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Modified drug releases dosage form based on cardiovascular system

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Abstract

A range of disease states, including atherosclerosis, ischemic-reperfusion injury, and various types of microvascular disorders, including hypertension, may be successfully treated via therapeutic administration to the cardiovascular system. Adenosin A2A receptor agonist (CGS 21680), CYPepoxygenases inhibitor (N-(methylsulfonyl)-2-(2-propynyloxy)-benzenehexanamide), trans-4-[4(3-adamantan-1-ylureido)cyclohexyloxy] benzoic acid, soluble epoxide hydrolase inhibitor (Nmethylsulfonyl Effective nanoproduct formulations have the potential to significantly improve patient treatment results by overcoming physiological obstacles. According to the research on targeted distribution to the cardiovascular system, we discovered that this field is still developing.compared to the more developed disciplines of tumour cancer or brain delivery, which have fewer publications focusing on the targeted drug delivery methods, are still in their infancy. We also demonstrate the importance of a thorough understanding of pharmacology in relation to the cardiovascular system. As a result, we covered numerous receptor agonists, antagonists, activators, and inhibitors in this review that would have an impact on the cardiovascular system.

INTRODUCTION

A key contributor to both health and illness in the body is the cardiovascular system, and any disturbances in this system's regulation can result in cardiovascular disorders such atherosclerosis, myocardial infarction, and microvascular disease[1,2]. High blood pressure, also known as essential hypertension (HTN), is one of the main risk factors for cardiovascular disease. One in three individuals in America, or around 75 million people, had high blood pressure in 2011, according to the CDC. Despite the fact that HTN is simple to detect and that it may be controlled with a good diet, regular exercise, and medication, untreated hypertension patients still run the risk of developing the dangerous illness. Additionally, hypertension changes the form and operation of blood arteries, damaging many organs like the kidneys, brain, and eyes[3, 4]. Angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists, diuretics, calcium antagonists, and alpha-receptor blocking medications are only a few of the antihypertensive medications used to treat hypertension. Combinations of two or more antihypertensive medications from different categories were typically advised for best blood pressure control results[5]. Adenosine receptors, nitric oxide synthase, cyclooxygenases, CYP-epoxygenases, soluble epoxy hydrolase, hydroxylases and their metabolites, among other substances, are involved in the regulation of blood pressure.

Cardiovascular illnesses may result from cardiovascular system deregulation. Understanding the physiology and pharmacology of a system is crucial before targeting it since compensatory processes may otherwise negate the effects of the target. For instance, the purine nucleoside adenosine is involved in a variety of physiological and metabolic processes[6, 7]. Most tissues and organs are affected by the physiological effects of adenosine[8–12]. As a result, it interacts with four subtypes of adenosine receptors (ARs): A1, A2A, A2B, and A3 and plays a significant role in vascular regulation[13]. In vascular tissue, both

A2A AR and A2B AR are primarily responsible for the vasodilation effect, while A1 AR and A3 AR are responsible for the vasoconstriction impact[20,21] .A2A AR participates in vascular relaxation through an endothelium-dependent mechanism, as was previously mentioned[7,17,19,22-25]. Another investigation established CYPepoxygenases' contribution to vascular relaxation[26]. They came to the conclusion that increased CYP-epoxygenases, which transform arachidonic acid (AA) into epoxyeicosatrienoic acids (EETs), are linked to the activation of the A2AAR[17]. Additionally, the data indicated that ATP-sensitive K+ channels, via CYP-epoxygenases, were involved in A2A AR-mediated vascular relaxation[27]. In contrast, 20-hydroxyeicosatetraenoic acids (20-HETE) via PKC-/p-ERK pathway contracted the mouse aorta in the absence of A2A AR[26,27].

The relationship between adenosine receptors activation and the role of soluble epoxide hydroxylase (sEH) was explored using soluble epoxide hydroxylase knockout (sEH−/−) and their respective wild-type (sEH+/+) mice. In sEH−/−, the adenosine-induced relaxation involved an upregulation of A2AAR, CYP-epoxygenases, and PPARγ, accompanied with downregulation of A1 AR and PPARα[28]. The cytochrome P450 (CYP450) family is divided into two subfamilies (enzymes), epoxygenases and ω-hydroxylases that involve in maintaining vascular tone[29–31]. The main function of CYP-epoxygenases is to metabolize whereas the -hydroxylases metabolise AA to 20-HETEs (vasoconstrictor), AA is converted to EETs (a vasodilator) by the former. Dihydroxyeicosatrienoic acids (DHETs), which are less active metabolites of EETs produced by further metabolism through sEH, counteract the vasodilator effects of EETs. Additionally, several polyunsaturated fatty acids (PUFA), also known as oxylipins or oxylipids, are produced as a result of sEH activity. A2AAR agonist (CGS 21680), CYP-epoxygenases inhibitor (MS-PPOH), sEH inhibitor (trans-4-[4-(3-adamantan-1ylureido)cyclohexyloxy]benzoic acid (t-AUCB), -hydroxylases inhibitor (Nmethylsulfonyl-12,12-dibromododec-11-enamide (DDMS), PP A defence mechanism against cardiac damage is CRH[32,33]. Inhibiting sEH increases CRH, which is protective against ischemia, whereas inhibiting CYP-epoxygenases decreases CRH, which is not protective against ischemia. PPAR activation and -hydroxylase activity inhibition also increase CRH[32,33].

This review's major objective is to analyse the current state of therapeutic agents or drug delivery methods to the cardiovascular system, with a focus on nanomedicine and delivery to the system's vascular endothelial cells. We build on previous reviews in this article by discussing newer approaches and therapeutic agents, such as siRNA, DNA, peptides, proteins, small molecules, and small molecules [CGS 21680, N-(methylsulfonyl)-2-(2propynyloxy)-benzenehexanamide, trans-4-[4-(3-adamantan-1ylureido)cyclohexyloxy]benzoic acid, N-methyls antibodies, too.

Methodology Delivery of Small Molecules Small compounds have historically been utilised to treat illnesses of the cardiovascular system. A few examples of frequently used medications are ezetimibe, atorvastatin, metoprolol, and valsartan. These medications are utilised in the chronic management of the condition and are primarily accessible in oral drug delivery methods. There is a strong interest in creating novel medications as well as for the delivery of these compounds due to the market share of over several billion dollars in the treatment of cardiovascular disease (Table 1)[36]. Therefore, small molecule medication delivery is a topic of interest that has seen the development of numerous technologies over the past few decades[34]. Poor pharmacokinetic behaviour is the main reason why substances fail in clinical trials, which has caused a paradigm shift in medication discovery recently has led to the incorporation of drug's pharmacokinetic features, such as absorption, distribution, metabolism, elimination, and toxicity (ADME/Tox), into the first stages of drug discovery[37,38]. The planned inclusion of the drug-like qualities earlier in the discovery pipeline has been made possible by this new addition of ADME features[39]

.Simple medicinal chemistry techniques haven't always been able to solve problems with dosage in a preclinical model or human disease for some substances. Formulation technologies have been used in this instance to transport the chemical to the target area as best possible[37,40,41]. These nanoformulation techniques can be used to get around some physicochemical characteristics of substances that are impeding adequate drug delivery, such as solubility[34,42-44]. In addition to the traditional method of obtaining fair distribution at the therapeutic target, drug delivery of small molecules employing nanomedicine also allows for the potential shielding of a substance to prevent the hazardous effect on target organs[34]. The recent publication by the team of Liu et al.[45] provides an example of a nanoformulation technique for the

cardiovascular system that increases toxicity by reducing the organ toxicity of platinum-containing medicines used to treat cancer. In order to dramatically lower the toxicity in organs like the liver, they employed an intralipid 20% and a hyaluronic acid polymer nanoparticle. Such as kidney, liver, and spleen[46]. The human clinical trial Cardiac Reperfusion With Intralipid® at Reperfusion (CREW-I) NCT02807727 is testing the effects of intralipid on reperfusion. With regard to medicinal delivery, liposomes in particular have been employed increasingly frequently, and the FDA has created sets of requirements to handle this[47].

In the recent years, various varieties of nanomedicine have been developed and can be used for particular tasks[43]. Which carrier formulation to utilise depends on a number of variables, including the drug's inherent chemical properties (for example, solubility (logS, logP, and logD7.4), molecular weight, and the therapeutic objective. For instance, if the compound's main purpose is to treat the peripheral organ systems, then the only formulation goal can be straightforward metabolism protection. In other circumstances, the dispersion of the drug to various target organs may be aided by the nanoformulation. The administration of medications to the brain is a prime illustration. The blood-brain barrier (BBB), the microvascular unit in the brain, is selectively permeable to organic molecules because tight intersections. Only transcellular or transporter-mediated absorption into the brain is possible as a result of the tight connections' restriction. The differences between the more restricted BBB and the more leaky peripheral vascular system are depicted in Figure 1. It's interesting to note that a recent study discovered that the A2A AR may contribute to the opening of the BBB. Adenosine injections caused the BBB to open in mice by simulating the A2A AR. This could be utilised as a covert method or Trojan horse to deliver drugs to the brain, such as chemotherapy medicines for the treatment of brain malignancies that cannot reach the CNS because of the BBB[47,48].

Liposomes, nanoparticles, nanocapsules, nanotubes, polymeric conjugates, and micelles are a few of the formulation forms employed for tiny organic substances (Figure 2)[43]. One may argue that cancer and diseases of the central nervous system (CNS)[49] are the two disease states for which each of these forms of nanoformulation has been used the most, with additional fields like orthopaedics and cardiovascular delivery also emerging as innovative delivery rich areas[35,50]. The standard approach for nanoformulations with small molecules is to encapsulate a medicine inside a polymer carrier system. These formulations work on the basis that the lipophilic chemicals bind to the lipophilic regions of the polymer, which then self-assembles and creates a barrier between the compound and the aqueous environment (Figure 3)[51]. Another approach is to conjugate a molecule to the polymer or by creating a compound with the system using substances like folate or glutathione[52,53]. An additional element for many of these systems is a targeting system, which may be a complex of antibodies or medications [CGS 21680, N-(methylsulfonyl)-2-(2propynyloxy)-benzenehexanamide, trans-4-[4-(3-adamantan-1ylureido)cyclohexyloxy]benzoic acid, N-methylsulfonyl-12,12-dibromododec-11-enamide, rosiglitazone and T0070907] coated in the nanoparticle.

Drug Delivery Systems

PLGA-based nanoparticles

Nanoformulations have made use of and produced polymers. The majority of the nanoparticles in these nanoformulations have a diameter of around 300 nanometers[54]. There are several of them, such as poly lactic-co-glycolic acid (PLGA), a polymer comprising poly lactic acid (PLA) and poly glycolic acid (PGA), a biomaterial that has received FDA approval[54]. By controlling monocyte recruitment to the vascular plaques, the team of Katsuki et al. successfully employed PLGA nanoparticle loaded with pitavastatin to suppress the rupture of atherosclerotic plaques[55]. The anti-diabetic medication pioglitazone, an agonist of peroxisome proliferator-activated receptor (PPAR), was also delivered via PLGA nanoparticles[56]. In a study by Nakashiro et al., macrophage activation was inhibited in hyperlipidemic ApoE / mice by thiazolidinedione (TZD) pioglitazone-encapsulated nanoparticles.halt the development of atherosclerotic plaques in mice[57]. Pitavastatin-encapsulated PLGA nanoparticles were able to effectively carry the medication to the vascular endothelium and induce therapeutic neovascularization[58]. The use of chemicals delivered to the heart after a myocardial infarction to reduce the ischemic tissue damage found in these patients was further investigated using pitavastatin PLGA nanoparticles. By activating the AKT/PI3K kinase signalling pathway, these nanoparticles were successful in minimising ischemic-reperfusion (I/R) injury in the heart.

Additionally, these nanoparticles were effective in reducing inflammation, which contributes to the MI-related secondary tissue damage. These pitavastatin nanoparticles are a good example of how pitavastatin may be used to treat organ ischemia in a variety of disease states[60, 61]. of cardiovascular drug delivery using nanoformulations.

PEG-based nanoparticles: Due to its wide range of applications in drug delivery formulations and its capacity to be used to stop or delay the clearance of nanoparticles from the blood stream into the reticuloendothelial system (RES), polyethylene glycol (PEG) has been widely used in the literature. Figure 4 displays an illustration of PEG-based nanoparticle delivery to the vascular endothelium. To extend the duration of retention in the body, PEG has also been coupled to peptides and antibodies. The benefit that formulations containing PEG have been licenced for use in humans[62] has led to the usage of PEG in numerous formulations due to its success in lengthening retention duration in the body. The PEG motif has undergone published changes.PLGA-PEG diblock and triblock polymers, for instance, can be employed for various delivery methods as well as controlled delivery systems. Recently, the team of Lundy et al. demonstrated that the use of PEG-modified polystyrene nanoparticles after a MI and the reperfusion injury in the heart had a size-dependent effect. They came to the conclusion that a nanoparticle between 20 and 200 nm in size was the ideal size to target the ischemic tissue following a MI. One cautionary note from this study is that fluorescent FITC-labeled nanoparticle suspensions only reach organ tissue in relatively low concentrations. Additionally, it appears that the majority of the nanoparticles are absorbed by the RES[63]. Similar to this, Paulis et al.'s group demonstrated that liposomes with a size of 100 nm were able to slowly exit the vasculature (extravasation) as well as display delayed tissue penetration and slower time-release of the cargo. Thus, they contend that this mode of administration is appropriate for the treatment of MI[64,65]. To enhance cardioprotection in a rat model of ischemia/reperfusion (IR) injury, Takahama et al. utilised liposomal adenosine[66].

Systems for delivering drugs using vesicles called liposomes are called liposome delivery systems. They develop as a result of the self-assembly of spherical liposomes from lipids and surfactants floating in an aqueous environment. See the study written by the team of Rao et al. [35] for a superb review. The lipophilic characteristic of the liposome's interior makes it possible for substances like medicines, which are typically lipophilic, to be included. The enhancement of oral bioavailability has always been a key driver for the packaging of small compounds into liposomes. The recent publication by the Patel et al. group, which describes the increased delivery of the hypertension medications telmisartan and angiotensin II receptor antagonists, is a nice illustration of this formulation method.irbesartan[67,68]. In order to create the requisite self-emulsifying drug delivery system (SEDDS)[35]—which enhanced the oral uptake of the compounds by more than 7.5 fold[67, 68]—castor oil was combined with the surfactants Tween 20 and Carbitol as co-solvent. As a result, both of these medications, which are not very water soluble, were given.

Delivery of Biologicals—Small organic molecules have historically been the only medications available for the treatment of cardiovascular disease. The use of medications to treat various illness states is not without its inherent difficulties, such as the chemical makeup of the molecule that may not allow for adequate distribution or, in some situations, the pathological state of the tissue in a disease state. The field of therapies for the treatment of cardiovascular disorders is currently undergoing a paradigm shift; biological antibodies, proteins, peptides, siRNA, and DNA are now included.

RNA-based delivery—Using nanoformulation, silencing RNA (siRNA) has been effectively administered to animals, with the added benefit that this therapeutic method can be applied to precision medicine. Leuschner et al.'s study used cholesterol, C12-200 lipid, disteroylphophatidyl choline, and PEG-DMG to synthesise siRNA into liposomes, which spontaneously generate micellular liposomes. The siRNA liposome was successful in suppressing CCR2 expression in monocytes from animals predisposed to atherosclerosis.

Exosome usage, which has also been employed to deliver therapeutic siRNA, is another illustration[69]. Exosomes have received new attention because of their function in cellular communication. Exosomes are used by cells to transmit RNA and microRNA, among other cytosolic components, from one cell to another[72]. Exosomes were successfully used by the Shtam et al. team to deliver siRNA and inhibit RAD51[71]. The delivery of siRNA to pulmonary microvascular endothelial cells by exosomes made from human iPSCs also reduced inflammation[69]. For example, Want et al. employed a polyethyleneimine-

based method to transport siRNA to the heart. Other types of polymers have also been effectively used to transfer siRNA to the cardiovascular system.

Proteins and peptides used therapeuticallyThe use of therapeutic peptides in the treatment of cardiovascular disease has also proved crucial. Peptides' susceptibility to blood enzyme breakdown, drastically decreased permeability through vascular endothelial cells, and limited distribution into tissues have made them more difficult to transport in the body[73]. Attaching PEG linkers to the peptide is a traditional technique for lengthening the residence period in the blood[73,74]. Creating a cyclic analogue of the linear peptide, which is less susceptible to metabolic breakdown in the blood stream, is an alternative strategy. For instance, the peptide HYD1 was cyclized by the team of Gebhard et al. to create MTI-101, which had improved activity in animal models[75]. Occasionally, the peptide is potentially useful as a targeting technique to direct the nanoparticles to a particular tissue or organ.

The PEGylated liposome was delivered to the cardiac cells of an infarcted heart by the Dvir et al. group using a peptide sequence to the angiotensin II type I receptor (AT1). A range of payloads, such as cytokines, growth factors, or other types of medicinal chemicals, can be delivered using this targeted nanoparticle[76]. Proteins' therapeutic potential has also been demonstrated in the cardiovascular system. In apolipoprotein E knockout mice, atherosclerotic plaques were treated and stabilised with apolipoprotein A-I[77]. The creation of nonpeptide mimics is a feasible solution to some of the inherent problems peptides face in medicine delivery. For instance, it was demonstrated that the non-peptide Ang-1(1-7) mimic AVE 0991 significantly reduced atherosclerotic activity in ApoE/+ mice[78]. In a similar vein, the Kamaly tribe Ac2-26, a peptide anti-inflammatory nanoparticle created by et al, can lessen chronic inflammation in conditions like atherosclerosis[79].

Conclusion

The cardiovascular system offers a variety of therapeutic targets, including atherosclerosis, myocardial infarction, and ischemic/reperfusion injury. The field of specifically targeted medication delivery to the cardiovascular system offers significant potential and key benefits. Several unique technologies have been created for both targeted and sustained delivery of novel treatments, including chemicals and biologicals. These new delivery methods open up a host of possibilities of obtaining the necessary tissue specificity and reduced system exposure that will allow us to use new pharmacological agents [CGS 21680, N-(methylsulfonyl)-2-(2-propynyloxy)-benzenehexanamide, trans-4-[4(3-adamantan-1-ylureido)cyclohexyloxy]benzoic acid, N-methylsulfonyl-12,12dibromododec-11-enamide, rosiglitazone and T0070907] for better treatment of patients in future.

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