Novel Nanocarrier Approaches for Controlled Delivery of Carvedilol

[1]Ankit, [2]Munish

[12]BDM College of Pharmacy, Jhajjar, Haryana 124106

***Abstract*—Carvedilol is a broad-spectrum, non-selective β-adrenergic and α-adrenergic receptor antagonist is one of the most commonly prescribed drug for hypertension, ischemic heart disease, and heart failure. In clinical practice, carvedilol's effectiveness is significantly limited by BCS Class II characteristics: pH-dependent low aqueous solubility, poor aqueous solubility and low precipitation, large first-pass hepatic metabolism mediated through CYP2D6/ CYP3A4 isoenzymes and rapid clearance (t1/2= 6h). These shortcomings compromise its oral bioavailability to (25%-35%) and demand multi-dose-a-day administration. Nanotechnology-based drug delivery systems, in a broader range which included Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), Polymeric Nanoparticles (PLGA and chitosan-coated PLGA), Self-Nanoemulsifying Systems (SNEDDS) and Deformable Vesicular platforms (Ethosomes and Transfersomes) to enhance the rate of dissolution, preserve pre-systemic degradation, promote enteric lymphatic transport, and allow non-invasive transdermal, intranasal and ocular delivery, have become promising alternatives. A deep and critical review of carvedilol biopharmaceutics, novel architectures of nanocarriers in combination with it, comparative pharmacokinetics and pharmacodynamics of various platforms and industrial scale-up, approaches and new regulatory guidelines are presented.**

***Index Terms*—Carvedilol, Nanocarriers, Bioavailability, Controlled Release**

I. Introduction and Biopharmaceutical Challenges of Carvedilol

Carvedilol, namely, chemically

$(\pm) - 1 - (carbazol - 4 - yloxy) - 3 - [[2 - (o - methoxyphenoxy)ethyl]amino] - 2 - propanol,$

is a non-selective β-adrenergic receptor antagonist coupled with an α-adrenergic blocking property [1] . Therapeutically applied in controlling mild-to-severe hypertension, ischemic heart disease and chronic heart failure, carvedilol could produce significant cardioprotective effects through antagonization of the sympathetic nervous system, a decrease of peripheral vascular resistance and unique antioxidative activity[2] . Currently widely used clinically, the therapeutic application of conventional carvedilol formulation faces with severely limitations because of its poor biopharmaceutical and pharmacokinetic properties.

According to the BCS class (Biopharmaceutical Classification system), carvedilol is a Class II drug (high permeability but poor aqueous solubility). Molecular weight of carvingol is 406.5g/mol, and its octanol-water partition coefficient (log P ~3.8-4.0) is relatively high, resulting in good lipophilicity and poor aqueous solubility and high pH dependence as demonstrated by high aqueous solubility within the acidic range (pH<2.0) and a nearly insoluble free form at intestinal environment pH (pH 6.8 -7.4)[3,4].

The main biopharmaceutical limit to carvedilol occurs due to a mismatch between the drug's intestinal absorption rate and its systemic bioavailability. When given orally, the drug absorption in the gastrointestinal tract is fast; ~80% is rapidly absorbed, but it goes through first-pass hepatic metabolism which is rapid and extensive (CYP P450 isoenzymes CYP2D6 and 3A4) [5]. Therefore, the absolute bioavailability is constrained to a narrow range, 25%-35%. In addition, the terminal half-life t1/2 is small, ~6 hours. This necessitates giving carvedilol several times per day to maintain therapeutic concentrations in plasma. Chronic diseases that require long-term medication therapy lead to variable plasma drug concentrations (especially with repeat doses), the trough concentrations were too low and peak concentrations could cause side effects, e.g., postural hypotension and bradycardia, in chronic treatment patients. This led to poor patient compliance [6]. To combat these anatomico-biochemical-physiological drawbacks, nanoparticle-based drug delivery systems have become a revolutionary tool in dealing with this issue. Formulation of carvedilol in the manufactured sub-micron nanocarriers- Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), Polymeric Nanoparticles (PNPs), Self-Nanoemulsifying Systems (SNESs), Deformable Vesicles and Nanosuspensions,- deals with the basic problem in poor oral bioavailability, in terms of improved saturation solubility, enhanced dissolution rate and protects the drug core from enzymatic degradation and avoids hepatic first pass effect by intestinal-lymphatic routes, also suggests alternate non-invasive routes- transdermal, intranasal, ocular.

II. Lipid-Based Nanocarrier Systems

Lipid-based nanocarriers are some of the most promising platforms in clinical use for entrapping and releasing hydrophobic compounds such as Carvedilol in a controlled fashion. Lipid-based nanocarriers are composed of biocompatible, biodegradable and Generally recognized as safe (GRAS) materials. Structures constructed from lipids mimic endogenous nutritional lipids; therefore, they may efficiently permeate and be processed by the intestinal tract without inherent toxicity [7,8].

Solid Lipid Nanoparticles (SLNs) are first-generation sub-micron colloidal carrier systems having droplet size in the range of 50 to 1000 nm, prepared using solid lipids stabilized by a layer of emulsifier in an aqueous medium. During solidification of melt lipids, oil drugs and lipids remain in solid form both at room temperature and body temperature of a human [9]. Examples of Solid lipids applied in carvedilol-loaded SLNs are long-chain fatty acids (stearic acid), mono-, di- or triglycerides (glyceryl monostearate, Compritol 888ATO), and synthetic waxes (cetyl palmitate). The principal mechanism underlying drug delivery by SLNs has relied on physicochemical entrapment of hydrophobic drugs inside solid crystalline lipid matrix, which protects carvedilol against inherent chemical degradation activities in gastric juices and intestinal hydrolytic processes in vivo after oral administration. Besides that, it also facilitates transmucosal transport and delivery by enhancing M-cell transmucosal transfer across the enterocytes, stimulating de novo chylomicron production in enterocytes so that a lymphatic transport pathway may occur into the thoracic duct and thus lead to an effective bypassing of liver CYP3A4 and CYP2D6 [10,11].

In contrast, there are inherent thermodynamic limitations with conventional SLN's. Post-manufacturing, for instance, using high-pressure homogenisation, lipid matrices are formed as high-energy metastable polymorphic forms i.e. α and β modifications [12]. On storage at ambient conditions, these high-energy lattices undergo spontaneous phase transitions to produce a thermodynamically stable, highly ordered, densely packed β-polymorphic crystal lattice. This arrangement reduces the number of lattice defects, hence low drug loading and hence loss of carvedilol through leaching from the solid matrix over the shelf life of SLNs [13].

A means by which limitations of lattice rigidity and drug leaching associated with SLNs can be overcome was the formulation of the second generation of Nanostructured lipid carriers (NLCs). A mixture of solid and liquid lipids are blended together at room temperature, at a weight ratio typically in the range of 70:30 to 99:1. As solid lipids are mixed with oils (liquid lipids)eg, oleic acid, Labrasol or Capryol 90, such mixing leads to a considerable spatial disorder in the lattice structure [14]. While SLN cores are created as relatively rigid, highly ordered lipid lattices that can transform to a dense crystal lattice, thus losing its drug payload over time, NLC cores are formed as spatially disordered liquid-disrupted lipids. The incorporation of spatially non-compatible liquid lipids results in a highly defective amorphous lipid matrix that exhibits expanded distances between the fatty acid hydrocarbon chains [15].

Several physical and biological advantages of the structural anomaly in the carvedilol-loaded formulation were observed. As indicated earlier, Carvedilol is highly soluble in liquid lipids like oleic acid. The liquid nanodomain lipid matrix hosted higher concentrations of carvedilol thus exhibiting entrapment efficiencies in the range of 85.1–95.6 %. The spatially disordered core, as it did not attain perfect crystallization in storage, maintained stability by preventing the phase transition and thus, avoiding early leakage of the drug[16].

Carvedilol-loaded NLC generally showed a biphasic release rate. The first burst release of the drug is due to high solubility and its dissociation in the shell made of outer liquid-lipid domains, and the second sustained release due to diffused mechanism of release through the inner solid core. Another benefit was inhibiting intestinal P-glycoprotein (P-gp) efflux pumps and localized CYP3A4 metabolic activity as these drugs can inhibit the drug by utilising liquid lipids like oleic acid and non-ionic surfactants like Poloxamer 188 or Cremophor EL and increase bioavailability [17,18]. Another lipid system that is important is Self-Nanoemulsifying Drug Delivery Systems (SNEDDS). SNEDDS is a blend of oils, solid or liquid surfactants and either co-surfactants and/or co-solvents that are made into an isotropic mixture. The anhydrous formulation will spontaneously undergo self-emulsification to an O/W nanoemulsion having a droplet size less than 100 nm once administration of oral dosage form takes place and gentle mixing occurs due to the mechanical stress of GIT motility [19].

SNEDDS drug delivery system can abolish dissolution, which is the slowest step of diffusion barrier and the rate-limiting barrier for drug absorption of BCS class II drug. By allowing drug in solubilized state within

lipid droplet, high concentration gradients are maintained. The larger surface area of the droplet allows higher interaction of the drug molecules with GIT lipases, which facilitate faster enzymatic degradation and development of mixed micelles by the endogenous bile salts, followed by absorption by enterocytes through transcellular and para-enterocylic pathway [20].

III. Polymeric and Hybrid Nanoparticle Technologies

Polymeric nanocarriers are amenable for structural flexibility, synthetic control over degradation kinetics of polymers, and versatility on surface modification. PLGA is FDA-approved, and it is a biodegradable copolymer that hydrolyses in the body to give endogenous metabolic products, lactic acid and glycolic acid. Entrapment of carvedilol is typically achieved through a nanoprecipitation and double-/single-emulsification solvent evaporation method. Drug release profiles and degradation kinetics for carvedilol-loaded PLGA nanoparticles heavily depend on the Mw and lactide-to-glycolide monomer ratio of the polymer[21].

Low Mw PLGA (7,000 to 17,000 Da) with shorter polymer chains and a higher number of hydrophilic end-terminal carboxylic groups give faster rates of water hydration, rapid erosion of matrices, quick diffusion rates and fast drug release. Large particles and higher rigidity, resulting in slow drug release rate for many days to weeks, come from PLGA with 50,000- 190,000 Da [22]. Strict sink conditions (at least three to ten times higher volume compared to volume saturation) must be maintained when performing in vitro testing of hydrophobic drug release in PLGA matrix systems. Accelerated dissolution testing methods that involve using USP Apparatus 4 (flow-through cell) along with non-ionic surfactants such as SDS or analogues of Poloxamer at pH 6.8 in order to get the Level A in vitro in vivo Correlation [23].

Uncoated PLGA nanoparticles have a negative surface charge and their mucosal interaction is non-specific and passive. Upon functionalizing the surface of PLGA nanoparticles with chitosan – a cationic and linear polysaccharide formed from deacetylation of chitin, the nanocarrier's behaviour in vivo is drastically changed. In contrast to the surface charge on uncoated PLGA NPs that fall between -15 to -25 mV, chitosan-coated PLGA NPs had a strikingly positive surface charge in a range of +20 to +45mV. The positive surface charge on the CS-covered PLGA NPs leads to the following significant biological functions: Cationic amino groups (-NH3+) on chitosan can be electrically coupled to negative sialic acid and sulfonic acid in mucosal mucin glycoprotein, which leads to the establishment of effective electrostatic mucoadhesion and prolonged residence of the nanocarrier in GI tract and epithelial wall by slowing down the peristaltic transit [24,25].

In addition, chitosan actively binds to tight junction-related proteins, including ZO-1 and occludin, thereby inducing their relocalisation, which enlarges the paracellular gaps for both free and encapsulated carvedilol to enter the intestine via paracellular pathways. Positively charged CS-covered PLGA NPs effectively bind to the negatively charged mucosal cell membrane, thus mediating the internalisation of the nanocarrier into the cells via clathrin-and caveolae-mediated endocytosis [26].

The inherent structural stability and control over drug release profile provided by the polymer matrix, combined with the excellent biocompatibility and the negligible interfacial tension of the lipid or phospholipids, make PLNs an interesting tool for drug delivery. A typical PLN is composed of an inner hydrophobic polymer core, such as PLGA, an outer monolayer of lipid or phospholipid such as lecithin or phosphatidylcholine as a molecular veil that reduces water entry and prevents clusterisation of NPs, and a hydrophilic, sterically stabilize outer shell such as PEG or surfactants. Added biomimetic modifications based on bile acids were made to enhance transcellular transportation. The conjugation of sodium taurocholate or its derivatives with the lipid shell of NPs helps the uptake of NPs via active transport with the expressed apical sodium-dependent bile acid transporter that is abundant in the terminal ileum and the delivery via receptor-mediated transcellular shuttling across enterocytes. It also has a significant increasing effect on oral absorption and systemic exposure [27].

Table 1: Comparative Pharmacokinetic Metrics Across Nanocarrier Delivery Routes

Formulation oute	**Animal Model & Dose**	**Peak Concentration (Cmax)**	**AUC & Bioavailability**	**Half-life**	**echanism**
S-SNEDDS with MSN (Oral)	Sprague Dawley Rats (40 mg/kg)	Significant peak plasma concentration elevation	Marked AUC increase vs. pure drug	Extended GI residence and release	Rapid supersaturation and direct intestinal lymphatic uptake
Cationic Bioadhesive SLNs (Oral)	New Zealand White Rabbits	Enhanced peak concentration	> 2-fold oral bioavailability enhancement	Mean residence time (MRT) extended to 23 h	Extended intestinal mucosa retention and transcellular M-cell transport
Intranasal SLNs (Nasal)	Rabbits	Rapid initial Cmax attainment	Absolute bioavailability = 50.63% (vs. 24.11% oral)	Extended circulation duration	Direct trans-nasal mucosal absorption bypassing hepatic first-pass loss
Optimized Carrier-free SNEDDS (Oral)	Wistar Rats	Cmax increased by 134.2% vs. pure drug	AUC increased by 85.2% vs. pure drug	Accelerated and sustained absorption profile	Intestinal lymphatic transport and P-gp efflux inhibition
Intranasal Transfersomes (Nasal)	Rabbits	High Cmax through vascularized nasal plexus	Absolute bioavailability = 63.4%	Prolonged therapeutic drug exposure	Deformable vesicle penetration through intercellular nasal epithelial channels

IV. Deformable Vesicular Platforms for Transdermal Delivery

A non-invasive alternative route for administration of the drug, carving, i.e., bypass of gastrointestinal degradation and bypassing hepatic first-pass metabolism totally with steady drug level into systemic circulation, transdermal delivery is feasible. However, the stratum corneum is a stratum corneum that the physiologist has constructed a strong tightly fitted layer of lipid which hinders the spontaneous permeation of lipophilic compounds (Log P > 3). Novel liquid crystalline carriers, namely novel deformable vesicles is designed for fluidity of and permeation of the stratum corneum barrier [28].

Ethosomes are non-invasive liquid crystalline vehicles made of phospholipids and water, with a notably high amount of short-chain alcohols and notably, the concentration of ethanol is between 20-40%v/v. During transdermal penetration of ethosomes, two collaborative phenomena occur: it fluidises the stratum corneum and high flexibility was developed within the ethosomes. Ethanol within the carriers fluidises the tightly spaced cell lipid membrane of the stratum corneum by intercalating in between the lipid alkyl chains, hence reducing the lipid phase transition temperature the stratum corneum and increasing fluidity.. This high concentration of ethanol was further dissolved into the phospholipid bilayer of ethosomes, which result in low rigidity of the liquid crystal nanovesicles and reduced surface area per molecule [29,30].

Soft and permeable vesicles will be facilitated to cross through the penetrated stratum corneum Lipid bilayer path by diffusion to a great deep epidermal tissue and be absorbed into the systemic capillaries. From a carvedilol ethosomes hydrogels formulation study of transdermal performance of carvedilol: 70% increment in absolute bioavailability compared with oral absorption, as high level of Jmax was achieved [31]. Transfersomes, also known as ultradeformable liposomes, are phospholipids that incorporate certain single-chain amphiphilic membrane-softening compounds called edge activators into their structure. Edge activators (e.g., non-ionic surfactants like Tween 80, Span 80 and Span 60 or bile salt as sodium deoxycholate) are mixed with phospholipids at optimal mass ratios (85:15-95:5 w/w), they integrate into the lipid bilayer and destabilise the planar packing arrangement of phospholipids, resulting in a depression of the main transition phase temperature of the lipid membrane. This makes the phospholipid bilayer become extraordinarily elastic and deformable [32].

Table 2: Anatomical and Physiological Barrier Bypass Mechanisms

Target	**Barrier Constraint to Carvedilol**	**Nanocarrier Platform Solution**	**Functional Excipient**	**echanism**
Gastric Acid & Enzymatic Milieu	Low gastric solubility, chemical instability, and burst release	Enteric/Polymer-Coated SLNs	N-carboxymethyl chitosan coat	Insulating coat resists gastric acid; dissolves at intestinal pH to enable controlled release
Epithelial Efflux & Intestinal Metabolism	P-gp efflux pump expulsion and enterocyte	Liquid / Solid SNEDDS	Capmul MCM, Peceol, Tween 80, Labrasol	Lipid/surfactant components downregulate P-gp efflux pumps and

	CYP3A4 clearance			suppress local metabolic enzymes
Hepatic First-Pass Metabolism	Pre-systemic hepatic clearance restricting oral bioavailability to 25%	SLNs, NLCs, SNEDDS	Chylomicron-mimicking lipid core	Direct uptake into intestinal lymphatic vessels via Peyer's patch M-cells into the thoracic duct
Stratum Corneum Lipid Matrix	Tightly packed intercellular lipids restricting transdermal flux	Transdermal NLCs & Deformable Vesicles	Liquid lipids and membrane edge activators	Disruption and fluidization of stratum corneum lipids, enabling vesicle squeezing under osmotic gradient
Nasal Mucociliary Clearance	Rapid clearance (15-20 min) preventing nasal absorption	Bioadhesive Nasal Transfersomes & SLNs	Positively charged lipids/polymers and bile salts	Electrostatic binding to negatively charged mucosal mucin, extending contact time for paracellular flux

Under non-occlusive conditions, there is a hydration gradient existing from the stratum corneum (15% water content) to the epidermis (75% water content) of skin. Such a transepidermal osmotic gradient provides the driving force to the deformable transferredosomes for high transdermal diffusion. Carvedilol transfersomes with an extraordinarily high deformability manage to negotiate the intercellular channel in the stratum corneum even smaller than their freely existing sizes, penetrating into pores of <20 to 30nm while keeping the transfer some sizes of 100 to 200nm and never rupturing [33] .

V. Alternative Non-Invasive Routes: Intranasal and Ocular Delivery

Besides general systemic cardiovascular use in various pathological conditions, repurposing of carvedilol to alternative routes is beneficial to broadening its therapeutic potential from general use into specific local target areas such as managing intraocular pressure in glaucomatous patients [34]. The nasal cavity has an ideal environment to form a highly vascular absorptive region of circa 150 cm^2 covered by microvilli, which enables rapid systemic absorption, avoiding first pass metabolism by the liver and enzymatic degradation by stomach enzymes. Due to rapid mucociliary clearance, which ensures elimination of nasal formulations within 15–20 min; carvedilol is formulated as a nanosuspension entrapped within an in situ gel-gelling matrix [35,36].

Systems using ion-activated polymers such as 0.5% w/v gellan gum change from a low-viscosity liquid spray into a tight, bioadhesive gel formation by the action of cationic ions present in nasal secretions like Na + , K + and Ca 2 +[37]. The tiny particle size of the nanosuspension also promotes solubility and rapid transcellular diffusion; however, the gel network prolongs local contact time. The in vivo studies conducted

using animals demonstrate the bioavailability of 69.38 % from intranasal carvedilol in situ gel-gelling spray, where compared to oral carotid lol 25.96% bioavailability and a mean residence time prolonged to 8.65 hours[38,39] .

The topic application of carvedilol on the eye for lowering intraocular pressure by acting on ocular beta 1,2-adrenoceptor on ciliary body and inhibiting aqueous secretion. Conventional eye drops result in poor ocular bioavailability (<1%-5%) because of loss through nasolacrimal drainage and blinking, tight corneal epithelial barrier. Advanced ocular nanocarriers such as cationic Leciplex systems, spanlastics and thermo-responsive in situ gels offer unprecedented prospects in the ocular topical delivery of carvedilol [40].

VI. Critical Evaluation of Formulation Parameters, Pharmacokinetics, and Performance Comparison

Bioefficiency, physical stability, and pharmacokinetic profile of carvedilol nanocarriers directly correlate to its physicochemical properties, core properties and the route of administration selected [41,42,43]. The following are few tabular representation which discusses core formulation parameters, particle characterisation and compare pharmacokinetic characteristics of major carvedilol nanocarriers:

Nanocarrier Platform	Primary Excipient Composition	Mean Particle Size (nm)	Zeta Potential (mV)	Entrapment Efficiency (EE%)	Primary Bioavailability Enhancement Mechanism	Target Route
Solid Lipid Nanoparticles (SLNs)	Stearic acid, Glyceryl monostearate, Cetyl palmitate, Poloxamer 188	100 – 300	−18 to −30	65% – 85%	• Intestinal lymphatic transport via M-cells; protection from gastric acid/enzymes	Oral
Nanostructured Lipid Carriers (NLCs)	Compritol 888 ATO, Oleic acid, Labrasol, Span 60	120 – 200	−20 to −40	85% – 96%	• Amorphous core prevents drug expulsion; CYP3A4/P-gp inhibition by lipids/surfactants	Oral, Topical
PLGA Nanoparticles	Poly(lactic-co-glycolic acid) (M_w 7 – 190 kDa), PVA	175 – 350	−15 to −25	70% – 90%	• Controlled matrix erosion; extended plasma half-life; bypasses dissolution rate-limit	Oral, Parenteral
Chitosan-Coated PLGA (CS-PLGA)	PLGA core, Chitosan polymer shell, TPP	200 – 450	+20 to +45	75% – 92%	• Electrostatic mucoadhesion; reversible tight junction opening for paracellular flux	Oral, Mucosal
Ethosomes	Phosphatidylcholine, Ethanol (20 – 40%), Water	150 – 300	−10 to −25	70% – 88%	• SC lipid interdigitation (ΔT_m reduction); enhanced membrane fluidization	Transdermal
Transfersomes	Phospholipids, Edge Activators (Sodium deoxycholate, Tween 80)	120 – 250	−15 to −35	65% – 85%	• Ultradeformability driven by transepidermal osmotic hydration gradient	Transdermal
Nanosuspension In Situ Gel	Carvedilol nanocrystals, Ion-activated Gellan gum (0.5%)	200 – 500	Uncharged / Neutral	N/A (100% drug core)	• Prolonged nasal residence time; high mucosal permeability; direct systemic entry	Intranasal
Spanlastic In Situ Gel	Span 60, Brij 97, Poloxamer 407/188 thermo-gel	100 – 220	−15 to −28	80% – 93%	• Precorneal gel retention; enhanced transcorneal permeability (P_{app})	Ocular

Figure 1: Formulation parameters, particle characterisation and compare pharmacokinetic characteristics of major carvedilol nanocarriers

The encapsulation of carvedilol in nanocarrier designs produced notable changes in kinetic parameters such as Cmax, AUC0-t, and Frel along with prolonged beneficial pharmacodynamics, which are summarised in the comparison table that follows [44,45]:

Formulation Strategy	Route of Administration	Peak Concentration (C_{max}) Impact	Exposure (AUC) & Relative Bioavailability (F_{rel})	Pharmacodynamic Outcomes	Primary Mechanism
Carvedilol NLCs	Oral	2.1 – 2.8-fold increase vs. raw drug	3.45-fold increase (F_{rel} = 345%) vs. drug dispersion	Prolonged blood pressure reduction in hypertensive rat models	Lymphatic uptake via thoracic duct; reduced CYP3A4 metabolism
CS-PLGA Nanoparticles	Oral	3.5-fold increase vs. pure suspension	3.5 to 8.0-fold increase in total systemic/ brain AUC	Sustained normotensive response over 24 – 48 h [cite: 17, 23]	Paracellular transport & mucoadhesive retention in GI tract
Ethosomal Hydrogel	Transdermal	Maintained steady therapeutic levels (C_{ss})	72% bioequivalence enhancement vs. oral tablets	Complete avoidance of peak-valley plasma fluctuations	SC lipid perturbation; total avoidance of hepatic first-pass loss
In Situ Nasal Spray	Intranasal	Rapid T_{max} (< 15 min); elevated C_{max} [cite: 6]	Absolute F = 69.38% vs. 25.96% oral route	Rapid cardiovascular systemic response	Nasal vascular plexus absorption; high MRT (8.65 h)
Ocular Leciplex	Topical Ocular	Local aqueous humor C_{max} increased > 2-fold [cite: 7]	2-fold hike in aqueous humor AUC_{0-6h} [cite: 7]	IOP normalized within 30 min; effect sustained over 24 h [cite: 7]	Positively charged mucin binding; extended precorneal contact

Figure 2: Formulation Strategies and their PK-PD advances

VII. Strategic Conclusions and Future Outlook

The evolution of carvedilol from a traditional oral, low-bioavailable beta-blocker into sophisticated nanocarriers demonstrates strategies to circumvent intrinsic biopharmaceutical barriers for high BCS Class II, extensive first-pass metabolism drug [46,47]. The high entrapment, long term stability Nanostructured Lipid Carriers via preventing lipid crystallization of core and enhanced oral lymphatic absorption providing 3.45-fold enhancement over conventional suspensions; surface modified, chitosan coated, PLGA nanoparticles with cationic electrostatic interactions provide high mucosal retainability and transient aperture openings of epithelial tight junctions, for both transcellular and trans-cellular absorption; adaptable vesicles e.g., ethosomes and transfersomes render the cellular lipid bilayer gel like structure for better transdermal absorption completely avoid GI and hepatic metabolism for sustained systematic level; while some targeted non-invasive systems like intranasal nanosuspension gel, ocular spanlastic, or Leciplex formulations achieve delivery of carvedilol across the systemic circulation or intraocular tissues for long-term IOP control in the management of glaucoma. Future endeavours are driven toward clinical translation, the crucial and obligatory tasks in terms of scaling up the manufacturing process, possibly by a microfluidic continuous system; stabilizing delivery forms by optimising the lyophilized states by controlling lyophilisation cycles; and establishing discriminating in vitro-in vivo correlation of Level A; finally, to conduct clinical studies in human beings with solid evidence of their pharmacokinetics, safety and efficiency.

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