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Nanotechnology: an effective tool for enhancing bioavailability and bioactivity of phytomedicine

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PEER REVIEW

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Comments

This is a useful summary of a range of different formulation approaches that can be used to improve bioavailability. The authors have focused on a range of actives and this paper gives a welcome insight into how pharmaceutical formulation has been applied to overcome a number of challenges.
Details on Page S6

ABSTRACT

To achieve the desired therapeutic objective, the drug product must deliver the active drug at an optimal rate and amount. By proper biopharmaceutic design, the rate and extent of drug absorption (also called as bioavailability) or the systemic delivery of drugs to the body can be varied from rapid and complete absorption to slow and sustained absorption depending upon the desired therapeutic objective. Phytomedicine have served as the foundation for a larger fraction of the current pharmacopeia. But the delivery of phytomedicine is always problematic due to poor aqueous solubility, poor permeation, low systemic availability, instability and extensive first pass metabolism. Current review will discuss in detail about how nanotechnology can enhance the bioavilability and bioactivity of the phytomedicine.

KEYWORDS

Bioavailability, Bioactivity, Nanotechnology, Phytomedicine

1. Introduction

The therapeutic effectiveness of any drug may obtained from plant, animal, sea or synthetic which depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response. This attribute of the dosage form is referred to as physiologic availability, biological availability or simply bioavailability[1]. For most drugs, the pharmacological response can be related directly to the plasma levels. Thus, the term bioavailability is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form. Sometimes, a fast absorption is desired when a rapid onset of action is needed in the treatment of acute conditions such as asthma attack, pain *etc*. A slow rate of absorption is needed when the objective is to prolong the duration of action or to overcome the adverse effect and extent of absorption which is also significant in the treatment of chronic conditions such as hypertension, epilepsy, *etc*. These can be achieved by altering the physicochemical properties of the drug and characteristics of the dosage form[1].

Phytomedicine have been serving as a crucial source of drugs since ancient times. Today, about 50% of useful drugs is obtained from natural sources[2]. The usage of phytomedicine has been increased due to their better therapeutic activity and less side effects as compared to the allopathic medicines.

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Phytochemical and pharmacological investigation have been done extensively and well established. Phytomedicines shows impressive *in-vitro* activity but less *in-vivo* efficacy due to their poor water solubility, lipophilicity and inappropriate molecular size resulting in poor absorption and hence poor systemic availability. A better understanding of the biopharmaceutics and pharmacokinetics of phytomedicine can also help in designing rational dosage regimens[3].

Nanotechnology is on the threshold of providing a host of new materials and approaches in revolutionizing medical and pharmaceutical field. Several areas of medical care are already profiting from the advantage of nanotechnology[4].

The use of nanotechnology for treatment, identification, monitoring, and managing biological systems have recently been referred to as nanomedicine. In the herbal formulation research, incorporating the nano-based formulation has a great number of advantages for phytomedicine, including improvement of solubility and bioavailability, safeguard from toxicity, enhancement of pharmacological activity, improvement of stability, increase in tissue macrophages distribution, sustained delivery, protection from physical and chemical degradation, *etc*.[5]. Thus nano phytomedicine have a prospective future for improving the activity and overcoming problems associated with herbal drugs (Figure 1).

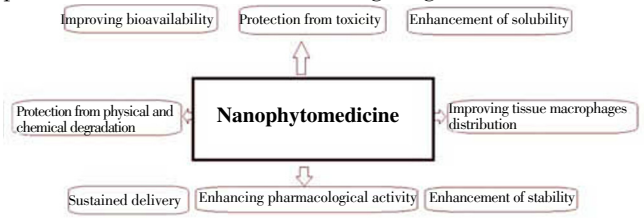

Figure 1. Applications of nanotechnology based phytomedicine formulation.

2. Problems encountered in phytomedicine product development

Mostly, phytomedicines are called as secondary metabolites and these metabolites are being chemically isolated and identified. The production of active constituents of phytomedince represents a lot of challenges[6]. These secondary metabolites which are present in plant are very low and their active constituents vary depending on a number of factors, such as botanical species, used chemotypes, the anatomical part of the plant used (seed, flower, root, leaf, and so on) and also storage, sun, humidity, type of ground, time of harvest and geographic area[7]. Phytomedicine screening from the plant is another challenge, and even though the high throughput methods are normally employed in the screening of drugs in pharmaceutical field, it is not suitable for the phytomedicine as crude extracts contain numerous drug compounds. Moreover, some active constituents present in the plant gave false information when screening by high throughput techniques[2]. In addition to this, identification, isolation of active constituents and fractionation process also takes weeks or even months and active ingredient supply is also another challenge, which needs several hundreds of grams for preclinical development depending upon the utility.

Many phytomedicine and extracts of plant despite of their surprising potential *in-vitro* finding, exhibit least or no significant *in-vivo* activity due to their poor solubility, poor lipid solubility and improper size result in poor absorption and bioavailability. Another problem is their structural instability in biological milieu, premature drug loss through rapid clearance and biotransformation and some plant extracts are destroyed in gastric juice during gastric emptying when administered orally.

3. Various nanotechnologies approaches for enhancing the bioavailability and bioactivity of phytomedicine

Phytomedicines are attracting more popular in the current world for their application to cure a variety of diseases with less toxic effects and high therapeutic property. However some limitations of phytomedicine are discussed in the previous section. Nanotechnology can serve as an efficient tool in eradicating the limitations stated above. By reducing the size of the phytomedicine into nano phytomedicine and modifying surface properties of phytomedicine, the aqueous solubility and permeability through biological membrane. Various novel drug delivery systems such as liposomes, niosomes, nanospheres and phytosomes have been reported to have the ablility of delivering herbal drugs. Incorporation of herbal drugs in the delivery system also gives aid to increase in solubility, enhance stability, protect from toxicity, enhance pharmacological activity, improve tissue macrophage distribution, sustain delivery and protect from physical and chemical degradation[8]. Moreover, to use nanotechnology, it may be likely to accomplish (1) enhanced delivery of poorly water-soluble phytomedicine; (2) targeted delivery of phytomedicine in a cell- or tissue-specific way; (3) transcytosis of phytomedicine across tight epithelial and endothelial barriers; (4) delivery of large macromolecule phytomedicine to intracellular sites of action; (5) co-delivery of two or more phytomedicines or therapeutic modality for combination therapy; (6) observation of sites of drug delivery by incorporating phytomedicine with imaging modalities[9,10].

3.1. Reducing the size of the phytomedicine into nanophytomedicine

Most of the phytomedicine formulation is administered orally because of patient convenience and manufacturing advantages compared with other dosage forms. For the orally administered drug, there are two critical slower rate-determining steps (RDSs) in the absorption. First is the rate of dissolution and the rate of drug permeation through the membrane is an another step. Dissolution is the RDS for hydrophobic in poorly aqueous soluble drugs and absorption of such drugs is said to be dissolution rate limited. If the drug is hydrophilic with high aqueous solubility, then dissolution will be rapid and RDS in the absorption of such drugs will be the rate of permeation through the biomembrane. That is said to be permeation rate limited or transmembrane rate limited (Figure 2).

A well formulated nanophytomedicine prepared through various routes of synthesis, by virtue of their size, enhances the dissolution, absorption and bioavailability of drugs while reduces in the dose. *Cuscuta chinensis* (*C. chinensis*) is a Chinese drug containing flavonoids and lignins as active medicament, which is poor aqueous solubility and poor absorption upon oral administration. The nano sized *C. chinensis* were prepared by a nanosuspension method for hepatoprotective and antioxidant effects after oral administration. The 25 and 50 mg/kg oral doses showed similar activity as that of 125 and 250 mg/kg ethanolic extract of *C. chinensis*, five fold reduction in dose