Chapter

Emphasis on Development of Novel Drug Delivery Systems for Vitamin C: A Review

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Abstract

Vitamin C, the most prominent single Vitamin is a far sighted entity having varied roles to play, from treatment of diseases to Prophylaxis. In recent years understanding of the potential uses of Vitamin C has come to lime light.Thus it becomes essential to develop new novel drug delivery systems, in order for delivering Vitamin C in a stable form so as to maintain the efficacy and to enable it to reach its targeted sites and achieve its intended goals. This paper illustrates the advances made in delivering Vitamin C in its natural form by using novel techniques with an aim of increasing the stability, giving a boost to its physiological function. Layered double hydroxides systems, Microemulsions System, W/O/W emulsions system, Solid Lipid Nanoparticles system, Chitosan delivery system, Chemically modified Vitamin C for drug delivery, Pectin coated Vitamin C liposome Systems are some of the novel modern techniques applied for delivering Vitamin C to its intended sites by increasing the Stability.

Keywords

Vitamin C; Novel Drug Delivery Systems; Conventional Delivery Systems

Introduction

After giving the world over hundreds of scientific articles on Vitamin C for many years, there was little doubt that it works well in reducing oxidative stress, from cancer to cardiovascular disease, it has curative effect; this is what Dr. Linus Pauling believed who is considered to be the father of Vitamin C, the most popular single vitamin. Traditionally this has been used to treat and reverse the physiological effects of scurvy but in the modern times the occurrence of scurvy is seldom [1]. Today most of the efforts to market Vitamin C is in the form of dietary supplement to aid good health and wellbeing and the most common use would be to curtail the common cold and its symptom's as advocated by Dr. Linus Pauling in his book "Vitamin C, the Common Cold and the Flu".A genetic disorder in newborns called tyrosinemia in which blood levels of the amino acid tyrosine are too high can be treated by taking Vitamin C by mouth or IV [2]. Being a water soluble vitamin and due to its immune system protective properties by scavenging free radicals, it can be considered a substitute to the treatment of cancer; more advantageous as it shows no side effects on healthy cells [3-9]. The glucose transporters are increased many folds in cancer cells, therefore the anticancer properties of this vitamin are also augmented and there is an increased uptake of it into cancer cells. As the chemical structure of Vitamin C is reasonably related to glucose it exhibits anti proliferative effects on the cancer cells [10,11]. In addition, the comparative scarcity of the catalase enzyme in tumour cells aids the vitamin to intra-cellularly produce hydrogen peroxide which exclusively kills cancerous cells helping and facilitate as a chemotherapeutic agent of selective and nontoxic nature [12-13].The cornea constitutes the primary lens. In order to fulfil the extremely crucial functions, the cornea requires sophisticated structures called the Descement's layer, Bowman's membrane, the stroma, epithelium and the endothelium. The complexity of this tissue is such that despite many efforts, yet it has not been possible to obtain clinically viable corneas in the laboratory. Ocular tissues, particularly the cornea, which might suggest that the cornea's different structures need this vitamin to fulfil their roles [14].

Derivatives of Vitamin C

It is observed that Vitamin C derivatives can also hold back the similar efficacy demonstrated by ascorbic acid; for instance, the antioxidant activity which is the prime function of this vitamin. But these derivatives are still in its infancy and lots of research work is needed to establish their efficacy [15].

The different Vitamin C derivatives are:

(a) Ascorbyl-2-glucoside (ASC-G):

ASC-G has many useful properties one amongst them is the high constancy against thermal and oxidative degradation. It is also observed that in blood and liver cells it is rapidly converted into ascorbic acid by α-glucosidase enzyme [16,17]. It is also anticipated to be employed in the evolution of lipid-soluble vitamins and also as the lead constituent in many cosmetic formulations [10].

(b) Ascorbyl-6-octanoate (ASC-8):

It was noted that ASC-8 has self-assembling and antioxidant properties[15]. Therefore ASC-8 can be considered a potential replacement for VC as an antioxidant in stable form.

(c) Ascorbyl-6-palmitate (ASC-P):

Nanosized lipid carriers have been modelled for using ASC-P as a potential drug candidate. The physicochemical properties and in vitro release works of ASC-P-incorporated nanostructured lipid carriers showed promising results. It has been used in food, pharmaceutical and cosmetic sectors as an antioxidant [18, 19].

(d) Ascorbyl-6-stearate (ASC-S):

Is another Vitamin C derivative which has shown potential in being used as an anticancer agent, it was noted that the anticancer activity of polymeric nanoparticles containing ASC-S showed increased activity as it was more readily taken up by the cancer cells relative to other normal cells in the body [20].

(e) Ascorbyl-2,6-dipalmitate (ASC-DP):

It has shown extremely low water solubility in contrast to the bioavailable form of VC [23].This unique property of ASC-DP has been exploited in the formulation of cosmetic products [21,22].

Table 1: Conventional delivery systems available in market for Vitamin C.

Sr. no	Brand Name	Manufacturer	Type	Unit
1	Celin	Smithkline Pharmaceuticals Ltd	Tablet	100mg
2	Celin-500	Smithkline Pharmaceuticals Ltd	Tablet	500mg
3	Celin Chewable	SmithklinePharmaceuticals Ltd	Chewable tablet	500mg
4	Citravite	Pharmed Limited	Tablet	Ascorbic Acid(100mg) Sodium Ascorbate(450mg)
5	C-1000	Vitamin Shoppe Industries, Inc.	Capsule	Vit- C (1000mg)
6	Cecon	Pfizer Ltd	Drops	100mg/mL
7	C-SALTS™	Wholesale Nutrition	Effervescent powder	4000 mg/serving
8	Ascorbic Acid Injection, USP	Mylan Institutional LLC	IV solution	500mg/mL

Rationale of Review

Vitamin C is a vital vitamin and an important water-soluble nutrient, many animals chemically synthesize it from glucose by means of enzymatic reactions, with L-gulono-γ-lactone oxidase being the last step. Humans are depending on exogenous source because of the absence of this enzyme. [24]. Among the multiple roles played by this vitamin, still many more are yet to be fully assessed which makes it a vitamin of interest to the researchers. Moreover, it is a powerful antioxidant because of its capacity to neutralize free radicals [25]. The chemistry, functions, metabolism, bioavailability, and effect of processing have been comprehensively reviewed [26,27]. Vitamin C is also important in minimizing the risk of serious diseases (e.g, cataracts, improving the immune system and cancer). The recommended intake is 30–40 mg per day [28], but some studies extend this limit to 500 to 1000 mg per day [29,30]. It is naturally present in many fruits and vegetables; however, exposure to high temperature during cooking and processing, moisture, oxygen, pH, and light deteriorate its antioxidant activity and results in the formation of toxic compounds [31]. Thus it becomes a vital need to delivery VC in a stable form to wangle its full potential. This review paper thus intends the researchers in understanding the importance of Vitamin C and the current novel developments achieved to deliver it in a stable and bioactive form.

Potential Novel Drug Delivery Systems for Vitamin C

Microemulsions with Alkyl Polyglycosidesas Vitamin C Delivery System

Microemulsion is regarded as a perfect liquid medium for delivery of the vitamin C owing to its various benefits,for instance, very tiny droplet size (<100 nm), thermodynamic stability, stress-free formulation, low viscosity and great surface area[32]. Compared to conventional formulations it is observed that the permeation rates are significantly higher in case of microemulsions which aids the release of the vitamin from the formulation [6,7]. If a best possible proportion of alkyl-polyglycoside and an appropriate co-surfactant is carefully chosen, microemulsion having very low interfacial tension can be designed giving rise to a stable formulation. [9,10]. High concentration must be used in transdermal application as very less quantity is able to penetrate through the skin [33,34]. Thus a novel technique needed for delivery through skin is needed which can be fulfilled by the formulation of vitamin C microemulsions with alkyl polyglycosides [35]. HLD (hydrophilic lipophilic deviation) was used to envisage new vitamin C microemulsions for tropical application. Microemulsion systems were optimised and then was loaded into them to form the final formulation. Realisation of ternary diagrams establishes the formation of microemulsion system. The well-recognized mechanism to characterize surfactant–oil–water systems is by connotation of HLD concept and dilution pseudo-ternary diagram which gives it an impetus to accomplish stable cosmetic microemulsions aiding to be used as a whitening agent. In addition, relative oxygen matrix damage can be curtailed by effectively delivering it to the dermis [35].

Layered Double Hydroxides as Vitamin C Delivery System

Layered double hydroxides (LDH) are made up of positively charged hydrotalcite kind layer of metal hydroxide and the interlayer region is characteristically full of anionic species and water molecules. The hydroxide interlayer is used to incorporate different kinds of inorganic or organic anions, simple ion exchange reaction or co-precipitation is used to stabilise them [36–38]. LDHs nanohybrid components' have gained prominence due to the subsequent intercalation composites are projected to have a novel nanostructure and new utilities [39–45].Thus intercalation compounds such as LDHs are capable of being used as material for transport, controlling the release of the active ingredient and storage of unstable and reactive molecules like vitamin C [46-48]. Anion exchange method is being applied for the formulation of Zn-Fe and Mg-Fe LDHs, with the view of adsorption of the vitamin, leading to effective intercalation into portico space of LDH offering a different route of preservation of biological action in addition to sustained release [49]. Analytical techniques such as FTIR, TG–DTA and XRD have facilitated in the characterization of this novel formulation. Rather fast adsorption of the anionic vitamin C by Zn-Fe LDH and Mg-Fe LDH were detected and the release profile observed by spontaneous de-intercalation with carbonate anion also showed satisfactory results [49]. In another study Ca/Al LDH were formulated as drug delivery system for this vitamin. The reports exhibited that incorporation in LDH was 36.4 wt% and also the thermal stability is suggestively enhanced after intercalation. The invitro drug release profile indicated maximum percentage released is 80%wt of the total [50]. Thus it can be noted that the stabilization can be achieved by using LDH with no deviation in its chemical as well as functional integrity.

W/O/W Emulsions Encapsulating Vitamin C

Double emulsions are diverse polydisperse structures in which water in oil and oil in water emulsions, are stabilized by lipophilic and hydrophilic emulsifiers respectively, allowing both the phases to simultaneously co-exist [51]. W/O/W emulsions are useful for producing lower-calorie encapsulated products than traditional oil-in-water (O/W) emulsions because fraction of the oily dispersed phase is substituted by aqueous droplets [52]. W/O/W emulsions have found a special place in pharmaceutical industry due to their wide array of useful applications particularly in targeted drug delivery systems. Encapsulation of bioactive and unstable compounds like Vitamin C in W/O/W emulsions is an emerging technology that has undergone intensive research in recent years. A variety of processes can be utilized to encapsulate the vitamin into W/O/W emulsion like spray drying, spray chilling[54], and extrusion [55]. A recent study has focused on formulating monodisperse food grade W/O/W emulsions enclosing an elevated amount in an internal aqueous phase using homogenization and subsequent microchannel emulsification technique [56]. In another study W/O/W double emulsions were prepared by addition of the primary emulsion W/O containing 74%wt of Chia essential oil, 6%wt of Vitamin C, and a 0.2 dispersed phase mass fraction W/O to aqueous solutions of mesquite gum, malt dextrin DE-10 and whey protein concentrate in varied quantities. Good stability was achieved despite the bimodal size distributions throughout the storage period suggesting double emulsion system as potential candidate for delivery of vitamin C by stabilizing it [57].

Vitamin C Loaded Solid Lipid Nanoparticles (SLN)

SLNs are observed to have trivial particle size, a decent physico-chemical stability, sustained release of actives and can also continue the controlled release of drug for a longer time period [58]. Vitamin C having apoptotic effect on cancer cells can be considered for treatment of cancer since it has no hostile consequences on healthy cells [59]. Besides, the vitamin incorporated in SLNs also intensifies the specificity to certain cells and tissues; increases the bioavailability of active components and also defends them from the external atmosphere [59–67]. In a recent study, anticancer properties of Vitamin C-SLN on H-Ras5RP7 and NIH/3T3 cell lines have been evaluated. Corresponding to MTT test report, VC-SLN displayed elevated cytotoxic activity in comparison to the free vitamin C against H-Ras 5RP7cells with no destructive outcomes on NIH/3T3 control cells [58]. The evidence for its activity has been established by Annexin V/PI andcaspase/3 assay and confocal laser scanning microscopy [58]. Thus it is noted that SLN formulations improve the properties of the vitamin by providing small particle size, sustained drug release profile and high encapsulation efficacy.

Chitosan as Vitamin C Delivery System

The N-deacetylation of chitin results in the formation of Chitosan, a cationic biopolymer, which are a naturally occurring polymer and the second most plentiful polysaccharide next to cellulose [68]. Non-toxicity, biodegradability, biocompatibility and bio-adhesion are some of the characteristic features of Chitosan [69,70]. By encapsulating active compounds, chitosan has the ability to protect them from severe conditions in the gastrointestinal tract and also augments their uptake [71]. Exogenous sources of vitamin C are needed by humans as it is not synthesized by us. It is liable to change and loses most of its performance in the course of dispensation and storage of food, as oxidative loses occur due to the elevated temperature, light and oxygen [72]. This drawback can be overcome by encapsulation is a suitable carrier such as Chitosan. Chitosan nanoparticle in a study has shown to be suitable carrier for nanosize and it also noted that chitosan is able to maintain the immune inducing of the vitamin. It was observed the release from the Chitosan nanomaterials is pH dependent. Release was rapid in 0.1M phosphate buffered saline (pH 7.4); whereas the release slowed down in case of 0.1M HCl [73]. In another study self-aggregated, size controlled N-acyl chitosan nanoparticles were developed as carrier system. Hydrophobicity and stability of the delivery system was improved by synthesising N-acyl chitosan having a variety of acyl chain lengths. Particle sizes were observed in the range of 444 nm to 487 nm and with several acyl chain lengths the particle size reduced to 216–288 nm with vitamin C loading. The incorporation effectiveness on N-acyl chitosan nanoparticles varied from 55–67%. Thus it was noted that release profile of the vitamin load reduced with ascending length of acyl side chain [74].

Pectin Coated Vitamin C Liposomes

Liposomes offer numerous benefits over conventional delivery forms, like improvement of drug penetration, improved bioavailability, controlled drug release, in addition to lessening of side effects [75–78]. Though, the solitary problem with liposomes in practical application is their unsatisfactory physical and chemical constancy, preceding to lipid oxidation, changes in particle size distribution and leakage of the encapsulated materials [79–81]. In order to overcome these limitations, the formation of bioadhesive and polymeric membranes around the liposomes have been developed to improve their storage stability or skin permeability, such as chitosan, polyvinyl alcohol[82], Eudragit EPO [83] and pectin coating. Pectin is a multifarious hetero-polysaccharide which is extensively dispersed in the cell walls and middle lamella of most of the plants [84]. Because of its gelling characteristics, bio-compatibility, bioadhesivity, biodegradability, and non-toxicity, pectin has received attentions in pharmaceutical and cosmetic applications [85,86]. In a study Storage stability and skin permeation of vitamin C liposomes was improved by pectin coating. A transdermal drug delivery system by high methoxyl pectin or low methoxyl pectin coated liposomes was prepared. Skin permeation of the vitamin was improved 1.7-fold for HMP-L and 2.1-fold for LMP-L after 24 h [87].

C_6O-Modified Vitamin C for Drug Delivery to Brain

The management of several central nervous system (CNS) ailments, for example Alzheimer's, Parkinson's and Dementia, is still a foremost challenge for the medical world. The staggering difficulty faced in delivering drugs to the CNS is the low permeability of active ingredients into the brain because of the blood brain barrier (BBB). The role of BBB is not only to pretend to be a physical obstacle but also a biochemical obstacle [88]. The bioavailability of drugs in brain for treating CNS disease is always hindered by difficulties in crossing the BBB. In latest studies, it was found out that brain tissues contained the highest concentration of Vitamin C, acting as an antioxidant and also assisting in other essential physiological functions [11,12]. Current studies have vividly showcased the transfer and storage means of the vitamin in the brain[89]. It is understood that the passage in the brain is usually centred on two distinctive modes: 1) The oxidized form of Ascorbic Acid is transported by the facilitative sugar transporters of the GLUT type, Dehydro-ascorbic acid (DHAA), which is then reduced into Vitamin C [90-93]; 2) Nab-dependent Vitamin C transporter SVCT2 transports the vitamin precisely into brain [94]. Thus it can be of concern to investigate the further use of it as a carrier to bypass the BBB [95,96]. And in this sense C_6O-modified Vitamin C has generated a lot of curiosity as a transporter [18,19].

Conclusion

As the medical science progressed it has opened the door for better insight into Vitamin C. The study on functions of the vitamin has now not just been limited to antioxidant properties but a passel of other possibilities are being uncovered as we look deeper into its functions. By getting an understanding of its significance in our lives and following the current trends in developing novel drug delivery systems, it is understood that a lot of work still needs to be done in order to maintain the efficacy to enable it to reach its targeted sites and achieve its intended goals. Thus it can be said that more work needs to be done in developing novel techniques for its delivery. By writing this review, the authors hope that some light is thrown at understanding the direction and magnitude of work that can be done in developing more novel techniques to deliver Vitamin C.

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