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Chapter 3

Emerging Technologies to Improve Capsaicin Delivery and its Therapeutic Efficacy

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Abstract

Capsaicin, a pungent alkaloid of chili pepper (*Capsicum annuum*) is responsible for the "hot and spicy" taste of chili. Also, Capsaicin is a pharmaceutical agent with broad therapeutic applications in controlling different diseases like diabetes, obesity, cancer, pain, and other inflammatory diseases. Capsaicin therapeutic effect is dependent on various factors like the concentration of capsaicin, delivery to different cell types, route of administration, and their metabolism. Improvement in the delivery of capsaicin will increase its therapeutic efficacy. Recent advancement in various technologies had provided numerous strategies to deliver capsaicin. This chapter outlines different strategies for using multiple new materials, formulations for the capsaicin delivery and improve their therapeutic efficacy as well their advantages and disadvantages.

Keywords: capsaicin, drug delivery, micro and nanotechnology tools, pharmaceutical formulations

1. Introduction

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide), one of the active ingredient of chili peppers, possess pungent flavor, was first isolated in 1816 in partially purified crystalline form by Bucholz and in a pure crystalline form in 1876 by Thresh [1], who named it capsaicin. Nelson partially solved the structure of capsaicin in 1919 [2], and the compound has initially been synthesized in 1930 by Späth and Darling [3]. Capsaicin is one of the member of capsaicinoids family and other members of capsaicinoids are shown in **Figure 1**. Capsaicin biosynthesis in

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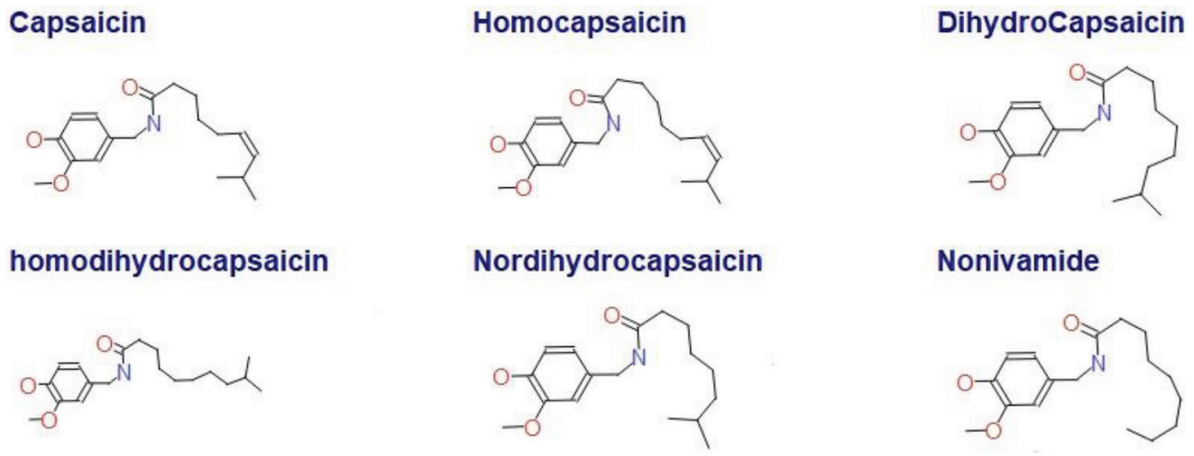


Figure 1. Three-dimensional structure representation of capsaicin and their derivatives present in chili pepper, were retrieved from PubChem database.

plants is defined by two pathways: phenylpropanoid, which determines phenolic structure; and fatty acid metabolism, which determines the molecule's fatty acids [3]. Capsaicin concentration increases gradually during fruit development reaching maximum levels at 40–50 days. Level of capsaicin increases by the increase in the activity of the enzymes phenylalanine ammonia-lyase (PAL), cinnamic acid-4-hydroxylase (C4H) and capsaicin synthase enzyme (CS), all involved in capsaicin biosynthesis [4]. Capsaicin is an odorless fat-soluble compound which is used to spice up cuisines, especially in Mexico and South America. Europeans introduced chili peppers to Asia and Africa, and they are now an essential ingredient of cuisines in Ethiopia, India, China, Sri Lanka, Thailand, Korea and Malaysia [5]. The Scoville heat units are used to measure the 'hotness' of chili peppers, which represents the number dilution required with water for it to lose its heat. Capsaicin scores about 16,000,000 units. The "heat

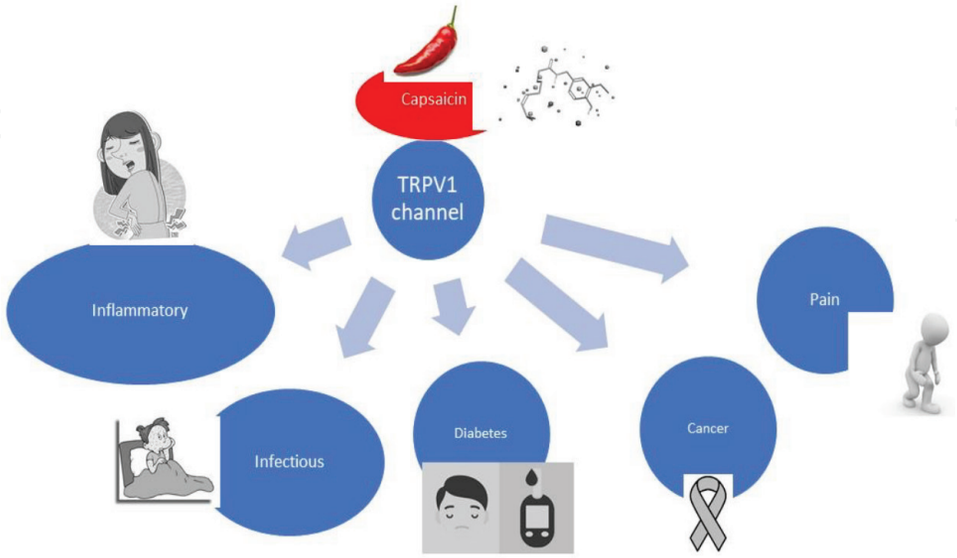


Figure 2. Pathological mechanisms involved when capsaicin modulates TRPV1 channel.

sensation" of capsaicin arises due to the binding of capsaicin to transient receptor potential vanilloid subfamily member 1 (TRPV1) ion-channel receptors. Capsaicin also is known as a modulator of TRPV1 [6]. A unique feature called as defunctionalization is responsible for capsaicin to use as therapeutic use. Capsaicin is proven to be beneficial in many physiological systems and can be used to treat diseases like pain, cancer, diabetes, obesity, infectious diseases, and inflammatory diseases (as shown in **Figure 2**). Many pharmacological and pain research studies have shown the multiple effects of capsaicin in a variety of physiological systems (cardiovascular, respiratory, and urinary) [7].

2. Mechanism of action

The device of action of capsaicin has been studied widely from the past decades. Nearly 20 years ago, it was demonstrated that capsaicin releases substance P from afferent nociceptive neurons. Capsaicin activates afferent nociceptive neurons and evokes sensations ranging from hotness to burning. The depletion of substance P mediates the analgesic properties of capsaicin that leads to the desensitization of small afferent sensory neurons [8]. Capsaicin binds to a specific nerve membrane receptor, the Transient Receptor Potential V1 receptor (previously known as vanilloid receptor, VR1 or TRPV1) encoded by gene TRPV1 gene. Capsaicin plays an essential role in the transmembrane signaling receptor. The TRPV1 receptors also respond to temperature, acidosis, painful stimuli, and osmolarity. TRPV1 has a central role in thermal nociception and inflammatory hyperalgesia [9]. The human and rodent TRPV1 receptor which consists of 838 amino acids (molecular weight of 95 kDa) was identified and cloned in rats in 1997 by Caterina [10]. The distribution of TRPV1 is there in other tissues such as the brain [11], bladder [12], kidney, and bowel [13]. Endovanilloids may regulate and activate the channels. TRPV1 is expressed not only on cellular membranes but also on

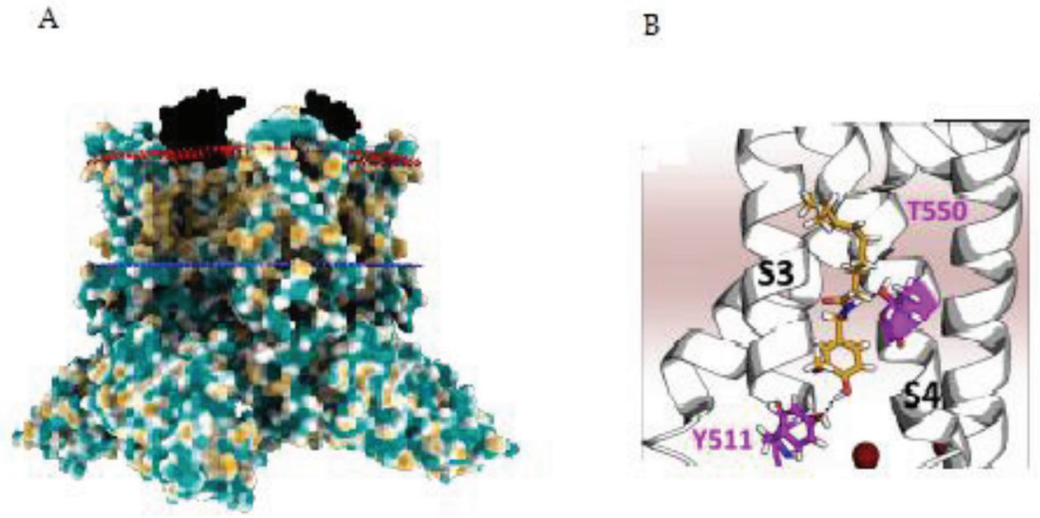


Figure 3. A represents the three dimensional structure of TRPV1 (adopted from PDB ID 3J5Q) and B represents TRPV1-capsaicin complex especially S3 and S4 domain interacting residues adopted from [17].

the endoplasmic reticulum [14]. Endoplasmic reticulum expression of regulates intracellular calcium levels, reverses the phosphorylation by involvement of kinases and phosphatases, role in formation of heteromers and regulate gene expression as well. Recently structural biology researchers, investigate the binding pose of capsaicin bound to TRPV1 channel, and it was resolved using cryo-EM. This study revealed that Capsaicin stabilizes TRPV1's open state by 'pull-and-contact' interactions between the vanillyl group and the S4-S5 linker. The interacting residues involved in capsaicin-TRPV1 channels are TYR 511, M547, and T550(as shown in **Figure 3**) [15]. Once, the agonists like capsaicin activate TRPV1 channels, many intracellular proteins containing Ankyrin repeats (AR) initiate signaling pathways, NFkB pathways, Apoptosis, degrade ubiquitin ligase, p38 -MAPK signaling pathway, controlling calcium ion concentration, regulating ATP metabolism, PIP2 hydrolysis, inhibiting CDk2, CDK4, and CDK6, and controlling cell cycle progression. Hence, Capsaicin-treated cells were proven to be anticancer, antidiabetic, and anti-inflammatory [16].

3. Metabolism of capsaicin

Metabolism of capsaicin is very rapid in the human stratum corneum, and it is dependent on the solubility of capsaicin in non-polar viscous solvents [18]. Oral administration of capsaicin is rapidly metabolized in liver, kidney, intestine, and in blood peak concentration is observed in 1 h [19]. In human studies, oral administration of 5 g of capsaicin and capsaicinoids to healthy volunteers had resulted in significant reduction in plasma glucose levels and also, increase in plasma insulin levels (Observed pharmacokinetics in this study are C(max), T(max), AUC(0-t), T1/2 are 2.47 ± 0.13 ng/ml, 47.08 ± 1.99 min, 103.6 ± 11.3 ng × min/ml, and 24.87 ± 4.97 min, respectively.) [20]. Topical administration of capsaicin [(640 μg/cm^2) like capsaicin patch, also called as NGX-4010] to different diseased patients, had resulted in quantifiable amounts of capsaicin. The amount of capsaicin detected in plasma is 31% for postherpetic neuralgia (PHN), 7% for painful human immunodeficiency virus-associated neuropathy (HIV-AN), and 3% for painful diabetic neuropathy (PDN) [21]. Intravenous administration of capsaicin leads to the rapid entry of capsaicin in the central nervous system, and their metabolism is low when compared to liver and kidney [22]. Bioavailability and half-life of capsaicin are low and is independent of the route of administration. This leads to investigate in the areas to design and develop new strategies to improve drug-delivery of capsaicin, to enhance their bioavailability and half-life.

4. General strategies for capsaicin delivery and their clinical challenges

To date, capsaicin formulations on the market include Capzasin-HP (Topical Analgesic Cream), Qutenza patches, LEADER CAPSAICIN (cream). The current administration of commercial capsaicin comprises topical delivery. Challenges in the clinical application of capsaicin are its short half-life, low bioavailability, produces burning sensation and side effects are dependent

on the concentration of capsaicin, skin irritation, burning and others. Alternative approaches have been extensively explored, to improve the delivery of capsaicin, including oral, gastrointestinal, intraperitoneal, subcutaneous, topical, and ocular. Emerging micro and nanotechnologies have attracted and lead to a general idea to encapsulate capsaicin to various carriers like lipid-based carriers (liposomes, microemulsion, solid-lipid nanoparticle), polymeric carriers (micelle, dendrimer, and polymersome), Inorganic carriers (metal nanoparticles, carbon spheres). The primary objective of chosen carriers is: (1) improve bioavailability; (2) enhance delivery to different cell types; (3) improve pharmacokinetics; (4) improve half-life of capsaicin.

5. Micro and nanotechnology tools to deliver capsaicin

Topical administration is the only method used in clinical use and as well to deliver capsaicin for pain treatment. Certain drawbacks observed by patients are, the short half-life of capsaicin, bioavailability is low, burning sensation of capsaicin had resulted in patient discomfort. In this study, we report different strategies proven to be successful at research level to improve the bioavailability, increase the half-life, reduce irritation, different routes of administration, use of micro and nanotechnology tools to improve the drug delivery and overcome the drawbacks of capsaicin treatment. Micro and nanotechnology tools were classified into three categories: lipid-based carriers, polymeric carriers, and inorganic nanocarriers.

5.1. Lipid based carriers

Liposome, microemulsions and solid lipid nanoparticles are chosen to be considered in the category of lipid-based carriers (as shown in **Figure 4**). Briefly, Liposomes (20 nm to several microns) can be used to encapsulate hydrophilic and hydrophobic compounds. Lipid constituent, surface charge, the physical state of the phospholipid bilayer plays a vital role in the enhancement of therapeutic efficacy of encapsulated pharmaceutical ingredients [23]. General methods used to encapsulate capsaicin are thin film hydration method, modified film method, film dispersion method [24]. Distinct advantages of using liposomes are high entrapment efficiency, non-toxic, biodegradable, active ingredients encapsulated in liposomes are protected

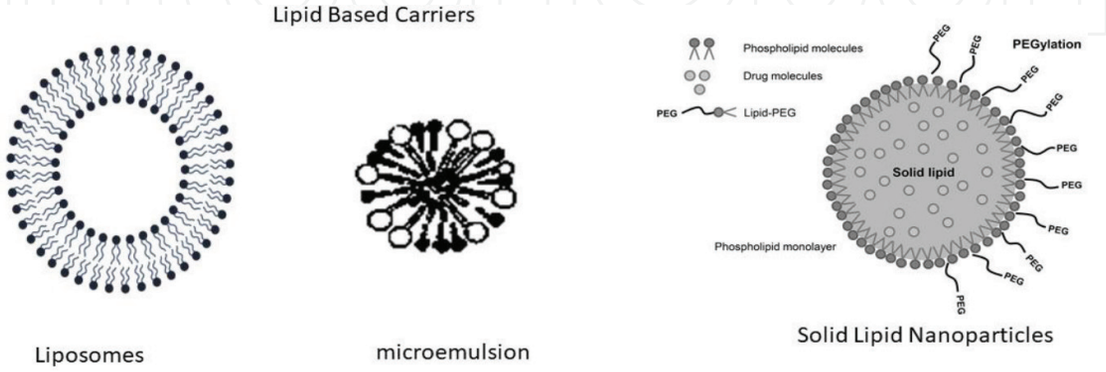


Figure 4. Lipid based carrier classification.

from immediate dilution or degradation. A microemulsion is defined as a system of water, oil, and amphiphile which is single optically isotropic and thermodynamically stable liquid solution [25]. Solid lipid nanoparticles are a new generation of colloidal drug carrier systems and consist of surfactant-stabilized lipids that are solid both at room and body temperatures [26].

5.1.1. Examples

Oral administration of Capsaicin Liposomes of mean size 52.2 ± 1.3 nm, had resulted in the encapsulation of Capsaicin with encapsulation efficiency 81.9 ± 2.43%, resulting in a 3.34-fold increase in bioavailability, as well the formulation reduces inflammation in gastric mucosa model [27]. Cather administration of phosphatidylcholine (PC) liposomes of the mean size smaller than 100 nm, were proven to benefit bladder irritation [28]. Oral administration of microemulsion consisting of Cremophor EL, ethanol, medium-chain triglycerides (oil phase) and water (external phase) of mean size 53.5 ± 1.6 nm with encapsulation efficiency 85.3 ± 1.1%, had resulted in the 2.64-fold increase in bioavailability, safe and effective [29]. Transdermal delivery of capsaicin, encapsulated in microemulsions based on non-ionic surfactants consisting of isopropyl myristate as the oil phase, Comperlan® KD as the surfactant, ethanol as cosurfactant, and reverse osmosis water as aqueous phase resulted in use of low dose capsaicin [0.15% (w/w)] as effective delivery when compared to current clinical products [30]. Solid lipid nanoparticles were used to encapsulate capsaicin with mean size 100 nm, prolonged release of the drug is observed for a duration of 14 h, encapsulation efficiency found to be 90%, and further studies are needed to understand PK and PD studies [31].

5.2. Polymeric carriers

Micelles and dendrimers are chosen under the category of polymeric carriers (as shown in **Figure 5**).Briefly, micelles are defined as nanoscopic core/shell structures formed by amphiphilic copolymers. These have a high potential to deliver compounds that are hydrophobic

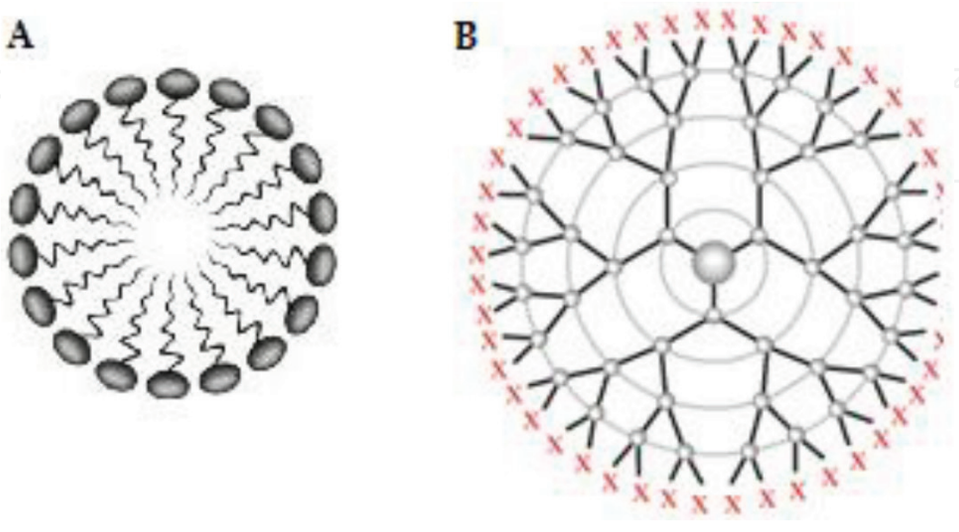


Figure 5. A represents micelle and B represents dendrimer.

and exhibit bioavailability. Dialysis method (organic-solvent free method) and solvent-switch method (direct dissolution method) are used for self-assembly of AB or ABA polymers into micelles in solutions. These are used primarily to incorporate water-soluble drugs. Direct dissolution and dialysis methods are used to synthesize polymeric micelles.

5.2.1. Examples

Oral administration of capsaicin with polyvinylpyrrolidone (PVP)/sodium cholate/phospholipid mixed micellar system was synthesized with mean size below 50 nm, with the 2.42-fold increase in bioavailability, as well reduced irritation on gastric mucosa [32]. Oral delivery of capsaicin using methoxy poly(ethylene glycol)-poly(ε-caprolactone) (called as MPEG-PCl) nanoparticles of mean size 82.54 ± 0.51 nm, acquired sustained release for 60 h. Pharmacokinetics revealed 6-fold increase and reduced gastric mucosa irritation is observed [33].

5.3. Polymeric dendrimers

Dendrimers consists of tree-like branches with many functional terminals ends also considered as monodisperse macromolecules. These are prepared using convergent or diverge methods and growth is dependent on cascade regions.

5.3.1. Examples

The oleoyl chloride, Polyethylene glycol (PEG) 400, and triethylamine were used to synthesize dendrimers using esterification process and bound with capsaicin. The resulting formulation possesses mean size 143.1 nm and resulting formulation was found to be cytotoxic to MCF-7 cells and Hep2 cells [34]and not toxic in case of zebrafish model [35].

5.4. Inorganic nanocarriers (metal nanoparticles, carbon spheres)

Inorganic nanocarriers are classified as metal nanoparticles and carbon spheres. Physical and chemical methods can be used to prepare metal nanoparticles, and they can exhibit multifunctional properties, size-dependent metal to non-transition. Functionalized with groups like thiols are responsible for bioconjugate chemistry application, fluorescent particles [36]. Till date, few applications support the use of inorganic nanocarriers. Use of copper sulfide (CuS) nanoparticles, when functionalized with antibodies targeting TRPV1, the complex acted as a photothermal switch, and results were found to be significant and can be used in future as a therapeutic tool, to attenuate atherosclerosis [37]. Another application revealed that capsaicin as bioreductant of silver nitrate to form silver nanoparticles and the resulting capsaicin-capped silver nanoparticles (mean size 20–30 nm) were found to be compatible with blood groups, and no further studies on this nanomaterial complex [38]. High sensitivity assay was developed when glass carbon electrodes are coated with carbon nanotubes, resulted in excellent detection of capsaicin in various pepper samples [39]. Based on the literature, it is evident that use of metal nanoparticles and carbon nanotubes to improve the bioavailability, increase the half-life and improve pharmacokinetic (PK) and Pharmacodynamic (PD) of capsaicin, is the new area to be explored to enhance the efficacy of capsaicin therapeutic.

6. Conclusion

Strategies to use micro-nanotechnology tools to deliver capsaicin have exhibited tremendous therapeutic potency for treating pain, cancer and other diseases at a research level. More studies are required at the basic and clinical stage to demonstrate their efficacy. The tools described in this study can also be used to deliver capsaicin through different routes of administration. Of course, potential challenges like delivery of the exact dose, maintain physicochemical properties of materials and capsaicin, the biodegradability of materials used to encapsulate capsaicin.

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Conflict of interest

The authors declare no conflict of interest.

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