Cockle Shell-Derived Calcium Carbonate Nanoparticles

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This entry is terms to explain the importance of CSCaCO3NPs as drug nanocarrier with emphases on cytotoxicity, pharmacokinetics, slow biodegradation, pH sensitive, safety and efficacy in addition to the good biocompatibility and osteoconductivity as bone substitute. The synthesis of stimuli responsive nanocarrier with sustain release is a significant innovation in the field of nanomedicine in which biogenic biodegradable inorganic CSCaCO3NPs for the delivery of both hydrophilic and hydrophobic drugs could be employed.

Keywords: Cockleshell ; drug delivery ; calcium carbonate ; therapeutics

1. Introduction

Recent developments in advanced active delivery systems for drugs, elicited by nanotechnology had led to their application in modern science [1][2][3]. Conventional free-drug delivery through subcutaneous, oral, intramuscular or intravenous routes, has led to drug biodistribution in the body via blood capillaries and accumulation to a certain concentration at the target site to exert therapeutic effects [2]. However, there is a paucity of the desirable effects of these free drugs due to poor bioavailability as a result of insolubility, hydrophobic nature, poor absorption and rapid metabolism [3]. In the quest to overcome some limitations associated with these therapeutic agents, the fast-growing field of nanotechnology focuses on diverse exploratory ways for researchers in the field of biomedical and pharmaceutical sciences. Advanced nanotechnology has paved ways for the use of convenient, affordable and noncomplex methods for synthesizing different nanoparticles from a range of abundant natural biomaterials and complex organic materials for industrial and medicinal purposes [4].

Nanoparticles are minute ultrafine particles with dimensions ranging between 1–1000 nm (usually 5–350 nm in diameter). They can be produced using different types of biocompatible materials [5][6]. The use of nanoparticle-based drug carrier systems in the field of nanotechnology has become an area with a novel attention in the past few decades due to their unique and superior properties that enable functionalisation at both molecular and cellular levels [7][8][9][10][11][12][13][14]. Advanced novel drug delivery systems help to boost the efficacy of therapeutic drugs as well as minimising the rate of a drug's off targeted effects thereby preventing cytotoxicity to normal cells [8]. This brought forth a useful enhanced therapeutic efficacy through suitable modifications of a drug's bioavailability, pharmacokinetics and serum stability [9] as well as specificity in drug release which is elicited by response to a particular stimulus such as ultrasound intensity, pH, magnetism and temperature [10].

Cockle (*Anadara granosa*) with a Malaysian native name "kerang" belongs to the family of *Cardiidae*, which is a small, salt water edible clam that is popularly referred to as marine bivalve mollusc [11]. It is native to coastal regions of South East Asia (Malaysia, Thailand and Indonesia). These important sea species mostly dwells in coastal area and it is a common important source of calcium carbonate ($CaCO_3$) with abundant biomaterials for biomedical purposes [12]. It has tremendous striking properties, also it is cheap and readily available with abundant high quality and pure $CaCO_3$ in aragonite polymorphic form, which is used in drug delivery [4].

$CaCO_3$ is an inorganic calcium salt originated from varieties of shelled molluscs, limestone, coccolithophores, plant ashes, chalk and marble which is recently being studied in the field of nanotechnology as one of the potential porous biocompatible and pH sensitive material [6][11]. Further, its solubility has been stated to be exponentially and inversely proportional to its pH [10][13]. Its physicochemical properties are easily regulated as well as surface morphological chemistry and method of production [14][15]. $CaCO_3$ is one of the emerging inorganic nanoparticles which exists in three different polymorphs such as vaterite, aragonite, and calcites [15]. It also possess a peculiar property of low thermodynamic stability thus, its size and shape are in concordance with the method and conditions of laboratory preparations [11]. In addition, numerous studies in recent years, were carried out on its toxicity to prove its wide safety margin both *in vivo* and *in vitro* [10][16][17][18][19][20].

2. Nanotechnology and Nanomedicine

Over the past few decades, nanotechnology has gained tremendous attention with good future prospects focusing more on nanoparticles, which is basically the bedrock of nanotechnology [1][13][17][21][22][23][24]. Nanotechnology is an important aspect of science that focuses on the continuous designing and manipulation of materials (atoms and molecules) to produce structures at the nanometre scale size ranging from smaller nanometre to 100 nm with unaltered initial unique features of the material used, with broad nanoscale schemes in clinical applications for therapeutic, protective as well as diagnostic purposes [8][25]. The entire application of nanotechnology from the synthesis processes, control release profiling, monitoring of biological processes and diagnosis is referred to as "Nano-medicine" [8]. This comprehensively means a process of transformation and encapsulation of a drug's molecules using nanostructures with or without the help of a carrier materials, masking some inherent drawbacks and limitations of free drugs such as poor bioavailability, hydrophobicity, high dosages, rapid assimilation, short half-life of photo degradation, poor selectivity as well as off targeted effects [26]. Conventional utilization of free drugs portrays poor bioavailability, low efficacy, non-selectivity and undesirable side effects [8][27]. For the past few years, a considerably large number of poorly soluble drug candidates has gradually increased as a result of the use of high-throughput screening and combinatory chemistry in drug discovery [28][29][30]. Approximately 70% of marketed drugs and many new chemical drug candidates, medicinal herbs as well as food supplements sometimes fails to be absorbed in the gastrointestinal tract (GIT) and often possess poor intravenous circulation and muscular tissue absorption after administration [31]. The low solubility nature of drugs limits their dissolution rate leading to a variety of issues which consequently results in low bioavailability as well as an erratic absorption pattern of drugs in biological systems [32]. However, an alternative way of overcoming such problems can be achieved by dose escalation although, this could result in undesirable effects associated with increased toxicity leading to patient's non-compliance [30]. Delivering therapeutic compound to the desirable localised site is quite challenging for the treatment of many ailments [27]. However, the application of nanomedicine have currently helped to overcome some of the problems of free dugs for therapeutic purpose [33]. This could be due to the uniqueness of the physicochemical properties presented by nanoparticles such as; (a) increased solubility; (b) increased drug pharmacokinetics; (c) co-delivery of multiple drugs to the same specific location at the same time (synergistic treatment); (d) enhanced bio distribution and bioavailability of drug to the targeted area; (e) improved drug permeability and retention effects; (f) increased specificity of drugs to targeted site of interest; (g) increased surface area to volume ratio and (h) decreased patient-to-patient variability [2][34].

3. Conclusions

Veteran $CSCaCO_3NP$ has recently been synthesized and developed by quite a number of scholars in the quest to overcome some biocompatibility issues associated with some therapeutic agents. The $CSCaCO_3NP$ among other nanoparticles, is one of the potential and toxic free nanoparticles due to its unique properties such as biodegradability, bioavailability, biocompatibility, large surface area and porosity nature. The top-down method adopted for the synthesis of $CSCaCO_3NP$ involves the use of simple suitable available and more cost-effective instruments in the presence of BS-12 surfactant, which is a biomineralization catalyst. $CSCaCO_3NP$ is applicable for the delivery of anticancer and antibiotics drugs with a remarkably effective role in bone remodelling and osteoporosis therapy. Nevertheless, the slow biodegradable nature of powdered cockle shells qualified its usage as an alternative construction material for artificial reef. Previous research literature highlighted some advantages of $CSCaCO_3NP$ as a nanocarrier for anti-cancer drugs and antibiotic focusing more on intravenous administration. Hence, the current review recommends more research on kinetic release mechanism of $CSCaCO_3NP$ in various different pH with emphasis on high acidic pH. Further improvement and modifications on the method of synthesising $CSCaCO_3NP$ to prevent problems of agglomerations is expected. Finally, research focus should be made on $CSCaCO_3NP$ as carrier system for various therapeutic agents such as anti-oxidants, anti-inflammatories using different routes of administration for effective applications at large.

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