Is nanoformulation a key player or spectator to enhance the solubility of Manidipine: Promising approaches

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Abstract

The solubility of drugs is a vital factor in dosage form development. When a poorly water-soluble drug has to be incorporated into a hydrophilic vehicle, the formulation tends to decrease the bioavailability. Various nanoformulations like nanoparticles (NP), nanosuspensions, nanocapsules, nanospheres, nanogels, nanotubes, etc, are used for improvement in dosage form regarding solubility, absorption, targeted drug delivery, and increase in half-life. Nanoparticles are being used for various drug delivery systems for the betterment of dosage forms as discussed in the current study. The current study has reviewed the problem of solubility of the poorly water-soluble drug manidipine, an antihypertensive drug with the application of nanotechnology nanocrystals. The drug manidipine is a proven antihypertensive drug and acts by blocking the calcium channels. The daily dose of manidipine is 10-40 mg. The manidipine drug is not prescribed as a drug of choice for the treatment of hypertension, the reason behind this is that manidipine is a BCS class two molecule which means poor solubility and high permeability, it is unable to reach in maximum amount to the systemic circulation because of its poor water solubility. The nanoformulation is used for improving the solubility of the drug by increasing its surface area. Nanocrystal (NC) one of the nanoformulation is having the

capacity to maximize surface area thus the contact area of the drug. This ultimately applied in the enhancement of the drug's solubility belonging to BCS class II. The goal of the review is the betterment of the poorly water-soluble drug manidipine using nanoformulation.

Keywords: Manidipine, Nanoparticles, nanocrystal, BSC class, solubility.

Introduction

A feature identified as solubility defines a substance's ability to dissolve in a solvent. Solubility is specific to the maximum quantity of solute that may be balanced, or dissolved in a solvent. Solubility is considered a vital factor while working with a pharmaceutical substance or drug. [1]. A multidisciplinary field, nanotechnology includes a broad range of products generated from engineering, biology, physics, and chemistry. Solid nanoparticles, polymeric micelles, PEG-coated liposomes, dendrimers, nanotubes, gold nanoparticles, lipid core nanocapsules (LNCs), nanoshells, and others are examples of different nano pharmaceuticals dosage forms. [2]. Amorphous or crystalline nanoparticles are also possible. Crystalline nanoparticles may only have one domain due to their small size. Metal, chalcogenide, nitride, and oxide nanoparticles are frequently single crystalline in nature. The term "nanocrystals" refers to crystalline nanoparticles. Generally speaking, crystalline drug particles less than 1µ in size are known as nanocrystals. [3] The term "nanocrystals" is frequently used in the pharmaceutical industry to describe drug material particles with a crystalline character in the submicron or nanoscale range. In most cases, either direct crystallization or milling of bulk material is used to create nanocrystals, which are solids having a periodic lattice of atoms, ions, or molecules (top-down approach). APIs that belong to BCS class II can now be delivered more easily and more effectively by using nanocrystal technology. The use of pharmaceuticals for pharmaceutical use or the nanonization of items, whether for medical use, food, or both, is a significant factor on the economic, medical, and pharmaceutical sides. [4] Poor bioavailability is correlated with poor solubility in water. Medicine won't be able to reach circulation, pass through the digestive system, and have an impact if there is no way to make it more soluble. Some poorly soluble medications can be solubilized in a variety of methods. However, these techniques are only effective for medications that have particular chemistry-related characteristics, such as a particular molecular size or ring shape. In addition, using surfactants or cosolvents is also an option, but doing so can occasionally increase the toxicity of some medications. By micronizing powders of the drug to size in the range of 1 to 10 µ is an effort to maximize surface area and hence the dissolution speed, the bioavailability issues of many

extremely poorly soluble medicines of the BCS class II cannot be remedied [5]. The process then transitioned from micronization to nanonization. Since the early 1990s, Elan Nanosystems (San Francisco, CA, USA) has championed the application of NC rather than microcrystals for intravenous or pulmonary drug administration, in addition to employing nanosuspensions i. e. nanocrystals suspended in water for those purposes. [6].

Solubility: A key factor for formulation

It refers to how thoroughly a component may dissolve in a solvent to create a solution. The at most quantity of a solid or liquid that may dissolve in a given volume of a solvent at a given temperature is known as its solubility. The qualities and pace of a solute's dissolution in a solvent are described by its solubility. The capability of a substance to mix in a different material is said to be solubility. IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units [7].

BCS classification

The Biopharmaceutical Classification System (BCS) is an experimental model that studies permeability and solubility considering given conditions [8]. (Figure 1)

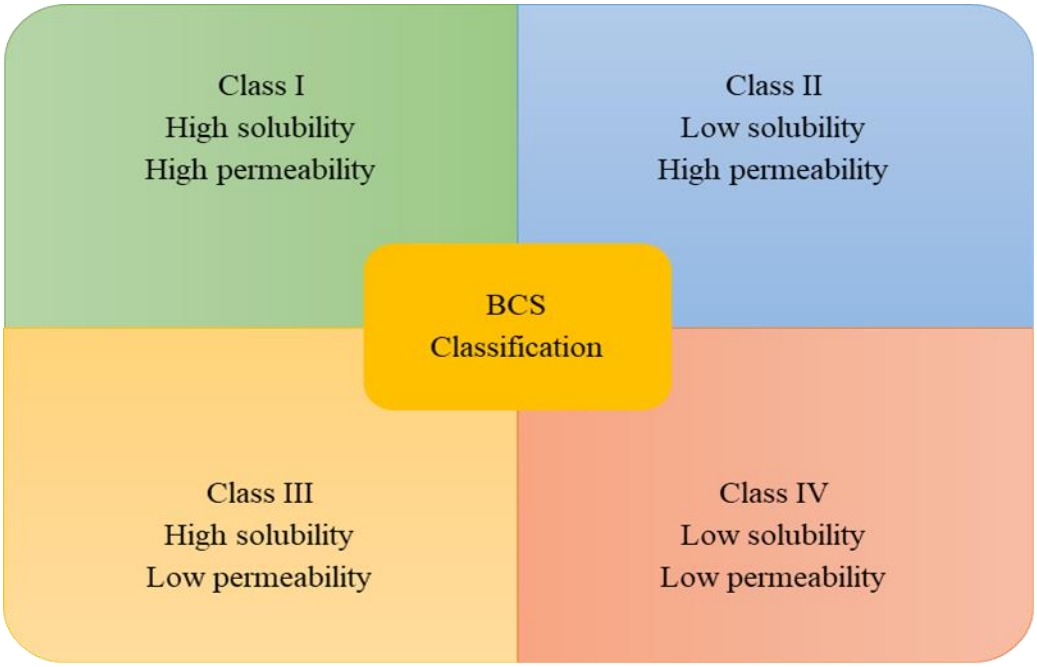

Figure 1: Biopharmaceutical classification system

BCS class 1 drugs are having high solubility and high permeability and thus are easy to modify in formulations. BCS class 2 drugs are with low solubility but with high permeability. BCS class 2 drugs are poorly water soluble and complicated for formulation development e.g. aceclofenac, clopidogrel, nitrofurantoin, manidipine, etc. Even if these drugs are with low solubility are able to formulate using various techniques [8].

Techniques to improve solubility

These methods can be classified into chemical modifications and physical modifications of the poorly soluble drug. Alteration of pH, cosolvency, derivatization, complexation, use of a buffer, salt formation, etc. is included under chemical modification [9-11]. In the physical modification method, morphological characters of particles are used to modify. Alerting the amorphous form and cocrystallization, crystal habits like polymorphs, solid solutions, and cryogenic techniques, solid dispersions, drug dispersion in carriers like eutectic mixtures. The particle size of a substance is a key factor in the solubility of the substance. A decrease in particle size enhances solubility. Thus the most developing technologies of the era deal with the micronization and nanonization of substances [12,13].

Nanotechnology: A pillar in the field of science

The prefix ‘nano’ is derived from the Greek language which means ‘dwarf’ or a very tiny thing and describes one thousand millionth of a meter (10^{-9} m) [2]. The National Nanotechnology Initiative (NNI) in the United States defines nanotechnology as “a science, engineering, and technology conducted at the nanoscale (1-100 nm) where unique phenomena enable novel applications in a wide range of fields from chemistry, physics, biology to medicine, engineering, and electronics.”[2] Nanotechnology is grasping every field of science for the betterment of human life. Various fields are now adapting this technology for fast growth and better output. This technology is being used in fields like computer technologies, energy, electronics, automobiles, biochemical, biomedical, pharmaceuticals, etc. [3]

Pharmaceutical industries develop medicines with nanotechnology in various ways. cardiology, endocrinology, oncology, ophthalmology, immunology, etc. are the medical specialization choosing nanotechnology on preference [3]. Pharmaceutical nanotechnology combines the techniques and tenets of nanoscience and nanomedicine with the pharmacy to create novel drug delivery systems that can outperform current ones. The future of the pharmaceutical business will be drastically altered by the specialist discipline of

pharmaceutical nanotechnology. Pharmaceutical nanotechnology aids in the prophylaxis and management of numerous diseases by identifying disease-related antigens as well as the microbes and viruses that cause the diseases. [5].

There are a variety of obstacles in the way of developing dosage forms. These obstacles can be removed with nanotechnology in various ways. Pharmaceutical nanotechnology has been crucial in overcoming several problems with traditional dose forms including tablets and capsules. Pharmaceutical nanotechnology was used to address the shortcomings of conventional forms, such as inadequate bioavailability, poor patient compliance, injury to healthy cells, etc. [5,6].

Role of nanotechnology in pharmaceuticals: Profound look

Conventional drug administration methods have several drawbacks, including poor patient compliance, a lack of selectivity, a higher rate of drug metabolism, cytotoxicity, and more. and by creating drug delivery systems employing the fundamentals of pharmaceutical nanotechnology, these obstacles may be removed. Characterizing and measuring biological processes in animals, like protein-protein interactions, cellular metabolism, signal transduction, gene expression, and both intracellular and intercellular trafficking, is the field of molecular imaging. Because it improves the qualities of potent medications and excipients, such as solubility and bioavailability, pharmaceutical nanotechnology is essential for the research and development of novel pharmaceuticals. [14]

Nanotechnology: An incredible approach in formulation development

For medications to be effective *in vivo*, solubility, bioavailability, and dissolution rate are crucial factors. The capacity of medications taken orally to be absorbed through the gastrointestinal system determines their bioavailability [2]. The pace at which a Class II pharmaceutical medication dissolves in gastrointestinal fluids restricts the absorption process for these medicines. Therefore, increasing the rate at which these medications dissolve will result in higher bioavailability. Too far, a number of approaches have been employed to increase the rate at which weakly water-soluble pharmaceuticals dissolve, including solid dispersion, complexation, solubilization, and the liquid-solid method. It appears that enhancing the solubility characteristics of medicines with low water solubility can result in an improvement in bioavailability [3]. Modern nanotechnology provides a number of techniques to increase the solubility of BCS class II molecules in water. A poorly water-soluble substance

can dissolve more quickly by being nanosized into nanoparticles, nanocrystals, or nanosuspensions without the need for expensive facilities and equipment or labor-intensive procedures. [5,6]. There are various pharmaceutical nanomaterials with unique advantages.

Nanomaterials are biomaterials applied to surfaces as coatings or surface changes to advance the biocompatibility and bioavailability of many more materials. [3]. Nanocrystalline materials are produced to serve as replacements for materials that have subpar bioavailability, solubility, etc. [4,5] Nanostructured materials are the treated forms with special dimensions and roles, from this microfluidics, microarrays, and nano- and micro-electromechanical systems. [5,6]. Nanotechnology-constructed creatures on a nanometer scale like carbon nanotubes, Biological nanomaterials, dendrimers, nanocrystals, etc. all are characterized by special features, some of which are discussed here [6]. Carbon allotropes having a cylindrical nanostructure include carbon nanotubes (CNTs). With a graphitic structure encircling a hollow core, they are made of one (single-walled CNT) or multiple (multi-walled CNT) layers of carbon. While the entire length of the tubes is often substantially larger, the dimensions of this core and the wall are both in the nanometer range. The features of composites made of CNTs distributed in matrix materials, such as polymers, are extremely intriguing and innovative. They might thus be helpful in a variety of industries, including materials research, electronics, optics, and more. [15] Nearly all of the mentioned configurations are possible for biological nanomaterials, however, they are often used as exosome-based nanoparticles for drug delivery, regenerative medicine, or as inactivated virus and virus-like particles in vaccines. Biological nanoparticles also include polymeric drug coatings, which are often employed as a technique for controlled distribution and improved stability. [16]

Dendrimers are radially symmetric, nanoscale molecules with well-defined, homogeneous, and monodisperse structures. They have an outer shell, an inner shell, and a core that is typically symmetric. They are known to produce very polydisperse products with a variety of molecular weights from their three typical macromolecular architectural classes. The biological properties of dendrimers include minimal cytotoxicity, polyvalency, electrostatic interactions, self-assembly, chemical stability, and solubility. There are several dendrimers. Dendrimers are a useful option in the medical industry due to their different features. [17] Liposomes belong to such kinds of nanoparticles with a hydrophobic tail and a hydrophilic head that collectively gives a phospholipid membrane. Liposomes are highly lipid-built spherical or multi-layered spherical construction that is divided as per a huge range of features, including preparation,

structural dimensions, structural parameters, size, synthesis techniques, and drug loading. Even though the a varied range of applications for liposomes, containing vaccine, drug, and gene delivery, biosensor manufacturing, diagnosis, and food product applications, their use is severely constrained by their physicochemical variability. Cholesterol acts on an essential role in the stability of the liposomal membrane.[18] Micelles have drawn attention because they can be used to deliver drugs with low water solubility. Micelles are created when amphiphilic molecules self-assemble. The structures have polar hydrophilic regions (head) and nonpolar hydrophobic regions (tail) [1]. In a hydrophilic solution, micelles are made with the nonpolar area forming the core and the polar region opposite the external surface of micelles. Both hydrophilic and hydrophobic agents can be delivered via micelles. Such structures are capable of delivering macromolecules as the encapsulated molecules are chemically and physically stable, have good tissue distribution, have a prolonged and regulated release of macromolecules, and have improved drug pharmacokinetics and bioavailability. Micelle formation is accomplished when the micelle concentration is above the threshold level. According to composition, micelles are typically spherical and range in size from 2 to 20 nm. [19].

They contain a liquid or solid core with a cavity in which the medication is deposited, encircled by a unique polymer membrane comprised of organic or synthetic polymers. Due to the protective coating, which is often pyrophoric, rapidly oxidized, and delays the release of active substances, they have drawn a lot of attention. [20] As a substantial drug delivery technology meant to get around different medications solubility issues, nanocrystals are shown promise. By having diameters in the nanometer range, nanocrystals are pure medication crystals. Technology from the bottom up or from the top down can be used to create nanocrystals. High drug stacking, excellent stability, and simplicity of scaling-up are advantages of nanocrystals, which are being extensively researched and employed to deliver medications that aren't very water-soluble. This information is summarized in Figure 2.

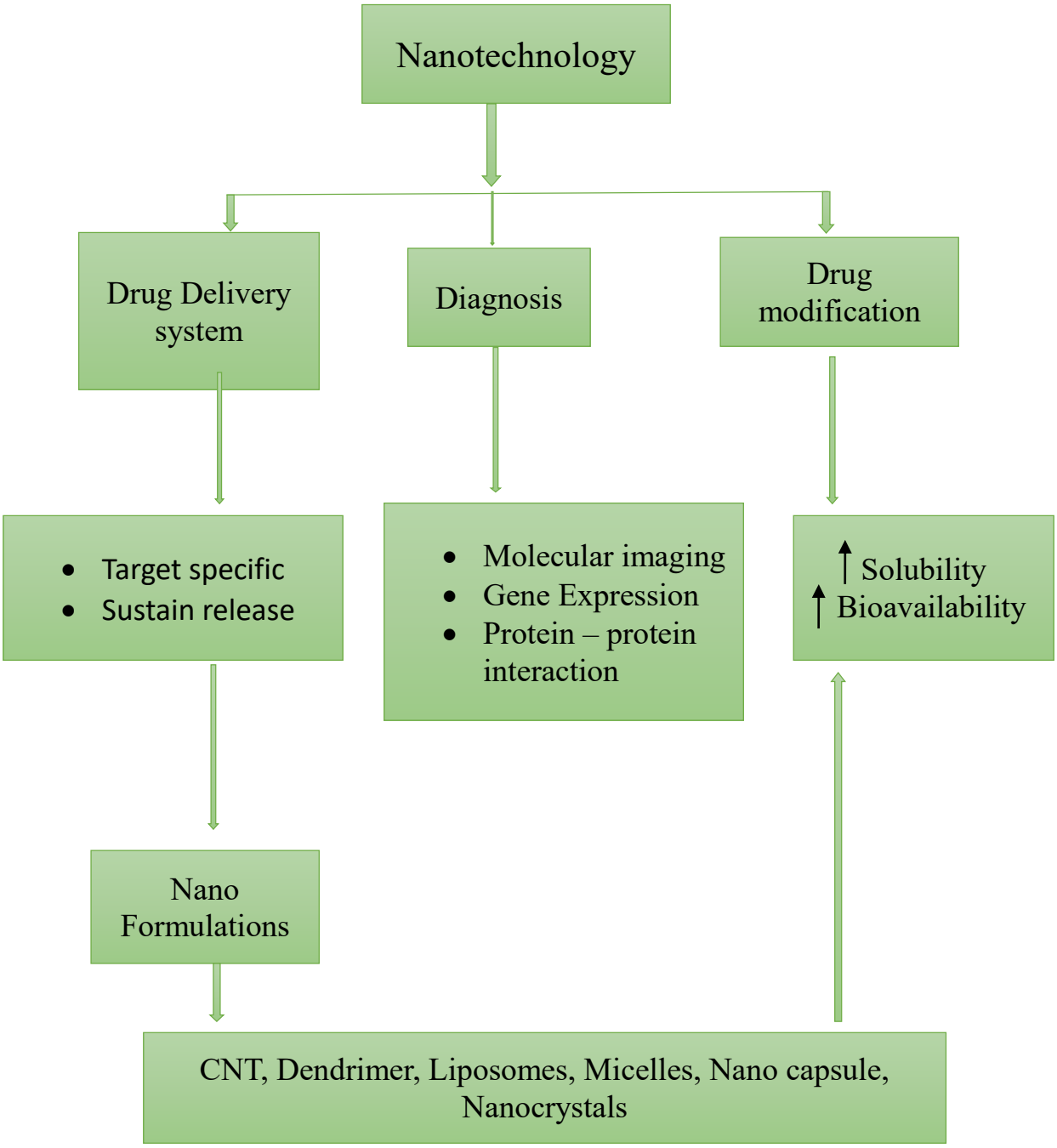

Figure 2: Overview of applications of nanotechnology

Nanocrystals as drug delivery system

There is a huge potential for employing nanocrystals to deliver medications through various modes of administration. The bioavailability of a medicine is influenced by its capability to get

dissolved in biological fluids, and traverse membranes, and successfully gets its pharmacological target. Pharmaceuticals in the biopharmaceutical categorization of pharmaceutical's Class II group have poor solubility but a strong capacity to cross membranes. The bioavailability of a Class II medication must thus be improved by enhancing drug solubility and/or drug dissolving rate. It has been found that nanocrystals improve the systemic reach of medications that are poorly water-soluble. [21]

Fields of nanocrystal application

Oral Drug Delivery

Oral administration is recommended technique for medicine therapy owing to its safety, convenience of production, patient compliance, and scalability; yet, its primary boundaries are caused by the drug's bioavailability. NC may increase bioavailability by enhanced solubility, and particle dissolution. [22]

Intravenous Drug Delivery

Because of the small particle size, nanocrystals have the advantage of being injectable by IV and achieving 100% absorption. NC between 100 and 300 nm could be injected by IV route without having any adverse side effects, such as a capillary blockage. Nanoparticles are capable to access the target tissue as a result of traveling through the circulation and dispersing in line with their dissolving properties.

According to Hollis *et al.,* the difference in distribution between the tumor and organs (brain, liver, spleen, and heart) was most likely caused by the paclitaxel nanocrystals quick assimilation into the macrophages. However, paclitaxel nanocrystals increased permeability and retention effect (EPR) was on par with that of the traditional formulation. As a result, paclitaxel's accumulation in healthy organs was lower than that of the conventional formulation, which accounts for the formulations lower systemic toxicity. This is true even though neither formulations drug accumulation into the tumour exceeded 1%, the dose that is thought to be effective in treating tumours. [23]

Pulmonary Drug Delivery

Despite the fact that this method of drug delivery is well known for its broad area of absorption, local action on lung infection, quick onset of action, etc., it also has disadvantages, including restricted dissolution of poorly soluble drugs, less residence time, frequent clearance because

of ciliary movements, and thus a lack of sustained action, as well as unintended retain of particles in the mouth and pharynx. While it has been argued that the best way to administer nanosuspensions is through the lungs, which would eliminate these issues, administering nanocrystals through this channel can take use of both the benefits of pulmonary administration of NC.[24,25]

Ocular Drug Delivery

Medication delivery to ocular tissues is most difficult due to the typically poor drug systemic reach, drug instability, brief retention time, less drug solubility, less amount of aqueous humour, and removal of drug with the tear. In addition to enhancing ocular medication penetration, favouring controlled release, and encouraging targeting, nanocrystals (nanosuspensions) offer less or more decreased unwanted effects than standard formulations. [26]

Dermal Drug Delivery

Using nanocrystals for dermal administration provides a number of important advantages. The larger particle surface area of NC can lead to enhancement in particle spreading and adsorption. Due to their greater saturation solubility, these formulations also offer higher molecular flow and dissolving rates. [27]

In addition to demonstrating that nanosuspensions may pass through the skin and collect in the viable epidermis, Vidlová *et al.*, also looked into the process by which curcumin nanocrystals pass through the skin.

Toxicity of Nanoparticles

The biophysical features of NPs, such as surface area, surface charge, size, and aggregation state, how it affects the system. The distribution and deposition of NPs in diverse organ systems as well as their molecular interactions with different proteins and other macromolecules have been demonstrated to be impacted by these features.

Endocytosis appears to be the main mechanism for the cellular uptake of nanoparticles (NPs). It has been claimed that NPs can stay inside cells for weeks or even months after being taken up by them. Despite this information, it is unclear how endocytosis affects the cellular toxicity of NPs. [28,29]

Acute Toxic Effects of Nanoparticles after Cellular Uptake

Acute toxicity of NPs can be impacted by their disintegration. After being taken up by cells, NPs are found in lysosomes, where the acidic pH of 5.5 promotes the NP's disintegration and subsequent release of potentially harmful heavy metal ions. It has been hypothesized that these ions harm cells through a number of methods, including the production of Reactive oxygen species ROS and the inactivation of enzymes. [20,31]

Nanoparticle Toxicity Following Chronic Exposure

For numerous reasons, assessing NP's acute toxicity is insufficient to determine their safety. First of all, exposure to NPs occurs continuously every day and might take the form of everyday use of cosmetics or exposure of employees in the manufacturing industry. Second, the removal of the treatment they are carrying may take considerably longer than the disintegration or breakdown of NPs, which probably takes a considerable length of duration. Additionally, NP's breakdown or degradation products may be harmful in and of themselves. Finally, there is a chance that NP biodistribution and accumulation will alter with time. Further research on the effects of NP chronic exposure is thus required. [32]

As discussed in the above references nanotechnology-nanocrystals are used for drug delivery in various routes of administration. Nanocrystal is said to be overcoming the obstacles of drug solubility, penetration, absorption, etc.

Nowadays multiple disorders are there which need lifetime drug therapy for example diabetes, and hypertension are affecting a huge population. The first-line agents prescribed for the diseases are constant in practice. Many more drug molecules can control such conditions but due to problems in the physiochemical characteristics of such drugs are not been prescribed.

Vascular disorder: hypertension

It is a well-known disorder in which force exerted on the walls of arteries is more than 120/80 mmHg and it's a dangerous cardiovascular event. The heart must work harder as a result of high blood pressure to pump enough blood to support normal physiological functions. If the condition is not treated, it may cause heart issues and harm to organs like the kidney, brain, and eyes. [33]

To control this increased pressure multiple mechanisms can be applied like widening of arteries, relaxing of artery muscles, thinning of blood, etc. Commonly prescribed medications

are beta blockers, Ca+ channel blockers, angiotensin II receptor blockers, ACE inhibitors, and thiazide diuretics. Tremendous drug molecules with the ability to reduce BP to normal or maintain BP are there but due to less solubility are not formulated and thus not used. In the era of nanotechnology, scientists are working on it. Nanocrystals are applied for some antihypertensive drugs for formulation development. [33]

Nanocrystals in the Treatment of Hypertension

Drugs have been transported to target organs using a unique delivery mechanism called nanoparticles (NPs). Tiny size, permeability, and retention action, NPs are absorbed through the target organ. The content of NPs controls the amount of drugs released through them. Medication-incorporated NPs for local delivery may thereby enhance drug effectiveness and reduce adverse effects. Studies in both fundamental science and medicine have used liposomes and polymers as nano-drug delivery systems (nano-DDSs.) [34,35,36]

Omoaki Ishihara *et al*., worked on the treatment of pulmonary arterial hypertension (PHA), with prostaglandin I2 and its equivalents, like beraprost sodium, being helpful in PAH. The therapeutic impact of beraprost sodium (BPS) on PAH and the standard of living of patients receiving this medication would both be improved by the incorporation of BPS in NC to give sustained release and targeting capabilities. Nanoparticles made from a copolymer monomethoxy poly(ethyleneglycol) and poly (lactic acid) and poly(lactic acid) homopolymer were used to encapsulate BPS. BPS-sustained NP's release and tissue targeting characteristics appear to be mediators of the positive effects on PAH animal models. Due to the lower doses and more frequent administration of BPS, BPS-NP can be helpful in the management of PAH patients.[36] New medication delivery methods have been developed using nanoparticles (NPs). Drug-incorporated NPs for local distribution may increase a drug's effectiveness and reduce its negative effects. Patients suffering from PAH had better long-term survival while receiving IV prostacyclin (PAH). BPS NPs prominently increase the rate of life in the monocrotaline rat model and considerably decreased right ventricular pressure, right ventricular hypertrophy, and pulmonary artery muscularization in the 2 rat models after a single administration. [37,38] As discussed in the above studies nanoparticles showed an increase in bioavailability and sustained and targeted drug delivery thus the formulation needed to be administered in a low dose that ultimately reduces the adverse drug effects. Many drugs are having the problem of solubility and thus are quite far from use in prescription e. g. Diltiazem, verapamil, manidipine, etc.

Calcium channel blocker: Manidipine

2-[-(diphenylmethyl)-1-piperazinyl]ethylmethyl-1,4-dihydro-2,6-dimethyl-4(m-nitrophenyl) 3,5-pyridine, also known as manidipine (MDP), Dicarboxylate methyl ester is a long-acting calcium antagonist antihypertensive vasodilator of the dihydropyridine type. It is a BCS class II medication. It has several unfavorable physicochemical and biological features as a result of its excessive lipophilicity, including very low water solubility and a considerable propensity to adsorb on glass and plastic surfaces. To treat various forms of hypertension, dihydrochloride salt (MDP.2HCl) is offered as once-daily 20 mg tablets. MDP has a limited systemic bioavailability due to its rapid clearance and first-pass metabolism, similar to other dihydropyridine derivatives. A nonlinear increase in plasma levels was seen when healthy volunteers received increasing doses (5 to 20 mg). It works as a powerful calcium channel blocker and an efficient antihypertensive. Nanotechnology can improve its solubility. [39]

A dihydropyridine calcium channel blocker called manidipine is applied to treat hypertension. A Ca++ channel inhibitor of the dihydropyridine type manidipine is employed in medicine as an antihypertensive. At therapeutically relevant levels, it is selective for vasculature and has no negative effects on the heart. [39]

Manidipine: A pharmacodynamic perspective

The manidipine is present in the solid state as yellow crystals and is poorly soluble in water. If MDP is administered by oral route, the plasma concentration reached is not sufficient to give a therapeutic effect at a common dose. MDP's limited water solubility causes it to dissolve less quickly in the gastrointestinal fluid after oral administration, which lowers its bioavailability. [40] G-proteins are involved in the voltage-sensitive inhibition of presynaptic N-type calcium channels. Gq-coupled receptors drive the contraction of vascular smooth muscle by causing calcium to be released from the sarcoplasmic reticulum. Following this, calcium channels open which are voltage-dependent, permitting calcium to enter the cell and eventually cause contraction. The L and T-type of smooth muscle cells of voltage-dependent calcium channels bind and disassociate from manidipine, inhibiting the entry of extracellular calcium and stopping the contraction. Vasodilation results from this ultimately lowering blood pressure. Renal vasodilation and a rise in natriuresis are brought on by manidipine. Lowering blood volume, probably adds to the antihypertensive impact. At therapeutically relevant doses,

manidipine is selective for the vasculature and has no appreciable action on the heart or central nervous system.

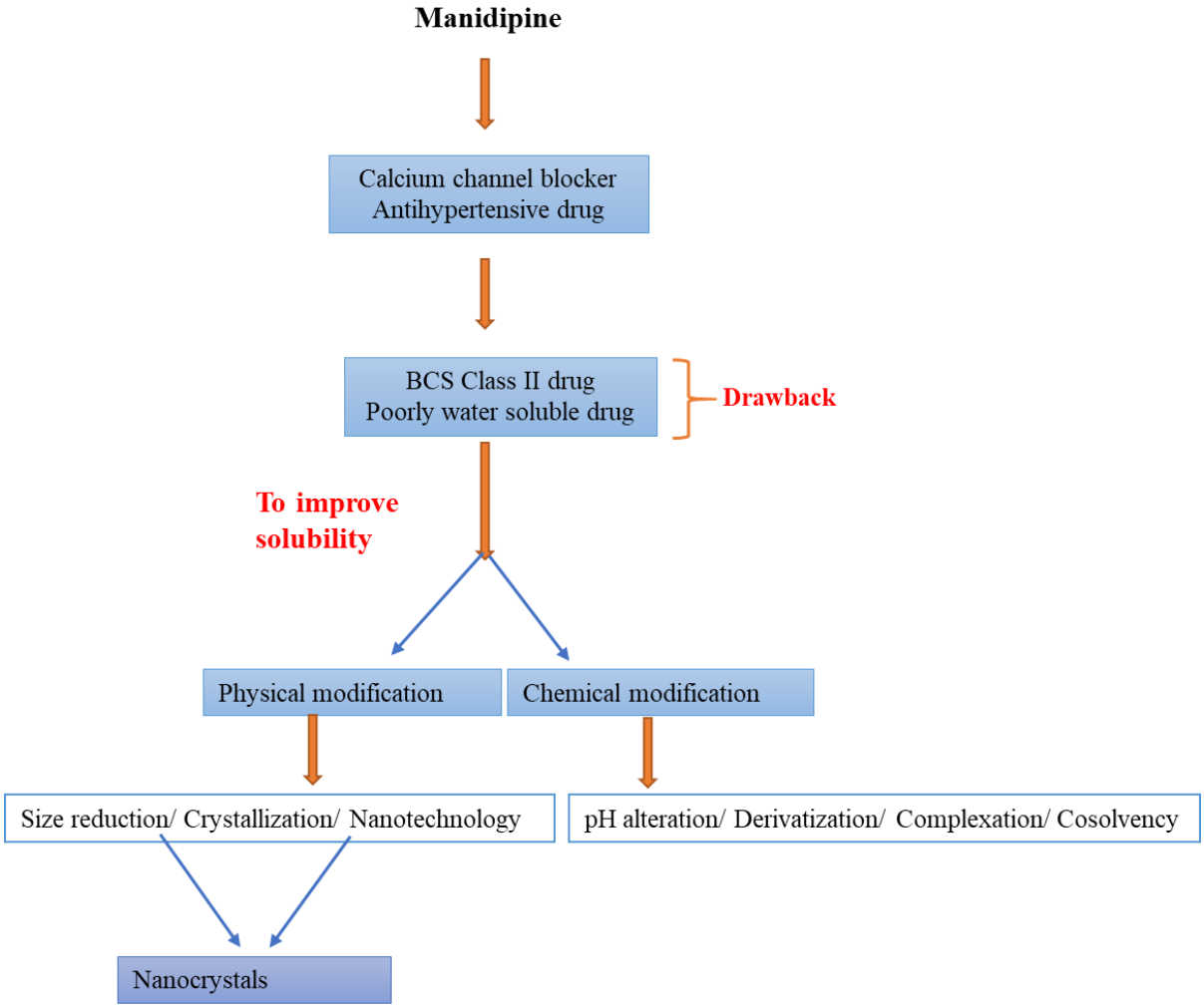

Figure 3: A review of manidipine

Taking both points together that is nanocrystals and manidipine, it can be concluded that if the nanocrystals of Manidipine are formulated, probably improve the solubility of the BCS class II drug manidipine (figure 3). Drugs can be transported to the target organ in nanocrystal formulation [31]**.** Nanocrystal formulation of beraprost sodium applied in pulmonary arterial hypertension. This formulation was sustained release and also target-specific. This can result in a better quality of life for the patient taking NC formulation of beraprost for PAH management. [36]**.** Drug-incorporated NPs effective for sustained release in PAH treatment without any negative effects [37].

Conclusion: Manidipine subjected for formulation in the form of nanocrystals it will enhance the solubility and bioavailability. As manidipine is a proven antihypertensive drug nanocrystal formulation of manidipine will definitely maintain the blood pressure but also will require less frequent dosing.

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