World Journal of Pharmaceutical Research
SJIF Impact Factor 5.045
Volume 3, Issue 4, 995-1019. Research Article ISSN 2277 – 7105

SIGNIFICANCE OF NANOPARTICLE DRUG DELIVERY SYSTEM THAN CONVENTIONAL DRUG DELIVERY SYSTEM OF ANTIHYPERTEENSIVE DRUGS

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Article Received on
05 April 2014,

Revised on 28 April 2014,
Accepted on 21 May 2014

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ABSTRACT

The main obstacles for the oral delivery of antihypertensive drugs are low bioavailability and its instability problems. Nanoparticles protect the labile drugs against the GIT harsh environment. Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000 nm. Nanoparticles are sub-nano sized colloidal structures composed of synthetic or semi synthetic polymers.[11] Polymeric nanoparticles have been extensively studied because of their unique and valuable physicochemical and biological properties. Indeed nanoparticles can protect the drug from degradation, enhance its transport and prolong its release; therefore they may improve the plasma half life of the drug. The nanoparticle preparations represent sustained release forms with increased bioavailability, a less pronounced initial antihypertensive effect and a long-lasting action with a good stability.

Keywords: nanoparticles, antihypertensive drugs.

INTRODUCTION

The oral route is the most convenient in terms of delivery and patient compliance, especially compared to parenteral route, because it avoids the pain and discomfort associated with injections (Shaji and Patole, 2008).[39]However, despite its desirability, oral application presents serious difficulties due to the nature of the gastrointestinal tract (GIT, e.g. the highly acidic pH and the presence of pepsin in the stomach and pancreatic enzymes in the intestine and brush-border enzymes). These conditions can cause drug degradation and loss of drug activity. At the same time, macromolecular drugs should have the ability to cross the intestinal membrane barrier to reach the systemic circulation. However, these drugs are too

large and too hydrophilic to cross this barrier. For these reasons, many drugs have low oral bioavailability (Bowman and Leong, 2006).[39]

The main obstacles for the oral delivery of drugs are low bioavailability and its instability problems (Garcia-Fuentes et al., 2005). The enhancement of the transport of drugs via nanoparticles is provided by different mechanisms (mucoadhesion, particle endocytosis and permeation-enhancing effect) depending on the nanoparticles composition (Garcia-Fuentes et al., 2005; des Rieux et al., 2006). In addition, nanoparticles protect the labile drugs against the GIT harsh environment (des Rieux et al., 2006).[92]

Many studies have endeavoured to improve the oral delivery of those drugs. The hard to target tissues such as blood-brain barrier permeation limitation can now be overcome allowing the use of therapies otherwise excluded by conventional dosage forms.[75] These new systems can hinder solubility problems, protect the drug from the external environment such as photodegradation and pH changes, while reducing dose dumping by controlling the release profile.[73,74] Moreover, controlled targeting at the site of action and reduced time of exposure at non-targeting tissues increases the efficacy of treatments and reduce toxicity and side effects[76] thus improving patient compliance and convenience. Polymeric nanoparticle systems are one of several approaches that have been explored to enhance the oral bioavailability of these drugs.[92]

This approach can improve the pharmacokinetic profiles of numerous drugs through the delivery of a higher dose at the site-specific organs by using ligands[77] while conferring a controlled release and degradation to non-toxic products. Meanwhile, oral administration is the most convenient route for drug delivery and the focus of recent research concerns the development of carriers that can cross biological barriers such as the gastrointestinal (GI) tract. In such a way it is necessary for the carrier to protect the drug against the hostile and degrading milieu of the GI tract while increasing the residence time (e.g. bioadhesion) and target specific cells to enhance absorbtion which will most likely require less frequency regimens[92]. Polymeric nanoparticles are attractive vehicles in pharmaceutical technology field due to their inherent stability in the GIT compared to other colloidal carriers, especially liposomes (des Rieux et al., 2006). These nanoparticles can protect encapsulated drugs against the harsh environment of the GIT and also enhance their transmucosal transport (des Rieux et al.,2006)[39]

Nanoparticle/nanomedicines are defined as engineered strutures with diameters of <100nm , and are delivery systems and devices contaning encapsulated,dispersed,absorped, or conjugated durgs and imaging agents which are produced by chemical and/or physical processes having specific properties. passive targeting is achieved by incorporating the therapeutic agent into a nanoparticle that passively reaches the target organ. Passive targeting refers to the increased accumulation of drug or drug-carrier at a particular site due to passive physiological factors[92]

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000 nm. Nanoparticles are sub-nano sized colloidal structures composed of synthetic or semi synthetic polymers.[11] Small nanoparticles (100–300 nm) with a narrow size distribution are usually prepared by nanoprecipitation methods using different polymers (e.g.PLGA,Eudragit, cellulose derivatives, poly"-caprolactones, etc)(Bilati et al., 2005; Cetin et al., 2010).[39]

Nanoparticles are becoming key components in a wide range of applications. Research encompasses numerous disciplines, e.g. nanotechnology, molecular engineering, medicine, pharmaceutical drug manufacture, biology, chemistry, physics, optical components, polymer science, mechanical engineering, toxicology, cosmetics, energy, food technology and environmental and health sciences. The use of nanoparticles for the development of new drug delivery systems seems very promising.[53] By highlighting the chemical, physical and biological phenomena/processes associated with nanoparticles and nanostructures ranging from molecular size to 100nm which exhibit improved properties or have novel applications due to their size. Submicron nanoparticles are included in special cases. The design of these types of systems has to take into consideration the characteristics of the drugs to be encapsulated. Example, hydrophobic drugs are more likely to be encapsulated in hydrophobic polymers and vice-versa [95]. To overcome this limitation, synthesis of new polymers such as (PLA- PEG-PLA)n or PCL-PEG can be produced.[95]

Nanoparticles can enhance drugs' absorption by optimizing their interaction with the absorption site in the GI-tract walls or by directly transporting these drugs through the intestinal mucosa to systemic circulation. In GI tract, there are several possibilities for the uptake of nanoparticles such as transcellular uptake, paracellular uptake and an uptake via the M cells, mainly located in Peyer's patches. Many factors (GI tract's physiology, the particle size/type/charge,hydrophilic/hydrophobic balance, polymer type used, the presence of a

ligand, etc.) play an important role for uptake of nanoparticles via these routes. Several polymers (chitosan, polyacrylates, etc.) interacting were used to enhance paracellular uptake of peptides through interactions between the negatively charged cell membrane and the positive charges of the polymer, or by complexing Caþ2 involved in the structure of tight junctions (Jung et al.,2000; des Rieux et al., 2006; Mohanraj and Chen, 2006;Pinto et al., 2006).[39]

Bioadhesive nanoparticles adhere to the mucosal surface leading to the modification of mucosal surface properties via bioadhesive polymers and improve the residence time and contact of the drug with the epithelium. Thus, the compound concentration increases in the absorption site(Garcia-Fuentes et al., 2005). In this way, active substance dilution and degradation by luminal contents can be minimized, resulting in an enhanced absorption into systemic circulation (Makhlof et al., 2011).[39]

In general, the mechanisms of intestinal mucous permeation by absorption enhancers include the following: (1) The absorption enhancers (such as surfactants, bile acid derivates) lead to membrane perturbation and increase the permeability of drugs via interactions of them with membrane lipid/protein (Sood and Panchagnula, 2001)[39]Nanoparticles are absorbed by different mechanisms but endocytosis is the most significant contributor to cell entry [54,90]. Also changing some technological features such as production method[91] and use of surfactant can promote different control release.[91]

The use of nanotechnology for drug delivery rapidly produced commercially available products and the term nanomedicine emerged. Nanomedicine is the application of nanometer scale materials in an innovative way to develop new approaches and therapies. At this scale, materials display different physicochemical properties due to their small size, surface structure and high surface area.[68] These properties allow nanoparticulate systems to overcome current limitations of conventional formula-tion as they facilitate the intracellular uptake to specific cellular targets. Thus, nanotechnology has been adopted in several fields such as drug/gene delivery[69,70] , imaging[71] and diagnostics[72].

Why Combinational Antihypertensive Therapy?

Benz, J R; Black et al. compares the antihypertensive efficacy and tolerability of valsartan, a novel angiotensin II antagonist, given with hydrochlorothiazide (HCTZ) vs placebo or vs valsartan or HCTZ alone. All combination regimens produced a statistically significantly

greater reduction in patients with essential hypertension than the corresponding monotherapies. Valsartan 80 mg and 160 mg act additively with HCTZ 12.5 mg or 25 mg to lower hypertension. The addition of HCTZ to valsartan 80 mg or 160 mg was well tolerated.[2] James L. Pool et al investigated the blood pressure (BP)-lowering effects of the oral direct renin inhibitor aliskiren, alone or in combination with the angiotensin receptor blocker valsartan. Coadministration of aliskiren and valsartan produced a greater antihypertensive effect than either drug alone, comparable in magnitude to the effect of valsartan/hydrochlorothiazide, with similar tolerability to the component monotherapies and to placebo. Aliskiren and valsartan in combination may provide additive BP-lowering effects with maintained tolerability.[3]

Individuals may be administered with multiple medications separately or in fixed-dose combinations, the latter reducing treatment complexity and potentially leading to improved compliance.[4–6] Treatment guidelines proved that the combination of an angiotensin receptor blocker (ARB) and a calcium channel blocker (CCB), similar to the combination of an angiotensin-converting enzyme inhibitor (ACEI) or an ARB plus a diuretic, provides an effective option for patients with hypertension.[7] ACEI/CCB and ARB/CCB combinations incorporate monotherapy components that act via complementary mechanisms of action[8,9] and therefore achieve greater sustained BP reductions than when the respective monocomponents are administered alone.[10-12] Tolerability benefits may also be gained from rational drug combinations, such as edema reduction when an ACEI or an ARB is added to a CCB.[13,14]

Similar reductions in BP values have been reported recently in patients with hypertension treated with amlodipine plus valsartan.[13] The edema rates reported in this study are higher than those reported in other studies involving similar doses of these agents.[12,15] Edema remains the most frequent adverse event associated with amlodipine and other long-acting dihydropyridine CCBs.[16] Frequencies of peripheral edema as high as 70% have been reported in various studies with CCBs.[17]Other studies involving amlodipine 10 mg monotherapy[18,19,20] have reported higher frequencies of peripheral edema than were found with amlodipine/valsartan 10/160 mg in this study, suggesting that ARBs may attenuate, but not eliminate, amlodipine-induced peripheral vasodilatory edema.[12,13,17]

Significance Of Nanoparticulate Drug Delivery Of Mono/Combined Antihypertensive Drugs

Polymeric nanoparticles have been extensively studied because their unique and valuable physicochemical and biological properties. Indeed nanoparticles can protect the drug from degradation, enhance its transport and prolong its release; therefore they may improve the plasma half life of the drug.[33,34]

Hsu et al.[51] showed that the absorption pathways as well as efficiency are affected by particle size. Moreover, the intestine has special mechanism(s) to absorb particles, and there may be a size-exclusion phenomenon in the gastrointestinal absorption of particles, with 100nm particles showing a significantly higher uptake (10- to 250-fold higher) than larger particles (10 μm).[51] Following oral administration, particles less than 500 nm can cross the M cells in the Peyer's patches and the mesentery on the surface of gastro-intestinal mucosa, delivering the drug to the systemic circulation.[52]

Acharya et al. (2010) reported that drug release from polymeric systems depends on at least three factors, such as the surface area, diffusion coefficient and concentration gradient of the drug. They also suggested that control of particle size of the formulation also resulted in a more accurate estimation and a greater reproducibility of the drug release properties of a given formulation.[39]Similarly, Dawes et al. (2009) reported that the decrease in particle size causes a higher rate of inclusion of water into the polymeric system in the release medium and thus a faster diffusion of the drug. The characteristics of the polymers, such as hydrophilicity, negative charge potential and the presence of hydro-gen bonds, can promote the formation of mucoadhesive bonds, which in turn determine the retention at application and target sites. The surface free energy of the polymer should permit sufficient wetting by the mucosal surface. Anionic and cationic polymers exhibit strong mucoadhesion (Patel et al. ,2011).[39]The mucoadhesive properties of anionic polymers are caused by the physical entanglement, hydrogen-bonding and vander Waal's interactions with mucus. These interactions are stronger than the electrical repulsion. On the other hand, cationic polymers interact with mucus largely through electrostatic forces (Shaji and Patole, 2008)[39]

A new drug nanocarrier was synthesized by coating chitosan and prindopril erbumine onto the surface of iron oxide nanoparticles by Dena Dorniani et al. using a simple coating method.It is apparent that prindopril erbumine was released in a controlled manner and

governed by first-order kinetics. Prindopri erbumine, iron oxide nanoparticles and its coated nanocomposite, FCPE were not toxic in a normal human fibroblast (3T3) cell line. Therefore, our nanocomposite containing prindopril erbumine is a possible alternative drug delivery method with minimal toxicity potential.[32]

Carvedilol has bioavailability of about 25 to 35% because of extensive first-pass metabolism.[35,36] Sovan Lal Pal et al. studied In vitro drug release of carvedilol nanoparticles having different theoretical loading as a function of time. It was observed that the nanoparticles containing higher amount of drug leads to quick release and the particle with small drug amount exhibit a sustained manner release.[37] In release kinetics higher initial drug loading results in faster drug release.[38] PLGA nanoparticles of Carvedilol that will improve the bioavailability of Carvedilol and sustain the release to reduce the initial hypotensive peak and to prolong the antihypertensive effect of the drug. Carvedilol encapsulated by Nanoprecipitation method by N. Jawahar et al using PLGA and Pluronic F-68 displayed that the drug encapsulation efficiency was high. In vitro cumulative release from the nanoparticles was sustained at 24hr. In vivo biodistribution studies in rats revealed that these particles are distributed in heart, liver and kidney at higher concentration may allow their delivery to target sites.[50]

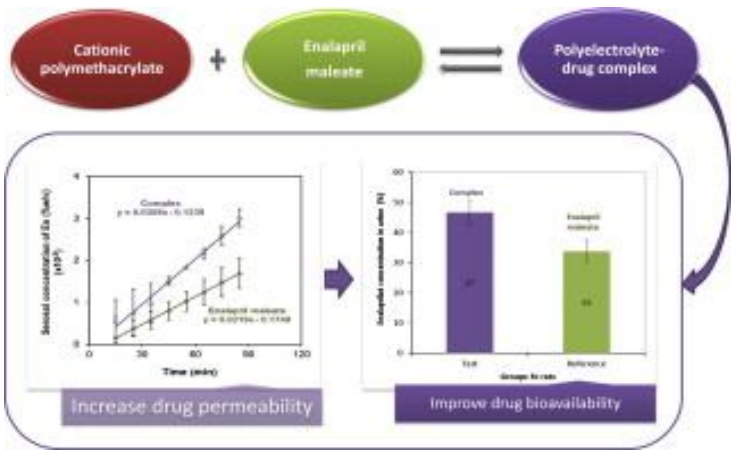
In order to improve patient compliance by simplifying its administration, improving its therapeutic effect, Carvedilol containing egg albumin nanoparticles were prepared by coaservation method using Gluteraldehyde ethanol as the cross linking agent. A. Ankarao1et al. prepared and evaluated the oral sustained release nanoparticles and the results shown that this method is reproducible, very easy and led to the efficient entrapment of drug. There is a maximum percentage drug entrapment and percentage yield. The sustained release behavior of egg albumin nanoparticles were evaluated both in phosphate buffer (pH 7.4) and simulated gastric fluid (pH 1.2), respectively, at 37±10c.[60]

Solid lipid nanoparticles (SLN) of carvedilol developed by N.L Prasanthi et al. with the help of hot homogenization followed by ultrasonication method. SLN were prepared by using tripalmitin as lipid at various concentrations and tween 80 as surfactant at various concentrations .The drug entrapment efficiency (EE %) of SLNs was more than 80% and increased as the concentration of lipid was increased and decreased as the concentration of surfactant was increased. The drug release was decreased as the concentration of both lipid

and surfactant was increased. In vitro release of carvedilol from SLN followed Higuchi diffusion and first order equation[63]

Enalaprilat is a typical angiotensin-converting enzyme inhibitor and is very poorly absorbed from the gastrointestinal tract. The aim of Ahlin P[1] et al. study was to design and characterize poly-(lactide-co-glycolide) (PLGA) and polymethylmethacrylate (PMMA) nanoparticles containing enalaprilat and to evaluate the potential of these colloidal carriers for the transport of drugs through the intestinal mucosa. Nanoparticle dispersions were prepared by the emulsification-diffusion method .The type of polymer has a decisive influence on drug content 07 and 13% for PMMA and PLGA nanoparticles, respectively. In vitro release studies show a biphasic release of enalaprilat from nanoparticle dispersions-fast in the first step and very slow in the second.[61]

The low bioavailability of enalapril maleate associated to its instability in solid state motivated María V. Ramírez-Rigo et al. to develop polyelectrolyte-drug complex between enalapril maleate and the cationic polymethacrylate Eudragit E100. The solid materials are stable amorphous solids in which both moieties of enalapril maleate are ionically bonded to the polymer. Their aqueous dispersions exhibited controlled release over more than 7 h in physiologic saline solution, being ionic exchange the fundamental mechanism that modified the extent and rate of drug release. Intestinal permeation of enalapril maleate was 1.7 times higher in the presence of the cationic polymer. This increase can be related with its capacity to adhere to the mucosa due to the positive zeta potential of the complexes. As a consequence bioavailability was significantly improved (1.39 times) after oral administration of the complexes. In addition, no signs of chemical decomposition were observed after a 14 months period. The results indicated that the products are new chemical entities that improve unfavorable properties of a useful drug.40



However, the chitosan-coated nanoparticles significantly interact with the tight junctions and enhance the paracellular transport of the drug released at the epithelial level compared to PEG-coated nanoparticles. These observations were explained by authors as follows: (1) the interaction of chitosan-coated nanoparticles with the mucus resulted in the diffusion of these nanoparticles through the mucus layer; (2) the site-specific delivery of drugs for prolonged time was ensured by these interactions, and as a result, a prolonged hypocalcemic effect was obtained and (3) the interaction of chitosan with the tightjunctions might enhance the paracellular transport of the peptide released at the epithelial level. [39]

Candesartan-cilexetil ,an angiotensin receptor blocker exhibits low bioavailability after oral administration due to its low water solubility. Chitosan is considered one of the most promising biopolymers for drug delivery as a vehicle and trimethyl chitosan is a water soluble chitosan derivative. Candesartan-cilexetil was loaded on trimethyl chitosan nanoparticles, trimethyl chitosan, gum arabic and commercial water soluble chitosan using an ultrasonic effect, and the potential of the polymers to increase the solubility of candesartan-cilexetil was investigated by Aylin Geçer et al.Trimethyl chitosan nanoparticles are a superior vehicle for increasing the solubility of candesartan-cilexetil compared to trimethyl chitosan, gum arabic or commercial water soluble chitosan.[41]

In fact, in vivo nanoparticles coated with PEG increase circulation time from several minutes to many hours and enhance residence times up to 200-fold in humans [82-84]. On the other hand, the effectiveness of PEG depends on surface density, chain length[85]and ability to avoid the liver uptake. However, PEG carriers are intended for intracellular penetration and sometimes PEG prevents normal interactions of the carrier with cells. Also, PEGylated nanocarrier systems have shown to induce an immune response, known as the accelerated blood clearance (ABC phenomenon) after repeated injection with subsequent increased accumulation on the liver and spleen [86]. Thus, new strategies have been pursued such as re-placing PEG with polyamino acid polyhydroxyethyl-L- aspargine (PHEA). This strategy demonstrated favorably long circulation times and reduced ABC phenomenon compared to PEG. [86]

Isradipine, an antihypertensive agent, was encapsulated by Leroueil-Le Verger M et al. by the nanoprecipitation method using polymers including poly(epsilon-caprolactone), poly(D,L-lactide) and poly(d, L-lactide-co-glycolide) The colloidal suspensions displayed a sustained release profile in comparison with the drug release profile of isradipine in a PEG solution.

Results from this investigation suggest that these nanospheres will be a good candidate delivery system for oral administration, to reduce the initial hypotensive peak and to prolong the antihypertensive effect of the drug.[42]

The therapeutic use of nifedipine is limited by the rapidity of the onset of its action and its short biological half-life. In order to produce a form devoid of these disadvantages Kim YI et al. made nanoparticles of nifedipine from three different polymers, poly-epsilon-caprolactone (PCL), polylactic and glycolic acid (1:1) copolymers (PLAGA), and Eudragit RL/RS (Eudragit) with Nifedipine in polyethylene glycol 400 (PEG) solution was used as a control. All of the nanoparticle dosage forms decreased Cmax and increased Tmax and the mean residence time (MRT) values. Relative bioavailability was significantly increased with Eudragit nanoparticles compared to the nifedipine/PEG solution. The nanoparticle nifedipine preparations represent sustained release forms with increased bioavailability, a less pronounced initial antihypertensive effect and a long-lasting action.[43]

Captopril (CAP) was the first angiotensin I-converting enzyme (ACE) inhibitor to be developed and is widely used in hypertension treatment The nanoparticles obtained by Mariangela de Burgos M de Azevedo1 et al. showed a potent and long-lasting inhibitory activity (~22 hours) on the angiotensin I pressor effect. The results suggest that the inclusion complex of CAP and α-CD can function as a novel antihypertensive formulation that may improve therapeutic use of CAP by reducing its oral dose administration to once per day, thus providing better quality of life for almost 25% of the world's population who suffer from hypertension.44.

Nimodipine (NMD) is highly lipophilic antihypertensive drug having (logP 3.41) and 13% oral bioavailability. Shailesh S. Chalikwar et al. made an attempt to increase oral bioavailability and to target intestinal lymphatic transport system, Nimodipine loaded solid lipid nanoparticles (NMD-SLNs) were prepared with palmitic acid (PA), poloxamer 188 and soya lecithin as a lipid, surfactant and co-surfactant respectively shows EE of 93.66±9.72% and cumulative drug release of 87.52±2.54% in 10h. The pharmacokinetic study of optimised SLNs showed 2.08-fold increase in relative bioavailability than that of NMD solution, when administered orally. Accelerated stability studies showed that there was no significant change. Due to enhanced bioavailability, these NMD-SLNs are considered to be promising vehicles for oral delivery.[45]

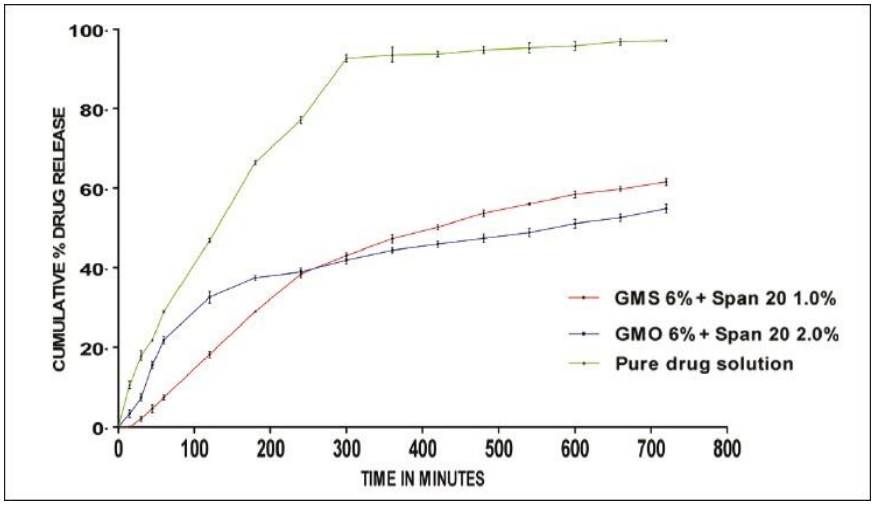
Ramipril, a widely used therapeutic agent used in the treatment of hypertension, exhibits poor aqueous solubility resulting in low oral bioavailability[54]. Its oral bioavailability is 28% and it is rapidly excreted through the renal route due to its short half life.This drug has many side effects such as, postural hypotension, hyperkalemia, and angioedema, when given as an immediate dosage form[48]. To overcome the side effects and to increase the bioavailability of ramipril, N.Jawahar et al. designed and characterized Poly (D,L-Lactide-co-Glycolide) (PLGA) nanoparticles of ramipril loaded by nanoprecipitation method using tribloere polymeric stabilizer. Nanoparticles of ramipril were obtained with high encapsulation efficiency (68-75%). The drug release from the ramipril nanoparticles was sustained for more than 24hrs with 72% drug release. This study by suggest that the feasibility of formulating Ramipril loaded PLGA nanoparticles can be used to improve the therapeutic efficacy of Ramipril in the treatment of hypertensive disorder.[46] Chadha Renu et al focused on optimizing this important physicochemical property by entrapping the drug into the nanoparticles. Besides this, drug complexed with beta-cyclodextrin is also incorporated in nanoparticles. The lecithin/chitosan nanoparticles prepared using solvent evaporation method a high entrapment efficiency of above 72.3% were achieved. The nanoparticles were spherical in shape and exhibited a high positive value of zeta potential (> 30 mV) which indicated the stability of the prepared formulations. A significantly improved in-vitro drug release in comparison to the free drug was observed. In vivo activity in deoxycorticosterone acetate salt induced hypertensive rats demonstrated 1.6 fold percentage decrease in systolic blood pressure. The prepared lecithin/chitosan NPs represent an efficient new drug delivery system for oral administration of this poorly water soluble drug.[54]

Ramipril loaded nanoparticles were prepared by high pressure homogenization technique using ammonio methacrylate copolymers by satish pandav et al. Eudragit RSPO and Eudragit RLPO, as coating materials with different amount of polymers with an objective to apply this technique in order to develop poorly water soluble drugs loaded nanoparticles with both these copolymers for the sustained release using modified O/W Emulsion Solvent Diffusion method. The sustained release nanoparticles of Ramipril with Eudragit in the different ratios were prepared using surfactant like polyvinyl alcohol. In vitro drug release rate for nanoparticles was found to be sustained over 12 hours and a burst release of Ramipril loaded Eudragit RLPO nanoparticles was observed prepared by the modified o/w method. Under buffered conditions (pH 6.8), about 75% and 66% of the drugs were found after approximately 3 h, while 97% and 85% of the drugs were released from Eudragit L100 and

Eudragit RSPO nanoparticles after 6 h. This effect was due to the pH-dependent and independent release behaviour of Eudragit L100 and Eudragit RSPO, respectively. Eudragit L copolymer was ionized and soluble at pH 6.8 and showed a relatively rapid drug release.On the other hand, approximately 65% and 50% of the drug were released from Eudragit L100-PLGA and Eudragit RSPO- PLGA nanoparticles within 3 h, respectively, and about 95% and 80% of the drugs were released from these nanoparticles after 24 h, due to the presence of PLGA in these formulations. Consequently, the properties of the polymer have a very important effect on the controlled drug release from the nanoparticles (Eerikainen et al., 2004; Bilati et al., 2005; Cetin et al., 2010; Glowka et al., 2010).[39]

The sustained release of drug from the ramipril nanoparticles suggest that the frequency of administration, dose and adverse effects of this molecule could be reduced. We can conclude that there is large scope for improving the use of ramipril in hypertensive treatments through nanoparticle as a drug delivery system. [57]

With a view to improve the dissolution rate of Ramipril,P Ekambaram et al. prepared and characterized the ramipril loaded solid lipid nanoparticles, using glyceryl monostearate and glyceryl monooleate as the lipid matrices and tween 80, poloxamer 188, and span 20, as stabilizers, which would increase the biological activities. A formulation containing glyceryl monooleate, stabilized with span 20 as surfactant showed prolonged drug release, smaller particle size, and narrow particle size distribution, as compared to other formulations with different surfactants and lipids.[47] Given that solid lipid nanoparticles, as an alternative colloidal carrier (transport) system, have the ability to improve the solubility/permeability of lipophilic drugs, they may enhance the drug absorption[48]



Characterization of lecithin/chitosan nanoparticles loaded with hydrochlorothiazide (HCT) (a poorly water soluble antihypertensive) and hydrochlorothiazide complexed with *β*-cyclodextrin (HCT-*β*-CD) with a view to improve its biopharmaceutical properties by Renu Chadha et al. revealed that HCT and HCT-*β*-CD loaded nanoparticles shown a maximum entrapment efficiency. *In vitro* studies have shown an improved and a sustained release pattern. *In vivo* activity in DOCA induced hypertensive rats demonstrates 1.5-fold percentage decrease in systolic blood pressure and a prolonged duration of action.[49]

Nitrendipine is an antihypertensive drug with poor oral bioavailability ranging from 10 to 20% due to the first pass metabolism. For improving the oral bioavailability of nitrendipine, Kumar VV et al. developed nitrendipine loaded solid lipid nanoparticles using triglyceride (tripalmitin), monoglyceride (glycerylmonostearate) and wax (cetyl palmitate). Poloxamer 188 was used as surfactant. Hot homogenization of melted lipids and aqueous phase followed by ultrasonication at temperature above the melting point of lipid was used to prepare SLN dispersions. Bioavailability of nitrendipine was increased three- to four-fold after intraduodenal administration compared to that of nitrendipine suspension.[56]The obtained results are indicative of solid lipid nanoparticles as carriers for improving the bioavailability of lipophilic drugs such as nitrendipine by minimizing first pass metabolism.[56]

Repaglinide (RPG) for oral delivery and to improve bioavailability, Jameel Ahmed S et al. developed prolonged release SLNs. SLNs were formulated using tristearin as the lipid core and poloxamer 188 and egg lecithin as a mixture of emulsifiers by microemulsion method. The in vitro release profile from SLN suspension exhibited biphasic pattern with an initial burst and prolonged release over 24 hr.[55]

General features of SLN are their composition of physiological compounds, possible routes of administration by i.v, oral and topical, the relatively low costs of excipients. The other advantage is easy large scale production.[94] Suffi cient data implicate that the bioavailability of poorly hydrophilic and lipophilic drugs can be improved when these drugs are encapsulated in SLNs.[95-97]

It is reported that the SLNS are a promising sustained release system for lipophilic drugs after oral administration to increase oral bioavailability, good physical stability, good tolerability, drug targeting ,improved therapeutic effect, protection of liable drugs, control release, lower

cytotoxicity ,possible sterilization and having the best production scalability(mader and mehnert,2011)[98]

Valsartan is an antihypertensive drug with poor oral bioavailability ranging from 10-35% because of poor solubility, dissolution and most importantly, extensive first pass hepatic metabolism. For improving solubility and oral bioavailability of Valsartan, Hiral Patel et al. loaded Valsartan in solid lipid nanoparticles (VSLNs) have been developed using stearic acid as lipid, Tween 80 as surfactant and PEG 400 as cosurfactant by the microemulsion method. In vitro drug release study of Valsartan nanodispersion as well as lyophilized VSLNs was performed and was found to be faster as compared to Valsartan nanodispersion. Ex-vivo drug release study was also performed for Valsartan nanodispersion and plain drug and drug release was found to be sustained than plain drug within 12 h. Stability study was conducted for six months. Based on all the results, it is concluded that SLNs prepared by microemulsification show promise for improving the oral bioavailability of Valsartan.[59]

B.Parmer et al developed characterised and in vivo ,ex vivo evaluated valsartan loaded SLNs using glyceryl behenate as the lipidand poloxamer 407(Pluronic F127) as the surfactant by the solvent injection method. Valsartan(class II) have bioavailability from 10-35% and extensive first pass metabolism.Based on the result ,it is concluded that SLns show promising for improving the oral bioavailability of valsartan.[99]

Nimodipine (NMD) is highly lipophilic antihypertensive drug having (logP 3.41) and 13% oral bioavailability. Nimodipine loaded solid lipid nanoparticles (NMD-SLNs) were prepared. Chalikwar SS et al. prepared NMD-SLNs with palmitic acid (PA), poloxamer 188 and soya lecithin as a lipid, surfactant and co-surfactant respectively using high pressure homogeniser. High EE and cumulative drug release in 10 h were noticed. The pharmacokinetic study of optimised SLNs conducted in male Albino Wistar rats showed 2.08-fold increase in relative bioavailability than that of NMD solution, when administered orally. Accelerated stability studies showed that there was no significant change for the period of three months. Due to enhanced bioavailability, these NMD-SLNs are considered to be promising vehicles for oral delivery.[62]

Qiang Fu[a] et al. developed nimodipine (NMD) nanocrystals with different sizes for oral administration and to investigate the relationship between dissolution and pharmacokinetics for NMD nanocrystals and Nimotop. NMD nanocrystals were prepared by combination of

microprecipitation and high pressure homogenization and were further lyophilized. The aqueous solubility was significantly improved and displayed a size-dependent manner. The nanocrystals exhibited lower dissolution patterns than Nimotop under non-sink condition, but bioavailability of the two nanocrystals was equivalent, about 2.6-fold higher than Nimotop. In conclusion, oral nanocrystal drug delivery system was a promising strategy in improving the oral bioavailability of poorly soluble or insoluble drugs.[64]

Atenolol is an antihypertensive agent used in the treatment of hypertension having moderate half-life of 6-7 hours thus it is a good candidate for the formulation of sustained release dosage forms[66]. Administration of conventional tablets of Atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting in manifestation of side effects or reduction in drug concentration at the receptor site. K.Sabarikumar et al. formulate the Atenolol loaded into chitosan nanoparticles by ionic gelation technique. The results were conclude that the formulation sustaining the release of drug for over 24 hours and can be considered as best alternate to sustained release tablets for the treatment of hypertention and can be best used with minimal or without any major side effects associated with sustained release tablets.[58]

Amar Singh et al. prepared atenolol loaded chitosan nanoparticles by ionic gelation of chitosan with tripolyphosphate anions. The in vitro release behavior from all the drug loaded batches were found to follow zero order and provided sustained release over a period of 24 hr. No appreciable difference was observed in the extent of degradation of product during 60 days in which nanoparticles were stored at various temperatures. The developed formulation overcomes and could possibility be advantageous in terms of sustained release dosage forms of atenolol[66]

Nifedipine was chosen as a model drug, Ping Li et al. prepared chitosan-alginate (cs/ALG) nanoparticles by ionotropic pre-gelation of an alginate core followed by chitosan polyelectrolyte complexation. Nifedipine released from chitosan-alginate nanoparticles was sustained for 24hours. This suggests that the release of nifedipine from nanoparticles was pH-responsive. Quick release occurred in simulated intestinal fluid (SIF, pH6.8) and phosphate buffer solution (pH7.4), while the release was slow in simulated gastric fluid (SGF, pH1.5). The release profile was characterized by an initial burst effect in three media, followed by a continuous and controlled release phase, the drug release mechanism from polymer was due

to Fickian diffusion. In conclusion, this new nanosystem also offers an interesting potential for the delivery of hydrophobic compounds.

Losartan nanoparticulate drug delivery system which prevents the high first pass metabolism of the drug and also provides sustained release reduced dosing frequency to effective management of Hypertension was developed by Ajay Verma et al.The Entrapment Efficiency of optimized formulation was found to be high.The In-vitro release study shows it maintains a sustained releases for 48 hours.No major changes in the content of drug was observed at the end of 3 months during Stability study. So data of stability studies revealed that formulation will be stable for longer period of time[67]

Felodipine is a poorly water soluble antihypertensive drug. To increase the dissolution rate of drug and to improve its oral bioavailability , Bhanu P. Sahu et al formulated and evaluated nanosuspension of felodipine prepared by nanoprecipitation alone and in combination with ultrasonnication method using ethanol as solvent and water as antisolvent. The dissolution of prepared felodipine nanoparticles markedly increased as compared to the original drug.It may be concluded that the nanoprecipitation with ultrasonnication have potential to formulate homogenous nanosuspensions with uniform-sized stable nanoparticles of felodipine. The prepared nanosuspension showed enhanced dissolution which may lead to enhanced oral bioavailability of felodipine.[93]

Diltiazem has an absolute bioavailability of 30-40% and its biological half life is 4-6 h. The main site of absorption is proximal small intestine. By increase gastro intestine retention time and mucoadhesion on gastric mucosa, Vaibhav shukla et al prepared and evaluvated mucoadhesive nanoparticles results in enhanced bioavailability.[100]

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