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Section C: Drug Design, Delivery & Targeting

Application of Several Nano Carriers to Improve the Solubility and the Bioavailability of Carvedilol

Doaa Mohamed[1]*, Yasmin Abo-zeid[1,2], Wedad Sakran[1]

[1]*Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Helwan University, Cairo 11795, Egypt.*
[2]*Helwan Nanotechnology Center, Helwan University, Cairo 11792, Egypt.*

***Corresponding author:** Doaa Mohamed, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Helwan University, Cairo 11795, Egypt. Tel. +20237831967*
Email address: doaa.mohamed@pharm.helwan.edu.eg

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ABSTRACT

Objectives: This review article highlights the problem of an example of a drug that is used to control Hypertension (HTN). HTN: that is one of eight mortalities worldwide. Approximately one-third of the world's adult population suffers from hypertension (31.1 %, or 1.39 billion people). Hypertension prevalence varies. The World health organization (WHO) Region of Americans has the lowest prevalence of hypertension (18%) and the WHO African Region has the highest prevalence of hypertension (27%) overall. In Egypt, according to WHO, Egypt estimated the number of adult people suffering from hypertension in 2017 was (29.2%) and in 2020, the total percentage of death from hypertension (was 3.93%) of total death. Hypertension is described as a disturbance in the circulatory system accompanied by a sustained increase in systolic and diastolic blood pressure to a level that is likely to have negative effects. The most popular hypertension types in people are first and second hypertension which need to adjust the lifestyle and take medications when these types are not controlled. Several types of medications can be used to control HTN such as Diuretics, Angiotensin-converting enzymes inhibitors (ACEIs), Angiotensin receptor blockers (ARBs) calcium channel blockers (CCBs), and beta-blockers (BBs). All of them can be used individually or in combination with each other to control blood pressure. Beta-blockers (BBs) are one of these drugs that are used for HTN, classified as (first, second, and third-generation). carvedilol (CAR) is one of the most popular drugs used in the third generation. It has additional advantages rather than first and second-generation that α_1 –adrenergic receptors antagonist. CAR belongs to BBs but has some drawbacks such as low solubility, low bioavailability, and hepatic metabolism that makes it need to be taken several times a day. **Methods:** This review contains several articles on CAR nanocarriers application between 2014 to 2022, reviewed by many accepted scientific journals. **Results:** by application of several approaches of a nanocarrier delivery systems that were used to overcome CAR drawbacks, nano drug delivery can encapsulate CAR lipophilic drug in their core, deliver it to the site of action, sustain CAR release, and enhance the solubility and the bioavailability of this lipophilic drug. **Conclusion:** This review summarized all recent works that attempt to improve the solubility and the bioavailability of CAR. after the application of several nanocarriers approaches to overcome the drawbacks of CAR, each of these approaches can increase the solubility and the bioavailability of CAR but all of these nanocarriers need many challenges to be applied to be applicable in the market.

Keywords: *Carvedilol, Nanomedicine, Hypertension, Bioavailability.*

INTRODUCTION

Hypertension (HTN): also known as High blood pressure (HBP), is a serious risk factor for developing cardiovascular disease in the future [1]. It is defined as a circulatory disturbance that is followed by a persistent rise in systolic and diastolic blood pressure to a level that is likely to harm people's quality of life. Whatever the cause, narrowed arteries increase blood flow resistance by making the heart work harder to push blood through tight vascular beds. Hypertension is a worldwide problem due to its negative impact on the lifestyle of people. the high morbidity caused by hypertension could be reflected by the number of people affected by this negative impact as heart attack, stroke, blindness, atrial fibrillation, dementia, and kidney failure[2],[3].

For instance, there are various types of hypertension; (primary, secondary, resistant, malignant, and isolated hypertension). (a) Primary or called essential HTN: the cause of it is not known but represents the majority of people, the cause may be due to age, salt intake, eating, stress, alcohol, and smoking a kind of need to change their lifestyle. (b) Secondary HTN: estimated 30 % of those ages 18 to 40 years old with hypertension have secondary hypertension, with identifiable causes including (thyroid gland abnormality, adrenal gland disease, narrowing in blood supply to the kidney, constriction in the aorta, and hormones abnormality). (C) resistant HTN: estimated 10% of people have this type which may be due to a secondary type and cause to people uncontrolled high blood pressure even using multiple medications. (d) Malignant HTN: this emergency case type (HTN is above 180/120 mmHg) may make damage to organs and need emergency conditions. (e) Isolated systolic HTN: this type with systolic blood pressure above 140 mmHg and diastolic under 90 mmHg, its prevalence according to a United Kingdom survey in 2016, 2% to 8% of younger persons have isolated systolic hypertension. That cause may be due to loss of the elasticity of the arteries. However, the first and second types are the most popular HTN types [2],[4].

According to the World health organization(WHO), hypertension is one of eight mortalities worldwide [4]. In recent decades, hypertension has increased in prevalence throughout the world. By the latest estimation, approximately one-third of the world's adult population suffers from hypertension (31.1 %, or 1.39 billion people), with two-thirds of those residing in low- and middle-income countries (LMICs)[4]. In 2021, Depending on the country and area, hypertension prevalence varies. The WHO Region of Americans has the lowest prevalence of hypertension (18%) and the WHO African Region has the highest prevalence of hypertension (27%) overall. According to statistics from WHO, Adults with hypertension climbed from 594 million in 1975 to 1.13 billion in 2015, with low- and middle-income countries (LMICs) seeing the majority of the rise. This increase is mostly caused by an increase in risk factors for hypertension in those groups [5].

Egypt, which is classified as an LMIC by the World Bank, has cardiovascular disease (CVD). The death rate of 40% each year. Egypt, being the most populated country in the Middle East and North Africa region, accounted for all CVD deaths in regions [6],[5]. And according to WHO, Egypt estimated adult people suffering from hypertension in 2017 was (29.2%) and in 2020, the total percentage of death from hypertension (was 3.93%) of total death.

Maintaining a healthy weight, cutting back on salt in the diet, managing stress, quitting smoking, and regular exercise can all help to avoid the need for drugs. However, if HTN is still uncontrolled, medication use should be taken into consideration [7].

Patients may need one class of medication or several classes according to WHO guidelines and strategies to control HTN [8]. Selection of pharmacological treatment of hypertension based on several parameters such as age, pregnancy, comorbidity, ethnicity, and specific regimen treatment. There are many antihypertensive drugs with different mechanisms of action used to manage HBP worldwide and they involve the following classes ;(a) Diuretics: that remove excess water and sodium from the body and are classified (thiazide, loop, and potassium-sparing) [9]. (b) Angiotensin-converting enzyme inhibitors (ACEIs): this help in the relaxing of blood vessels by preventing the formation of angiotensin II that narrows the blood vessels [10]. (c) Angiotensin receptor blockers (ARBs): block AT1 receptors located in the kidney, blood vessels, and heart to lower blood pressure. (d) Calcium channel blockers (CCBs): block calcium to enter the cells of arteries and the heart to prevent the contraction effect of the calcium in the heart. and (e) beta-blockers(BBs): act on $ß_1$-and $ß_2$-receptors [11]. in some case-control of hypertension by using a combination of several classes is more effective than monotherapy as a (a) combination of atenolol with amlodipine was significantly more effective in lowering systolic blood pressure and diastolic blood pressure than monotherapy [12], (b) a combination of carvedilol with Lisinopril improved endothelial function in the obese hypertensive patient compared to hydrochlorothiazide and Lisinopril [13]. As mentioned above, ß-blockers used as mono or in combination therapy that act on ß1- adrenergic receptors located in the heart and kidney and $ß_2$ – adrenergic receptors located in the lung- GIT- liver-uterus- smooth and skeletal muscles and ß3- located in fat cells [14].

ß-blockers classified into three classes: (a) first generation: Non-selective ß-blockers that act on $ß_1$-and

ß$_2$-receptors(Propranolol, Nadolol, Timolol, Pindolol, Timolol, Sotalol, Tertatolol, Pindolol, Carteolol, Oxprenolol, Alprenolol), (b) second generation:ß$_1$ -selective as (metoprolol, atenolol, bisoprolol, Esmolol, Acebutolol), (c) Third generation with additional vasodilating effect as (Carvedilol, Nebivolol, labetalol) [15].

As mentioned that un selectivity of first and second generations of BBs that antagonist the binding of epinephrine and norepinephrine on ß$_1$-and ß$_2$-receptors that produce by sympathetic nerves can make several side effects due to the mechanism of action such as bradycardia, Atrio Ventricular block, vasoconstriction also Bronchoconstriction can occur especially when BBs give to asthmatic patient [16].

The third generation can overcome these drawbacks by acting on blocking ß$_1$-and ß$_2$- and α_1-adrenergic antagonist receptors. It is also recognized that vasodilating ß-blockers have a favorable metabolic and tolerability profile compared with traditional blockers [17], [18].

One of the third generations that are applicable in the markets with several concentrations is carvedilol (CAR) found in the market as monotherapy or in combination with other classes to control HBP, it is lipophilic, act on ß1- and ß2 receptors(non-selective blockers) also has additional advantages of block norepinephrine binding to α_1 –adrenergic receptors, so control blood pressure by its mechanism[8], it reduce tachycardia through inhibition of beta-adrenoreceptors, has an action on α_1 –adrenergic receptors relaxes the smooth muscles in the vasculature, leading to reduced peripheral vascular resistance and an overall reduction in blood pressure[19],[20], indicated for the chronic therapy of heart failure with reduced ejection fraction (HFREF), reduction arterial BP, left ventricular dysfunction myocardial infarction (MI) in the clinically stable patient. On the other hand, CAR is completely absorbed from GIT. However, CAR has several drawbacks such as low aqueous solubility, and hepatic first-pass metabolism rendering its systemic bioavailability very low ranging from 25-35% [21,8].

Carvedilol (CAR) as mentioned above is lipophilic that belongs to the Biopharmaceutics classification system II (BCS II) drugs. BCS II drugs have low solubility and high permeability that need to be improved [22],[23]. Several approaches have been investigated to improve the drawbacks of CAR as its low solubility and low bioavailability like (a) solid dispersion technique, (b) hydrotropic technique by using (hydrotrope molecules that amphiphilic groups), (c) complexation and micronization (by decreasing the diameter of solid particles by milling or grinding). these approaches have shown improvement in therapeutic effect but up to limit due to some limitations such as patient compliance, under and over-medication, failure to achieve a steady state, slow onset of action, and lack of dose proportionality, etc. [22].

Nanotechnology has greatly impacted the field of pharmaceuticals and drug delivery. Nanomedicine is the branch of medicine that use particles sized from 1 to 1,000 nm for either therapeutic or diagnostic purposes[24,25,26]. Nanomedicine as a drug delivery system was used to target the drug to a specific site and consequently overcome drug accumulation at off-target tissues and consequently side effects associated with drug administration[27],[28]. This made nanomedicines able to overcome the limitations of conventional therapy [29],[30] such as high frequency of drug administration [31], improve the delivery of the hydrophilic drug into cells [32] improve the bioavailability of the poorly soluble drug, control/sustain drug release [33–35] Nanoparticles (NPs) have been previously applied to treat many diseases such as viral infections with promising results [25,36–38] and also showed good antibacterial activity against multidrug-resistant bacteria [37,39–41] wound healing [42,43], and inflammation [44], anticancer [45] aid crossing the blood-brain barrier [46,47] and has a potential to be used for diagnostic purposes [48]. Nanoparticles have the advantages of controlling particle size, and changing kinetics and could overcome the first-pass effect [49]. However, although the massive volume of research published regarding the application of nanomedicine for the treatment of different diseases and diagnostic purposes, the nanomedicines approved currently by the food and drug administration (FDA) or under clinical trials are very small [50]. A total of 45424 articles were identified in PubMed by searching for "nanomedicine" on June 17, 2022 (**Figure 1**), While only 51 nanomedicine products have been approved by the FDA and another 77 are at different stages of clinical trials and none of them are including nano-formulation for hypertension management [50], [51]. Formulated nanomedicine approved by the FDA is classified into(polymers, micelles, liposomes, anti-body drug conjugate, protein nanoparticles, organic nanoparticles, hydrophilic polymers, and nanocrystals), and 8 of 11 nanomedicine drugs approved by The European Medicines Agency (EMA) as first generation nanomedicine (liposomes, iron-containing formulations) and 48 nanomedicine under clinical trials in EU[52].

Many studies have investigated nanotechnology for antihypertensive drugs to improve drug efficacy and solubility. a total of 4009 articles were found in PubMed by searching "nanotechnology for antihypertensive drugs" on June 17, 2022 (**Figure 1**), However, a total of 85 articles were found in PubMed by searching for "Beta blockers nanotechnology" on June 17, 2022, also, 19 articles were found in PubMed by searching for

"nanotechnology for Carvedilol**"** on June 17, 2022 (**Figure 2**).

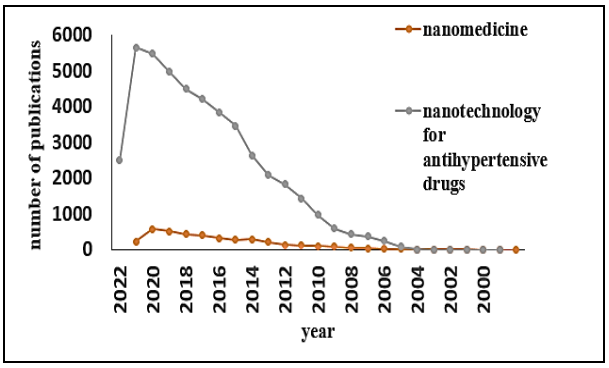

Figure 1. Data extracted from PubMed using the term"nanomedicine" and "nanotechnology for antihypertensive drugs".
Adapted from:
https://pubmed.ncbi.nlm.nih.gov/?term=nanomedicine
https://pubmed.ncbi.nlm.nih.gov/?term=nanotechnology+for+antihypertensive+drugs%E2%80%9D.

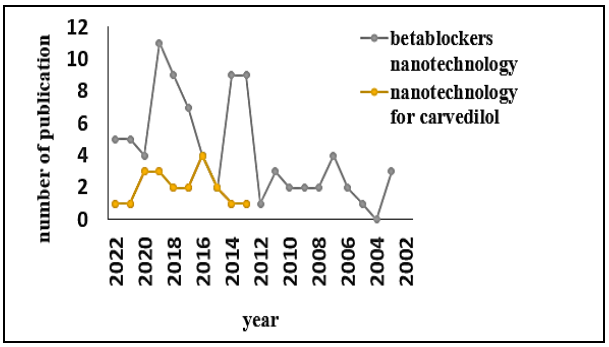

Figure 2. Data extracted from PubMed using the term"betablockers nanotechnology" and "nanotechnology for carvedilol".
Adapted from:
https://pubmed.ncbi.nlm.nih.gov/?term=betablockers+nanotechnology
https://pubmed.ncbi.nlm.nih.gov/?term=nanotechnology+for+carvedilol

MATERIALS AND METHODS

Search Criteria

Original articles and research papers published in Google Scholar, and PubMed Central on Carvedilol drug and nanocarrier applications then were collected and studied. The collected data were chosen when the keywords "Carvedilol, Nanomedicine, Hypertension, bioavailability" were written in the search engines.

RESULTS AND DISCUSSION

In this review, we focused on different strategies of nanotechnology applied to improve the solubility and bioavailability of CAR, in addition to discussing different challenges facing their clinical translation. Scientific literature reported CAR encapsulation into Self-emulsifying drug delivery systems (SEDDS), lipid nanoparticles, Polymeric micelles, Liposomes, Ethosome, Nano sponges, Nanofibers, and Niosomes as presented in (**Table1**). These nano-delivery systems are discussed below in detail.

1. Self-emulsifying drug delivery systems (SEDDS):

It is an isotropic mixture of drug compounds in a combination of oils, surfactants, solvents, and co-solvents/surfactants that produce O/W emulsions upon moderate stirring in an aqueous phase such as GIT fluid[53]. Generally, SEDDs are classified as: (a) self-emulsifying (SEDDs) with the droplet size range of (100-250nm) also known as self-micro emulsifying (SMEDDs), (b) self-nano emulsifying drug delivery system (SNEDDs) that droplet size range is smaller than 100 nm [54]. Poorly water-soluble pharmaceuticals can be more effectively formulated using SEDDs, which may also improve the drug's solubility, gut permeability, and GIT dissolution behavior [55]. SEDDs are prepared by the trial-error method, altering the ratio of the components or by the application of ternary phase diagram [52], but to develop and optimize SEDDs with desired drug release and pharmacokinetic parameters, formulations have recently been developed by two methods (hydrophilic-lipophilic balance; HLB coupled with response surface methodology; RSM) [56].

When developing SEDDs, a few security-related considerations should be taken into account. Because each lipid and surfactant may be able to create a complex reaction or interaction with the physiologic environment and because many oils or lipid components are susceptible to changing into toxic materials when dispersed into the nanoscale, this involved choosing the type and concentration of the lipids and surfactants that were used with high ratios to prepare SEDDs. To select the most secure lipids and surfactants to be utilized in the manufacturing of SEDDs, the united states FDA (US FDA) has published a list of safe materials [57].

Salimi and colleagues reported to increase the solubility and oral bioavailability of carvedilol, researchers are attempting to construct SEDDs combining components (oleic acid/labrafil/Labrafac) with poloxamer or hydroxypropyl methylcellulose (HPMC) as a polymer. The results demonstrated a correlation between particle size (P.S) and in vitro release after 24 hours for each type of polymer; however, HPMC size was (0.25 to 0.91 m) and in vitro

release was (74.26-91.11%) for HPMC polymer but in intestinal permeability test after 4 hrs was (69.75%) in poloxamer formula with small P.S 0.248µm, concluded that decreasing in P.S made an increase in the permeability of the formula through the rat intestine [58.] Singh and colleagues reported trying to prepare CAR SNEEDS with small particle sizes. First, use a pseudo-ternary phase diagram to determine CAR solubility. The results showed that all formulations had globule sizes between (46-475 nm) and that the optimum SNEDDS formula had emulsion droplets smaller than 100 nm by TEM. The in vitro release results also demonstrated a significant improvement in drug dissolution of the optimal SNEDDS formula, which nearly completed dissolution in 20 minutes as opposed to the marketed formula and pure drug suspension, respectively. An in situ intestinal perfusion investigation revealed that the optimal SNEDDS formula bioavailability percentage was 86% higher than that of the marketed formula (21%) [59]. From two applications we showed that using of SNEDDs was better than SEDDs, whereas. SNEDDs had nanosize that resulted in more perfusion of the formula so increasing intestinal permeability.

2. Lipid Nanoparticles:

It is a binary mix of lipid matrix as a hybrid carrier with a surfactant, it is prepared by different methods (high-pressure homogenization, solvent evaporation/evaporation technique, microemulsion formation technique, ultrasonic solvent emulsification technique). There are two types of lipid nanoparticles: solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)[60].

SLNs have several disadvantages due to their perfect crystalline structure, they have low drug efficiency and initial burst release but NLCs overcome these limitations of SLNs as NLCs have an imperfect crystal structure that provides more space for drug dissolution.

Generally, SLNs and NLCs for oral administration have the advantages of sustained release, high specific surface area, and higher saturation solubility, however, they have some disadvantages as Drug expulsion during the storage, polymorphic transition, limited loading capacity of hydrophilic drugs [61], [60].

Mishra and colleagues reported that one of the nanoparticle applications for the improvement of carvedilol oral bioavailability and solubility is nanostructured lipid carriers (NLCS) that promote the uptake of nanovesicles drug by payer´s batch or lymphatic tissues. To prepare stable NLC dispersion formula, using the micro-emulsion technique with probe sonication by adding a mix of lipids (stearic acid and oleic acid) with tween 80 as surfactant and PEG4000 as co-surfactant in aqueous media to form an emulsion that finally freeze-drying technique is used. By investigating the difference between (CAR-NLCs) and CAR suspension, the Result showed that NLC showed enhancement in oral bioavailability and solubility of the drug than suspension, as increased solubility of the drug in NLC formula made an increase in entrapment and loading of the drug (69.45-81.34 %) and (9.58-12.56 %), respectively. Also, in vitro release study compares the release from NLC selected formula versus suspension: the selected formula showed biphasic release firstly burst release at 23.42% after 2hrs then sustained release at 77.56% after 22 hrs., and suspension not affected the achievement of sustained release profile, EX-Vivo study by using diffusion cell (stomach mucosal surface) that cumulative amount in NLC was higher than the suspension, in vivo study to compare of both the oral bioavailability of NLC 3.95 fold increased than suspension, concluded: CAR-NLC selected formula showed enhancement in oral bioavailability of drug than suspension [62].

Patil and colleagues reported that by using solid lipid glyceryl-monostearate (GMS), liquid lipid oleic acid, poloxamer 188 surfactants, and tween80 co-surfactant with high-pressure homogenizer method. with the assistance of 2^3 full-factor designs to optimize the dependent parameters particle size (P.S), Polydispersity index(PDI), and entrapment efficiency (EE%), the result showed optimum formula had P.S (110.1±1.3) with PDI(0.373±.03), EE%(85.11±3.7) and in vitro release showed 40% release is 2 hrs and followed by sustained release to optimize the dependent parameters (P.S), (PDI) and (EE%), the result showed optimum formula had P.S (110.1±1.3) with PDI (0.373±.03), EE%(85.11±3.7) and in vitro release showed 40% release is 2 hrs and followed by sustained release, concluded: NCLs may be a carrier for CAR, but clinical research is required to analyze the NLCs that have been investigated to increase their marketability [63].

3. Polymeric micelles (PMs):

Polymeric micelles are formed by the self-assembly of amphiphilic polymers in an aqueous environment to the formation of micelles, PMs are prepared by different methods (Direct dissolution, evaporation or film method, freeze-drying method, o/w emulsion), so micellization leads to form ordered structure. PMs have several advantages as (solubility enhancement, improved oral bioavailability, high structure stability, improve drug loading, and low toxicity). However, industrial growth of PMs is hindered due high cost of preparation and difficulty in drug loading, Dialysis technique needs 36 hrs. for a coefficient load of drug and the emulsification technique needs to use a chlorinated solvent that is not safe, now using water/tertiary-butanol mix to overcome these limitations also an imbalance of

hydrophilic/lipophilic region to increase lipophilic drug load may decrease polymeric stability, to overcome these limitations using lyophilized technique [64].

Wegmann and colleagues reported that for CAR pediatrics nanomicelle formula using copolymers like D-a-tocopherol polyethylene glycol 1000 succinate (TPGS) and poly (vinyl caprolactam)-poly (vinyl acetate)-poly (ethylene glycol) (Soluplus) and Pluronic F127 each of them individually dispersed with carvedilol in distilled water by magnetic stirring then micelle size and morphology were characterized and in vitro release study and in vivo were investigated. Firstly by determining the aqueous solubility (Si) of CAR in PH 5.2 and PH 7.0 the result was Si values were (1.15 and 0.05 mg/ml), respectively secondly investigation of the drug encapsulation in each polymer to obtain a clear solution by calculating the apparent solubility (Sa) of CAR and solubility factor(Fs) of CRV in each polymer in different concentrations (1-10%) that showed TPGS had high encapsulation than soluplus and F127 according to this result concentration 5%of TPGs and CAR(1mg/ml according to dose per weight adjustment) chosen to study. Particle size for TPGs was 10.9±0.8 nm and PDI 0.123 and for soluplus P.S was 81.9±5.6nm and PDI 0.232, by TEM TPGS was spherical in shape and soluplus was rod shape micelles.in physical stability, the study showed no precipitation of CAR for both TPGS and soluplus. In vitro drug permeation was employed on bovine duodenum through a biological membrane at different times (1, 2, and 3 hrs.) drug permeation after 3 hrs. to TPGS and soluplus were (1.25 and 2.45 µg), respectively.in vivo study applied on Wistar rats by comparison the PK of TPGS NMs and soluplus NMs and micelle-free drug solution AUC_{0-2} were (120.1, 61.3, and 40.6 ng/ml), respectively. Cmax were (108.6, 51.8 and 56.9 ng/ml). concluded that CAR encapsulated with TPGS and soluplus show enhancement in relative bioavailability especially TPGS(4.95 folds) and faster absorption rate of TPGS shown by high Cmax and shorter Tmax, the results showed new novel for using TPGS and soluplus as polymers [65].

4. Transdermal Ethosomes:

It is a novel lipid carrier consisting of phospholipids, ethanol (high concentration), and water to form vesicles, those vesicles' sizes can be modulated from tens of nanometers to microns. Ethanol is a powerful permeation enhancer that works by altering the stratum corneum's intercellular area, thereby ensuring deep drug penetration also ethanol gives a negative charge on the surface of vesicles that gives stability due to electrostatic repulsion. the high concentration of ethanol gives high solubility of lipophilic drugs so high EE%, finally, Ethosomes are less toxic and cause less skin irritation hence making Ethosomes suitable for transdermal delivery [66].

Amarachinta and colleagues reported comparing of characterization of the Ethosomal gel formula with the non-gelling ethosomal formula and CAR gel formula only without any additions. Firstly, Ethosomal formulae were obtained by mixing between different ratios of soya phospholipids, Propylene glycol (PG), ethanol, and water by a cold method then by investigation of all formulae the optimum formula was chosen to prepare ethosomal gel by adding different ratios of Carbopol 934 polymer as a gelling agent. This chosen Ethosomal gel formula showed had P.S 130 nm, zeta potential -31 mv, PDI 0.23, EE% 99.12, and cumulative in vitro release was 97.89% that was better-sustained release than all formulae over 72 hrs. finally this formula when compared with non-gelling ethosomal formula and CAR gel formula only The result showed that gel formulas (optimum formula) had good PH(5.5-6.8) that make less skin irritation and had good spreadability (5.37-8.24 gm. cm/sec.) also the viscosity of optimum ethosome gel was(1.2-19.7 Pa.s) ,also in vitro drug release showed optimum formula gel had <50% release over 8 hrs then sustained release over 72 hrs compared with all that formula consist of Carbopol(1% w/w), this formula chosen in EX-Vivo test that optimum ethosomal gel formula showed good penetration in the skin (89.64±7.26 $\mu g.cm^{-2}.h^{-1}$) rather than CAR gel formula((54.59±6.21 $\mu g.cm^{-2}.h^{-1}$) may be due low viscosity and the skin retention studies of the optimum ethosomal gel also showed better retention capacity (10.86%±3.21), compared to CAR gel (4.63%±1.23). Moreover, ethosomal gel considers a good carrier due to a gradual reduction in blood pressure for 24 h in rats compared to marketed formula [67].

5. Nano sponge:

Nano sponges are a new type of hyper-crosslinked polymer that polymeric dispersion lyophilized to give porous solid structure based colloidal structure made up of colloidal-sized solid nanoparticles and nanosized voids. its range of dimensions (1µm or less), They are nontoxic, porous particles that are insoluble in most organic solvents and can withstand temperatures of up to 300°C and a pH range of (1 - 11), Because of their 3D structure, which includes nanometric-sized voids and variable polarity, they can catch, transport, and selectively release a wide range of chemicals also Crystal structure of nanosponge plays a very important role in their complexation with drugs [68].

a- Carboxymethyl cellulose (CMC): a well-known polysaccharide-mucoadhesive, water-soluble, ionizable polymer in which the glucose units of the cellulose chain are substituted with -CH2COOH groups [69].
b- Hydroxypropyl cellulose (HPC): is another cellulose derivative that comes in a variety of

molecular weights and is soluble in water and most organic solvents. Because of its thickening and stabilizing qualities, it is a desirable biomaterial [70].

Khafagy and colleagues reported that they prepared novel drug delivery formula called bilosomes nano-sponge formula that also compared finally CAR sponge formula, whereas bilosomes nano sponge formulas were prepared by using thin film hydration - sonication technique to prepare bile salt (sodium deoxycholate (SDC)) enriched liposomal formulas called (bilosomes) to load CAR then optimum formula in P.S, zeta potential, and drug release are chosen. The optimum formula chosen was incorporated in CMC-HPC polymers and lyophilized to obtain the mucoadhesive nano sponge formula gel by solvent casting method. the result showed the optimum bilosomes had P.S(217.2 nm), zeta potential (-46.1%), EE (87.13%), DL (0.78%), and in vitro release was (20.03 to 44.67%) in 3 hrs to all bilosomes formulas also EX-Vivo permeation study from CAR bilosomes formulas showed high permeation 2.9 folds than CAR suspension but selected formula showed higher permeation (548.43±6.98 µg/cm^2) than all formulas. Then by comparing between CMC-HPC bilosomes selected formula and CAR-sponge formula , result showed: formula bilosomes nano sponge with drug content(97.25%) give high porosity structure than CAR-sponge only due to incorporation into suspension form and also give residence time (170 min.)suitable for making a connection with buccal mucosa helping to wet the dosage form with the mucosal substrate, the release of drug from bilosomes nano sponge was 64.77% while form CAR sponge was 84.83% may be due sponge contains CRV encapsulated into bilosomes which may greatly delay the drug release of drug from suspension then from gel matrix and Histopathological studies showed the superiority of bilosomes sponge in the protection of heart tissues over Carvid tablet in market, concluded that The data collected suggested that a bilosomes-based sponge would provide a significant improvement in CRV buccal administration while also protecting cardiac tissue more effectively than the existing product Carvid [71].

6. Nanofibers:

Nanofibers are fiber shape nanostructures for various applications in biomedicine, solid fibers, have a high surface area-to-volume ratio with high porosity, and potential conversion of a drug from a crystalline state to an amorphous state, they are useful for improving the dissolution rate and solubility of the poorly water-soluble drug and their bioavailability, the disintegration of nanofibers can make in few seconds and release the drug content [72].

Nanofibers can be fabricated by an electrospinning technique that is generated by electrostatic forces applied to a polymer solution to obtain solidified nanofibers. Electro-spun consists of three main components (a) high voltage power supply, (b) spinneret, (c) conductive collector also the properties of electrospun nanofibers as(high surface area-to-volume ratio, porosity, controllable fiber diameter, and fibrous structures can be altered by modulating parameters[73]. as:(1)processing parameters(flow rate, feeding rate, distance between the capillary and collection, electric potential), (2) the molecular weight of polymers and polymer solution properties (viscosity, conductivity, dielectric constant, and surface tension) and (3) control post-processing parameters (such as heating rate and heating temperature) [74].

Until now electro spun nanofibers limited to just drug loaded and characterization of nanofibers, the dis advantage of electro spun is difficult to load the drug concentrations into nanofibers and also need to add sweeteners and flavors· the therapeutic application of nanofibers is limited due to proper functionality, capacity, toxicity, and large-scale production limitations [75].

Polyethylene oxide (PEO): polymer used to increase the dissolution of lipophilic drugs such as CAR and enhance the wettability of drug by surrounding the drug molecules with hydrophilic molecules of PEO, in the other manner the hydrophobic parts of PEO also tend to attract the similar part from carvedilol molecules. A drug is thoroughly dispersed in a water-soluble carrier [76].

Marko Krstic and colleagues reportenanofibers (aim to compare applying of electrospun method to form nanofibers and casting method to form oral films by using CAR with polymer polyethylene glycol(PEO) then dissolved in water only or in water-ethanol mixture, then compare the difference between the two methods which of them chosen to produce formula with high drug content and fastest drug release and characterization of nanofibers and oral films with carvedilol prepared by electrospinning and solution casting method ,prepared ten formulas with two solutions from CAR dissolved in polyethylene glycol(PEO) 5%and 10%and water or PEO with water/ethanol mix , two solutions prepared by film casting method and electrospinning nanofibers(by change in flow rate) ,result showed carvedilol content in oral film regardless the type of solvent was over 92.8% but formulas made by nanofiber depend on solvent used in water was(92.4-98.4%) increase than water/ethanol(45.7-47%) that due to evaporation of ethanol during the process made the CAR precipitated in the collector and not entrapped in nanofibers. by field emission scan electron microscope (FESEM) two formulas nanofibers in water diameter were 132nm and 161nm with beads on the surface indicating an uneven distribution of CAR, the other three formulas nanofibers

in water were (144nm,197nm,345nm) and contained a high content of CAR and good distribution but in water/ethanol low content of CAR. DSC showed a degree of crystallinity of films higher than nanofibers and the crystallinity of fibers in water lower than in water/ethanol.in vitro drug release compared the pure drug with all formulas all had percent of drug release (higher than 80%) in 30 min. higher than the pure drug, comparing the dissolution profile of nanofibers and oral films formulations with water solvent showed a high dissolution rate from nanofibers formulas and the difference in dissolution rate depends on flow rate and collector size, a diameter of fibers, the distribution of carvedilol without beads. Concluded that nanofibers can be used to increase the dissolution rate of carvedilol and the optimum formula prepared by electro-spun by using water as a solvent with a flow rate (1ml/hr.) had a diameter of 345 nm and high drug load (86.32%), as well as fastest drug release (86.40%)in 30 min [77] .

7. Liposomes:

Liposomes are small spherical artificial vesicles that can be made from cholesterol and nontoxic phospholipids. Liposomes are attractive drug delivery devices due to their size, and hydrophobic and hydrophilic properties (along with biocompatibility). Liposome characteristics vary greatly depending on lipid composition, surface charge, size, and manufacturing method. They have a lipid membrane with an interior aqueous core that distinguishes them [78].

Ghassemi and colleagues reported that used the approach of surfactant-liposome CAR by using phospholipid Egg phosphatidylcholine (EPC) with cholesterol individually as conventional formula or both with several types of surfactant by thin film hydration technique followed by probe sonication ,the result showed no change in particle size, zeta potential and PDI between conventional liposome and all surfactant liposome formula, in vitro release showed the release of all formulations higher than suspension formula (80-100%) after 10 hrs in simulated intestinal fluid(SIF) also in vivo showed that formula with Labrasol surfactant give improvement in AUC 1.4 fold higher than conventional formula and 2.3 fold higher than suspension , finally when compared cellular uptake of suspension, conventional formula and Labrasol-liposome formula by using Caco-2 cells, the result showed high cellular uptake from Labrasol formula(4.1 ng/mg protein) and in cytotoxicity showed liposome showed high cell viability >95%. Concluded that the incorporation of surfactant as Labrasol in liposome increase peak plasma and oral bioavailability and also cell viability increased [79].

8. Niosomes:

Niosomes are a novel drug delivery system, non-ionic surfactant-based vesicles that are prepared by admixing cholesterol with non-ionic surfactant in optimum ratio with subsequent hydration in aqueous media or buffer media [80], Niosomes can entrap both hydrophilic and lipophilic drugs in an aqueous layer or vesicular membrane made of lipid [81], Niosomes reported to high stability and low cost than liposomes, they can prolong the circulation of drugs because the presence of the surfactant with lipid and also these vesicles can improve the drug bioavailability encapsulation efficiency with desired targeting efficiency [82],[83].

Shivare UD and colleagues reported that used Span 60-based niosomes to encapsulate CAR. Niosomes were prepared by thin film hydration technique and then incorporated into an aqueous gel base using Carbopol 934 and then using Eudragit RS 100 and PVP polymers to hold gel into a transdermal patch by mercury substrate method, the study showed that an increase in the concentration of cholesterol made an increase in P.S and in vitro release follow Peppas model and the formula with span60: Ch. (80:60) give the highest entrapment efficiency (65.4%) and also highest release (94.3%) up to 12 hr. [84].

Taymouri and colleagues reported that investigation of different surfactants on physical properties and stability of carvedilol nano-niosomes, prepared niosomes by thin film hydration method to insert CAR, using different ratios mix from surfactant (Span 20, span 40, span 60, tween 20, tween 40, tween 60) each of them with different ratios from cholesterol, physicochemical parameters including particle size, encapsulation efficiency, the release of encapsulated drug and their stability were evaluated. The result showed that Noisome prepared from 50% of cholesterol with 25% of span/tween 60 showed particle size 341.9±5.5, PDI 0.7±0.1, zeta potential -32.3±5.2 and encapsulation efficiency 77.7±5.1 and showed also Niosome prepared from 40% or 50% of cholesterol with 25% or 30% of span/tween 60 showed high stability due high transition temperature and solid state features of span/tween 60 and in vitro release study all formulations released 100% of loaded drug with no significant difference in their data release except formulations with span/tween20 due low encapsulations efficiency, concluded nano-Niosomal carriers could be considered as good carriers for oral delivery of carvedilol [85].

Barriers to oral drug delivery system:

The oral route is the preferred mode of drug administration owing largely to simplicity, patient compliance, flexibility in dosage administration, and not require high cost, however, oral route drugs suffer from many barriers along the gastrointestinal tract (GIT) to enter the blood circulation firstly as (enzymatic degradation and PH variation) that affect the potency of the drugs[86]. Secondly, the drug needs to penetrate the mucus layer: the hydrogel layer with a mesh pore size

Table1. Summary of several approaches applied to carvedilol.

Type of carrier	Method preparation	Particle size	Zeta potential	PDI	Encapsulation Efficiency EE%	Drug load DL%	In vitro and/or in vivo	REF.
1- The self-emulsifying delivery system								
a-SNEDDs campulPG8 cremphor EL transcutol HP	Emulsification	46 to 475 nm	NF	NF	NF	NF	In vitro optimum Formula Nearly Complete dissolution Marketed:77%, Pure drug:67%. In vivo: Bioavailability Fraction: Optimum:86% Market:21%, So bioavailability Improved by SNEDDs.	58
b- SEDDs oleic acid labrafil Labrafac PG poloxamer or HPMC	Emulsification	Poloxamer: 0.248 to 0.387µm HPMC:0.25 to 0.91 µm	Poloxamer: 0.37 and 0.38 HPMC: 0.35 to 0.41	NF	NF	NF	In vitro: Poloxamer (61.24 to 70.61%) HPMC (74.26 to 91.11%) permeability: poloxamer: 69.78% in 4 hrs	59
2-lipid nanocarriers:								
a-nanostructured lipid carriers (NLCs) Oleic acid: stearic acid PEG4000 Tween80	Microemulsion Technique Then probe sonication. Finally Freeze drying.	165.11 to 204.45 nm	NF	0.402 to 0.511	6.45 to 88.56%	9.58 to 12.56	In vitro: 77.55% of drug Release for selected the formula in 22 hrs That improved solubility of the drug so increase the dissolution rate of the drug formula.	62
b-nanostructured lipid carriers: glyceryl-monostearate (GMS), tween80, poloxamer188.	High pressure Homogenization.	110.1 to 194.5 nm	-26 to -25	0.233 to 0.437	65.08 to 75.77	8.35 to 14.06	40% after 2 hrs	63
3-liposmes Labrasol-Liposome	Thin film hydration-Probe sonication	76.2-104.3 nm	+8 to+17	0.1 to 0.32	79.8 to 90.4%	NF	In vitro (80-100) % After 10hrs in SIF In vivo: Suspension, Cmax:190 ng/ml, AUC:470 (h.ng/ml) Conventional liposome formula: Cmax:252ng/ml, UC:822(h.ng/ml) Labrasol formula: Cmax:557 ng/ml, AUC:1115(h.ng/ml) That	79

							liposome enhances bioavailability more than suspension.	
4- polymeric Micelles (Polymeric nano micelles)	Polymer Water dispersion	TPGs: 10.9 nm Soluplus: 81.9 nm	NF	TPGs: 00.123 Soluplus: 0.232	NF	NF	In vitro: Drug permeation, TPGs:1.25µg, Soluplus:2.45µg In vivo: TPGs: Cmax: 108.6 ng/ml, AUC:308.6(ng/ml/h). Fr%: 495% Soluplus: Cmax:51.8 ng/ml, AUC:159.1(ng/ml/h) Fr%: 255 So, using of TPGs. Increase CAR bioavailability.	65
5-transdermal Ethosome (Soya phospholipids Ethanol Water Carbopol 934	Cold method then add Carbopol gel By Solvent casting method	130 to 1200 nm	-27.8 to -44.5 For Ethosome formulas	<0.45 For Ethosome Formula	44-99% For Ethosome Formulas	>90% For Ethosome Gels	In 72hrs: 64.89 to 99% in 72hr For Ethosome formulas In Ethosome gel formula: <50% in 8hrs Then sustained release Over 72 hrs. In vivo study: Gradual reduction of systolic blood Pressure in 24 hrs for gel formula.	67
6- Nanofibers a- Polyethylene b- oxide c- (PEO)	Electro spun Method	144 to 345 nm	NF	NF	NF	45.70 to 98.4% For nanofibers	In vitro: After 120 min. from nanofibers: 93.13 to 98.12% From CAR tablet: 92.69% Form CAR pure suspension: 42.02%	77
7-nanosponge	Thin film hydration Then solvent Casting method and lyophilized.	211.3 to 311.5 nm For Ethosome Formulas	-46.1 to -26.11 mv For Ethosomal formulas	0.18 to 0.54 For Ethosomal Formulas	51 to 87.13% For Ethosomal formulas	97.75% For bilosomes nano sponge formula	In vitro release bilosomes nano sponge was: 64.77%	71
8- Niosomes:								
a- transdermal Patches	Thin film hydration	3.35 to 4.18µm	NF	NF	28.17 to 66.23%	NF	In vitro release: 79.68 to 96.24% Up to 12 hrs	84
b-Oral drug delivery (span/tween)	Thin film hydration	167 to763 nm	-23 to -9.1	0.4 to 0.8	22.2 to 77.7%	NF	In vitro release: Almost 100% release	85

(100-200 nm) that hinders the particle diffusion and may suppress it then transport to the epithelial cell layer called also basal lamina acts as a filter that followed by connective tissues [87]. Finally, the drugs enter the systemic circulation by the portal vein or lymphatic system. Such above-mentioned problems can be overcome by applying Nanoparticle systems (NPs) such as using a polymeric matrix to encapsulate the drug from the enzymatic problems in the stomach (alginate gels) and using Eudragit polymer for coating the drug against acidic PH [88]. However, several considerations should be taken for NPs as particle size, surface charge, and shapes that may affect the cellular uptake of NPs, many researchers investigate the effect of NP size, surface charge, and shape to overcome all biological barriers[89]. The effect of particle size and shape on the cellular uptake of drug from GIT was investigated on Caco-2 cells by using polystyrene particles and the result showed that small size and rod-shaped particles have high transport efficacy than large particle size and spherical shape [90]. Also, one study investigates the effect of surface charge on cellular uptake of NPs by using: polyethylene glycol-block-polylactic acid (PEG-PLA) as a polymeric nanoparticle and incorporating differently charged lipids (positive, negative, and neutral) with the same particle size and result showed the positively charged lipids facilitate the cellular uptake in vitro and in vivo to NPs. Adding to this, the systemic circulation that may hinder the NPS by the effect of the reticuloendothelial system and that may be overcome by using PEG onto the surface of NPs that increases the circulation of the NPS in the system [91].

Technical challenges for Nanomedicine development:

In the pharmaceutical industry scale, the production of the dosage form is crucial and should be reproducible. The nanomedicine field needs careful design and engineering more than conventional drugs. NPS consists of several complicated components that need additional tests, that are commonly performed for conventional dosage form as recommended by the FDA to achieve the stable biological behavior, physicochemical character, and pharmacological effect to nanoparticles (NP), for example, particle size, size reduction, surface charge, release of the drug, surface functionalization, toxicity, purity also preclinical and clinical studies to determine the safety and pharmaceutical effect of NP [92]. These tests are crucial to physicochemical characteristics to control NPS. Toxicity, interaction with cells, other biological components [93].

Size controls the movement of nanomaterials through the bloodstream, their ability to pass physiological barriers, their localization to specific sites and cell types, and the induction of cellular responses [94], [95].

Surface characteristics include surface charge, which may have an impact on receptor binding and the penetration of physiological barriers, as well as surface energy, which is relevant to the dissolution, aggregation, and accumulation of NP and is determined by Zeta potential.

The shape of nanomaterials influences how drugs are delivered, degraded, transported, targeted, and internalized. It also influences how drugs adhere to body tissues and how long they stay in circulation [96].

Pharmacological efficacy is another challenge for NPs manufacturing, the plasma drug concentration is used as a standard approach to measuring the pharmacokinetics (PK) parameters in conventional dosage form but Nano medicine needs more approaches to evaluate it, for instance: accumulation of NP at the target size could be more relevant to assess the therapeutic activity of NPs. Achieve a high efficacy-to-risk ratio compared to conventional dosage form, the measured concentration reflects the nature/number of NP circulated and this cannot be directly correlated to pharmacological and topological effects [94]. As Nano pharmacoeconomic studies must be carried out to establish the economic and social worth of NPs goods for them to be approved, the cost is still another factor in the manufacture of NPs.

All these tests should be considered to increase the production and reproducibility of NPs on large scale and to achieve their efficacy and safety[39].

CONCLUSION

The global population is turning to nanocarriers to cure the problems of conventional dosage forms. Although nanocarriers were applied, only a small percentage of the many nanocarriers were approved in the market which may be due to a lack of clinical trials. CAR is one of the BCS class II drugs that have low solubility and low bioavailability. Several approaches applied to overcome these problems. From this review, we can conclude that several nanocarriers can be applied as a promising approach to improve the bioavailability and solubility of CAR. Each carrier as mentioned in the review has advantages and disadvantages to be applied. Although several types of research that made to improve CAR drawbacks, many challenges should be considered for nanocarriers in the future: (a) production of these nano carries from the laboratory scale to the pharmaceutical scale. (B) some factors such as cost, reproducibility, and safety issues on the production scale. (C) benefits to humans owing to variations in the pharmacokinetics of the drugs. nanocarriers try to improve drug efficacy and patient compliance.

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