissolution.

V Jishnu, et al., (2011)\textsuperscript{87} formulated and evaluated the extended release film coated matrix tablets of cephalexin using binary mixture of two grades of hydrophilic polymer and hydroxypropyl methyl
cellulose (HPMC) by direct compression method. A $3^2$ full factorial design was applied to study the effect of concentration of polymers on drug release from matrix tablets. The dissolution data were fitted into zero-order, first-order, Higuchi, and Korsemeyer–Peppas models to identify the pharmacokinetics and mechanism of drug release.

Raghavendra Rao N.G, et al., (2009)\textsuperscript{88} developed the sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. Hydroxypropylmethyl cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG).

Krishnarajan. D, et al., (2013)\textsuperscript{89} formulated and evaluated the sustained release matrix tablets of Levofloxacin using natural polymers. Xanthan gum, Guar gum, and Karaya gum were used as natural polymers and the effect of various formulation factors such as polymer proportion and effect of filler type on the in-vitro release of the drug were studied. The Levofloxacin matrix tablets were prepared by direct compression technique with an average weight of drug of 250 mg. The tablets were evaluated for weight variation, friability, hardness, thickness, and in-vitro dissolution.

Potu Apparao, et al., (2011)\textsuperscript{90} developed the sustained release matrix tablets of Lamivudine using natural biodegradable and biocompatible polymers. These tablets were successfully formulated, evaluated, and found to be suitable candidates in extending the release of the drug from the matrix tablets.
Somnath Sakore, et al., (2013)\textsuperscript{91} developed and evaluated the sustained release matrix tablets of Enalapril maleate. The tablets were formulated using HPMC KM and HPMC K15 M polymers by wet granulation method. The in-vitro drug release study was carried out in a simulated gastric fluid (0.1 N HCl) for the first two hours and in a phosphate buffer (pH 6.8) for the next three hours using the USP apparatus II paddle method.

Kotta Kranthi Kumar, et al., (2013)\textsuperscript{92} formulated the bilayered tablets containing Pioglitazone hydrochloride for immediate release using cross Povidone as super disintegrant, Metformin hydrochloride for sustained release, and poly ethylene oxide (PEO-303) as matrix forming polymer. The tablets were evaluated for physicochemical properties.

Indranil Kumar Yadav, et al., (2010)\textsuperscript{93} developed the oral sustained release matrix tablets of aceclofenac using hydrophilic and hydrophobic polymers. Aceclofenac is a nonsteroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, and its biological half life is four hours. FTIR studies were carried out to know the interaction between the drug and polymer. Controlled release formulations of aceclofenac (200 mg) were prepared by direct compression method. The tablets were subjected to physicochemical, in-vitro drug release, and stability studies.
Sameer Shafi, et al., (2011)\textsuperscript{94} developed the sustained release (SR) sintered matrix tablets of Diltiazem hydrochloride (DTZ). The tablets were prepared by trituration method using 4\% and 8\% HPMC K\textsubscript{4}M and HPMC K\textsubscript{15}M and then sintered. The prepared tablets were transferred to the sintering chamber (desiccator filled with acetone in the bottom and equilibrated for 24 hours with vapour) and exposed to different sintering time like three hours and six hours. The release characteristics study was carried out using the USP XXI model.

Afrasim Moin, et al., (2010)\textsuperscript{95} developed the sustained release matrix tablets of DTZ using Karaya gum (KG) alone or in combination with locust bean gum (LB) and hydroxypropyl methylcellulose (HPMC) by direct compression. The matrix tablets were evaluated for hardness, friability, in-vitro release, and drug content. The formulations were also characterized by scanning electron microscopy (SEM), fourier transform infra-red spectroscopy (FTIR), and differential scanning calorimetry (DSC).

Esra Baloglu, et al., (2010)\textsuperscript{96} designed and evaluated the layered matrix tablet formulations of Metaprolol Tartrate. Seven different swellable polymers (carrageenan, hydroxypropylmethyl cellulose, pectin, guar gum, xanthan gum, chitosan, and ethyl cellulose) were evaluated alone or in combination as release-retardant layer. The tablets were tested for weight variation, hardness, diameter/thickness ratio, friability, and drug content uniformity, and subjected to in-vitro drug release studies.
S. Chandran, et al., (2008) designed and evaluated ethyl cellulose-based matrix tablets of Ibuprofen with pH Modulated release kinetics. Cellulose acetate phthalate was incorporated in the matrix in varying amounts in order to prevent the initial release of the drug in the acidic environment of the stomach. The combination of cellulose acetate phthalate and ethyl cellulose in the matrix base can be an effective means of developing a controlled release formulation of Ibuprofen with very low initial release for 14-16 hours.

2.2. Literature Survey on Pulsincap

Kamalakkannan V, et al., (2014) developed the time delayed capsule device for Chronopharmaceutical drug delivery system of Diltiazem hydrochloride by using polymers like Eudragit S-100, L-100 (1:1, 1:2), Guar gum, HPMC, Sodium alginate. The entire capsule device was coated with 5% CAP. The formulated pulsatile device was evaluated by weight variation, thickness of CAP, IR, and in-vitro release kinetics study.

Kommineni veditha, et al., (2013) developed the pulsatile drug delivery systems for salbutamol sulphate by using different ratios of swelling and rupturable polymers [HPMC: Edragit]. Modified pulsincap is based on cross linked hard gelatin capsules with formaldehyde and filled with hydrogel plug. The hydrogel plug was prepared with different ratios of swellable polymer HPMC and dilute Dicalciumphosphate. Pulsincap technique was found to be more
suitable to achieve the prolonged lag time when compared with the compression coated tablets.

Mayee RV, et al., (2012)\textsuperscript{36} reviewed pulsatile drug delivery system (PDDS) gaining importance as it offers a more sophisticated approach to traditional drug delivery. The pulsatile system delivers the drug at the right site of action, at the right time, and with the right amount, thus providing spatial and temporal delivery and increased patient compliance.

Senthilnathan B, et al., (2012)\textsuperscript{52} formulated and evaluated the pulsincap for antidiabetic drug Glibenclamide to control the increased blood glucose level after food consumption in diabetic patients by allowing the drug to release immediately after a lag time. Microsponges of different concentrations were prepared and the best formulation for the development of pulsincap was selected and the optimized microsponges were subjected to electron microscopy, FT-IR, and in-vitro studies.

Muniswamy P, et al., (2012)\textsuperscript{37} formulated and evaluated the pulsatile drug delivery system to achieve the timely release of verapamil HCL, based on pulsincap approach. The basic design consists of an insoluble hard gelatin capsule body filled with a mixture of verapamil HCL, HPMC, Guar gum, and lactose and sealed with a sodium alginate and Karaya gum plug. The verapamil HCL pulsing cap was prepared by the physical mixture method and it was
evaluated for the micromeretic property, percentage yield, drug content, IR, and in-vitro release study.

Srujan kumar M, et al., (2013)\textsuperscript{99} reviewed on pulsatile drug delivery system, in which the system controls the lag time independent of environmental factors such as pH, enzymes, gastrointestinal motility, etc. The rational behind the use of pulsatile release is to avoid a zero-order release. Designing of proper pulsatile drug delivery will enhance the patient compliance, provide optimum drug delivery to the target side, and minimize the undesired effects.

Anil kumar A, et al., (2012)\textsuperscript{100} developed and evaluated an oral pulsatile drug delivery system to mimic the circadian rhythm of the disease by releasing the drug with a distinct predetermined lag time of 5 hours (+ 0.25 hrs). The basic design of pulsincap formulations of metaprolol provides time controlled release to treat the nocturnal symptoms of hypertension and angina pectoris. Granules were developed by wet granulation technique using guar gum polymers in different ratios. These granules were filled into the formaldehyde treated capsules and plugged with optimized HPMC plug to maintain the 5-hour lag time.

Sandeep M, et al., (2013)\textsuperscript{101} prepared and evaluated the chronopharmaceutical drug delivery of Lansoprazole. Lansoprazole matrix tablets were prepared by wet granulation method and sealed with HPMC K 100 plug. The plugs of varying thickness and hardness
were prepared by direct compression method and were placed in the capsule opening.

Bhushan prabhakar kolte, et al., (2012)\textsuperscript{102} assessed the colon targeted drug delivery system. This article discusses on the introduction of colon, need and approaches of colonic drug delivery, factors effecting colonic transition, colonic diseases, and the novel and emerging technologies for colon targeting.

Karthi keyan M, et al., (2014)\textsuperscript{103} designed chronomodulated metaprolol tartarate pulsatile drug delivery system to mimic the circadian rhythm by releasing the drug at the desired time by means of an internal preprogrammed designed dosage form that is initiated when the dosage form comes in contact with gastrointestinal fluids, especially in colon. The prepared dosage forms were optimized and evaluated for in-vitro and in-vivo studies.

Sharma GS, et al., (2012)\textsuperscript{104} developed the modified pulsincap technique for oral controlled drug delivery of Gliclazide by using sodium CMC as polymer. The solubility of Gliclazide was enhanced by using Methyl β cyclodextrin (MβCD). The complexation between Gliclazide and MβCD was confirmed by phase solubility studies and X-ray diffractions studies. This technique is more suited for preparing better controlled release formulations.

Mohammed Gulzar Ahmed, et al., (2013)\textsuperscript{105} redesigned the pulsatile device to achieve time or site specific release of losartan potassium based on chronopharmaceutical considerations. The
prepared formulations were subjected to evaluation of various parameters like weight variations, percentage drug content, in-vitro drug release, and stability studies.

Piduguralla surendra, et al., (2013)\textsuperscript{106} reviewed that the pharmaceutical market has been increasingly preferring controlled and targeted drug delivery system. This article explains the development of pulsatile drug delivery system and the body biological rhythm.

Anantha Nayak Ravula, et al., (2011)\textsuperscript{107} defined pulsatile delivery as the rapid and transient release of certain amounts of drug molecules within a short time period immediately after a predetermined off-release period, i.e. lag time. Some of the conditions in which PDDS are promising include duodenal ulcer, cardiovascular diseases, arthritis, asthma, diabetes, neurological disorder, cancer, hypertension, and hypercholesterolemia.


Supriya Shidhaye, et al., (2012)\textsuperscript{109} reported that the pulsatile drug delivery system has developed because of its multiple advantages over conventional dosage forms. This system is designed according to
the circadian rhythm of the body, and the drug is released rapidly and completely as a pulse after a lag time or an off-release phase..

Priyanka modi, et al., (2013)\textsuperscript{10} designed and evaluated the modified pulsincap of tramadol HCL according to the circadian rhythm using formaldehyde vapour for cross linking to make capsule body insoluble and hydrogen plug to achieve a predetermined lag time for chronotherapy of rheumatoid arthritis.

Bhawna gauri, et al., (2011)\textsuperscript{11} studied to develop a colon targeted system for metronidazole using guar gum and xanthan gum. Matrix formulations containing various proportions of guar gum and Karaya gum were prepared by wet granulation technique. Later on, multilayer tablets were prepared by using 50 mg and 100 mg of guar gum as release controlling layer on either side of the matrix tablets of metranidazole.

Rubinstein, et al., (1995)\textsuperscript{12} showed that calcium pectinate-indomethacin tablets of both types, i.e., compression-coated and matrix tablets give no release of indomethacin at pH-1.5 for two hours. When these tablets were shaken at PH-7.4, a drug leak was seen in the plain matrix tablets but not in compression-coated tablets. In the presence of pectinolytic enzymes, a sudden release of indomethacin was seen in both types of tablets but the rate and the percentage of release were lower (only 57.6\#2.5\%) in compression-coated tablets as compared to plain matrix tablets (74.2\#4\%) after 12 hours.
Mastiholimath, et al., (2007) made an attempt to deliver theophylline into small intestine by taking the advantage of colon having a lower pH value (6.8) than mixture of the polymers, i.e., Eudragit L and Edragit S in proper proportion, and obtained the pH dependent release in the colon.

Dasharath M Patel, et al., (2011) developed a modified pulsincap dosage form of 5-fluorouracil to target the drug to colorectal carcinoma according to daily oscillations of rate-limiting metabolizing enzyme dihydropyramidine dehydrogenase.

Srinivas L, et al., (2013) formulated and evaluated the ibuprofen pulsincap technique that the pulsatile drug delivery system used, which releases drug on a programmed pattern especially at appropriate time and at appropriate site of action. In PDDS, a pulse is designed in such a way that a complete and rapid drug release is achieved after the lag time so as to match the body’s circadian rhythms with the release of drug. In the current study, an attempt was made to formulate and evaluate ibuprofen as pulsincap technique. The prepared capsules were evaluated for uniformity of weight, drug content, and in-vitro release.

Ram S Sakhare, et al., (2010) reviewed that the pulsatile drug delivery system is a novel strategy developed to improve the efficiency of controlled drug delivery system in the treatment of diseases such as asthma, arthritis, duodenal ulcer, and cardiovascular diseases. It releases drug in a pulsatile or staggered profile. PDDS are gaining
importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. This review focus on various methods that have been used for pulsatile release of drug.

Jonathan CD Sutch, et al., (2003)\textsuperscript{117} investigated the coating-dependent release mechanism of a pulsatile capsule using nuclear resonance microscopy. Chronopharmaceutical capsules exhibited clearly different characteristics when coated by organic or aqueous processes.

Nageswara Rao V V, et al., (2012)\textsuperscript{118} modified the pulsincap technique for oral controlled release of Rosiglitazone maleate. The modified pulsincaps were prepared with different proportions of the hydrophilic polymer and HPMC. Drug-polymer mixtures were prepared in the ratios of 5:2, 5:3, 5:4, and 5:5, respectively. The prepared drug-polymer mixtures were evaluated for micromeretic properities and to conform the reproducibility of the method variation, drug content, and drug release kinetics.

Swatic C Jagdale, et al., (2014)\textsuperscript{119} formulated and evaluated Rizatriptan Benzoate in the modified pulsincap drug delivery system. Drug excipient interactions were carried by UV spectroscopy, FTIR, and DSC. The prepared pulsincap was coated with 5% CAP. The pulsincap was evaluated for in-vitro dissolutions studies and release kinetics.
B Venkateswara Reddy, et al., (2014)\textsuperscript{120} reviewed that the pulsatile drug delivery systems are classified into site-specific, where the drug is released at a desired site within the intestinal tract, and time-controlled, where the drug release is controlled by the delivery system and not by the external environment. This review covers various pulsatile systems like capsular systems, osmotic systems, and single and multiple systems.

Yang L, et al., (2002)\textsuperscript{121} reported that the four systems were unique in terms of achieving in-vivo site specificity, design rationale, and feasibility of the manufacturing process (pressure controlled colon delivery capsule (PCDCs), colon drug delivery system (CODES) based on pectin and galactomannan coating, and Azo hydrogels). He concluded new approaches in in-vitro and in-vivo evaluation of colon specific drug delivery systems.

Hideki Ichikawa, et al., (1997)\textsuperscript{122} designed the prolonged release of micrcocapsules containing diclofenac sodium for oral suspension and their preparation by the wurster process.

Sindhu Abraham, et al., (2007)\textsuperscript{123} reported the modified pulsincap dosage form of metranidazole to target drug release in colon by using extrusion spheronization method.

Sungthongieen, et al., (2004)\textsuperscript{124} reported the development of pulsatile release tablet with swelling rupturable layers. The system released the drug rapidly after a certain lag time due to the rupture of ethyl cellulose film.
Khan MZ, et al., (1999)\textsuperscript{125} formulated a pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers. Drug release was manipulated using Eudragit 100-55 and Eudragit s-100 combinations. The coated tablets were tested in-vitro for their suitability for pH dependent colon targeted oral delivery.

Amol M, et al., (2012)\textsuperscript{126} designed and evaluated pulsatile drug delivery system of atenolol for chronomodulatory therapy. The pulsatile release tablet comprises of a drug containing core and pH sensitive polymeric coating capable of delaying drug release and providing gastric resistance to overcome gastric emptying variability, thus allowing colon delivery to be pursued according to the time dependent approach. A suitable dosage form was developed by using different sensitive pH polymers like Edragit s-100, ethyl cellulose, and sodium alginate.

\textbf{2.3. Literature Survey on Matrix Mini-tablet}

Hitesh p, et al., (2011)\textsuperscript{127} reported that compressed mini-tablet systems are provided as a biphasic delivery system. The outer layer that fills the void between the mini-tablets was formulated to release the drug in a very short time (fast release), while the mini-tablets provided a prolonged release. The fast releasing component comprised super disintegrant croscarmellose sodium, while the mini-tablet was formulated using different concentrations of HPMC K100M to obtain different drug release rates. The in-vitro performance of these systems showed the desired biphasic behavior. The drug contained in the fast
releasing phase (powder enrobing the mini-tablets) dissolved within the first 15 minutes, whereas the drug contained in the mini-tablets was released at different rates, depending upon the composition of mini-tablets.

Matthew Roberts, et al., (2012)\textsuperscript{128} assessed the development and evaluation of sustained-release compritol 888 ATO matrix mini-tablets.

Sandhya. p et al., (2014)\textsuperscript{129} formulated and evaluated repaglinide biphasic mini-tablets, which were encapsulated in a capsule. Immediate release mini-tablet (IRMT) was manufactured by direct compression using various super disintegrating agents and polymers. The drug excipients compatibility studies were performed using FTIR techniques. The in-vitro performance showed the desired biphasic behaviour.

Carlo M Lopes, et al., (2006)\textsuperscript{130} developed the directly compressed mini matrix tablets containing Ibuprofen and hydroxypropylmethyl- cellulose (HPMC) or ethylcellulose (EC) as a release controlling agent.

Sunil Reddy, et al., (2009)\textsuperscript{131} adopted a novel approach in designing sustained release matrix tablets of Eplerenone, a water soluble drug, using cellulose polymers as release modifiers in the form of matrix mini-tablets. Matrix mini-tablets containing cellulose polymers like HPMC K4M and HPMC K15M were prepared by wet granulation technique using PVP K60 as a tablet binder. The FT-IR
and DSC studies did not show any interaction between Eplerenone, polymers, and excipients used in the formulation. The results clearly indicated that the novel approach of designing controlled release formulations of Eplerenone in the form of matrix mini-tablets could be successfully fabricated using an appropriate ratio of cellulose polymers like HPMC K15M and HPMC K4M.

De Brabander et al., (2000)\textsuperscript{132} reported that the matrix mini-tablets based on a combination of microcrystalline waxes and starch derivatives were prepared using ibuprofen as a model drug. The production of mini-tablets was preferred over the production of pellets, as up-scaling of the pelletisation process seemed problematic. Melt granulation in a hot stage screw extruder and milling were required prior to tabletting.

Tafara Jambwa, et al., (2011)\textsuperscript{133} investigated the potential use of gel and whole leaf materials from Aloe vera and Aloe ferox as excipients in the formulation of controlled release matrix-type mini-tablets. The chemical composition of the freeze-dried aloe materials was determined through proton nuclear magnetic resonance spectroscopy.. Matrix-type mini-tablets manufactured from the aloe materials alone and in combination with other polymers were evaluated in terms of their physical characteristics, mucoadhesive properties, swelling behaviour, and drug release kinetics.

Abdul Hadi Mohd, et al., (2014)\textsuperscript{134} developed matrix mini-tablets of lornoxicam filled in capsule targeting early morning peak symptoms
of rheumatoid arthritis. Matrix mini-tablets of lornoxicam were prepared by direct compression method using microsomal enzyme dependent and pH-sensitive polymers, which were further filled into an empty HPMC capsule. Pure drug, polymers, and their physical mixture were performed to assess the compatibility, FT-IR, and DSC studies.

2.4. Literature Survey on Bosentan

Serasil E, et al., (2010)\textsuperscript{135} reviewed the dual endothelin receptor antagonist used for the treatment of pulmonary arterial hypertension. This addresses and highlights pharmacological aspects of bosentan such as safety, tolerability, and drug interactions.

Eli Gabbay, et al., (2007)\textsuperscript{136} reviewed and assessed bosentan as an orally active therapy, which is effective in the management of pulmonary arterial hypertension. This review critically appraises the evidence for the efficacy of bosentan in idiopathic and familiar PAH, PAH associated with connective tissue disease, and PAH developed in association with other conditions.


Maurice Beghetti, (2004)\textsuperscript{138} reported that bosentan in pulmonary arterial hypertension is associated with congenital heart disease (congenital cardiac shunts).
Kamyar Afshar, et al., (2009) assessed that bosentan is proving to be a viable therapeutic action in alleviating manifestations of systemic sclerosis other than pulmonary hypertension. There are many reports in the literature profiling bosentan’s safety, efficacy, and tolerability in patients. The clinical indications for use of bosentan in a wide array of patients have served as a valuable asset in the medical management of systemic sclerosis.

Shahzad G Raya, et al., (2008) reviewed that the arterial pulmonary hypertension (PAH) is a debilitating disease associated with significant morbidity and high mortality if left untreated. Bosentan is an orally active dual endothelin receptor antagonist. This drug has shown to improve the exercise capacity and survival in patients with PAH. This review article discusses the pharmacology of bosentan and shows the current evidence for the safety and efficacy of bosentan for PAH.

Nakwan N, et al., (2009) reported that the successful treatment of persistent pulmonary hypertension of the newborn with bosentan is limited in developing countries. Alternative (less expensive) treatments are being sought and bosentan, an oral dual endothelin-1 receptor antagonist, may be an option for the treatment of PAH.
2.5. Conclusion

Controlled release drug delivery systems enable prolonged and continuous output of the drug to the various parts of the gastrointestinal tract and improve the bioavailability of medications.

From the review of literature it could be understood that CDDS provides a means to utilize all the pharmacokinetic (PK) and pharmacodynamic (PD) advantage of controlled release dosage forms for antihypertensive drugs.

Based on the literature surveyed, it may be conclude that drug absorption in the gastrointestinal tract is a highly variable process and prolonged drug release of the dosage form extends the time for drug absorption. Due to complexity of pharmacokinetic and pharmacodynamic parameters, further studies are required to establish the optimal dosage form for antihypertensive drugs used for the treatment of Pulmonary Arterial Hypertension.

For certain drugs interplay of its pharmacokinetic and pharmacodynamic parameters will determine the effectiveness and benefits of the CDDS as compared to the other dosage forms.