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Research Article

Nano-Technology In Aspects Of Phenolic Drugs

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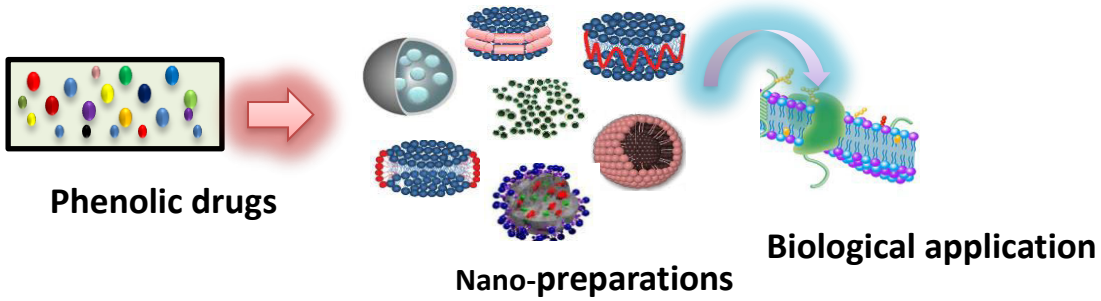
ABSTRACT

Nowadays, there is a growing research on phenolic medications. It is due to the phenolics (phenolic compounds) are one of the major dietary supplements, having important applications in cosmetics and toiletries, preservation of food and drinks, as well as in medical and pharmaceutical fields. To date a number of phenolics have been introduced in modern medicines. However, solubility, release and permeation, bioavailability, odor and easily destruction problems are the restricting factors of phenolics in biological system. The nano-encapsulation of substances may overcome those problems. Therefore, phenolic medications can be incorporated into nano-carriers by means of a number of nano-carriers and nano-technologies. This review aims to sketch a current scenario of nano-delivery advances for phenolic drugs in the pharmaceutical context. The finding suggests that phenolics can be encapsulated by the polymers (e.g. - biodegradable), polymeric complexes, cyclodextrins, caseins, nanocrystals, electrospun nano-fibers, electro-spraying, and nano-spray drying. However, we need to perform adequate toxicological tests along with the biological fate during digestion, absorption, and excretion of polymeric nano-particle and nano-carriers containing phenolics after nano- encapsulation. In conclusion, inclusion of phenolics into nano-carriers is an interesting and hopeful aspect in many areas, especially in the pharmaceutical sector.

INTRODUCTION:

Among the others, phenolic molecules (phenolic (OH: hydroxyl) group containing substances) have been gaining much attention day by day due to their promising biological roles. Many of them are now included in our regular diets. They are mainly known for their antioxidant, anti-inflammatory, anticancer, organo-protective, especially the nervous system and so on (Islam et al. 2016a). Generally, phenolics are sourced from plants and beverages. These are mainly two types (i) water-soluble (e.g. – phenolic acids, phenyl propanoids, flavonoids, and quinones) and (ii) water-insoluble compounds (e.g. – condensed tannins, lignins, and cell-wall bound hydroxycinammic acids) (Rafiee et al. 2012; Taghvaei and Jafari 2013; Rahmanian et al. 2014, 2015). Incorporation of pure phenolics in biological systems is restricted due to their low solubility, fast release, low permeation, low bioavailability, and easily destruction by the influence of the host environmental stresses. However, micro or nano-encapsulation methods can be used to design to overcome the biological installation problems.

This text sketches a brief note on the advances of nano-delivery (both technology and carriers) of phenolics drugs.



Findings

Nano-materials are the sub-micron substances, while nano-spheres are matrix and nano-capsules are the vesicular systems (Couvreur et al. 1995). Nowadays, biodegradable polymeric materials such as proteins (such as, gelatin and milk proteins), polysaccharides (such as chitosan, sodium alginate and starch), and synthetic polymers (such as poly (D, Llactide), poly (lactic acid) PLA, poly (D, L-glycolide), PLG, poly (lactide-co-glycolide), PLGA, and poly (cyanoacrylate) PCA) are popularly used for nano-encapsulation (Jackanicz et al. 1973; Bae and Kataoka 2009; Garg et al. 2015).Most commonly used polymeric nano-particle preparation methods are: (i) solvent evaporation method (e. g. – quercetin and curcumin nano–encapsulation) (Tsai et al. 2011), emulsification/solvent diffusion (e. g. –curcumin nano–encapsulation) (Reis et al. 2006), ionic gelation method (e. g. – rutin nano–encapsulation) (Konecsni et al. 2012), self-assembly(e. g. – ellagitannins nano–encapsulation) (Li et al. 2011), coacervation-phase separation technique (e. g. – resveratrol nano–encapsulation) (Karthikeyan et al. 2013), and polymerization of monomers (e. g. – curcumin nano–encapsulation) (Soppimath et al. 2001). The nano-particles can be fabricated by controlling the assembly of two different phases by means of a complexation from a non-covalent association (mainly by electrostatic interactions) (Bouyer et al. 2012). For examples, anthocyanin interactions with protein isolate (WPI) and beet pectin (BP) nanoparticles (Arroyo-Maya et al. 2015) and bovine serum albumin (BSA)/i-carrageenan nanoparticles as a protective carrier for (-)-epigallocatechin-3-gallate (Li and Wang 2015).

Furthermore, polymeric nano-micelles colloid systems can be applied for nano-encapsulation of poorly aqueous soluble and amphiphilic phenolics. In this regard, hydrophobic biodegradable polymers such as poly (b-benzyl-l-aspartate), poly (dl-lactic acid), or poly (e-caprolac tone) can be used to cover the insoluble bioactive compounds. Generally, micelle formation occurs as a result of two forces. An attractive force leads to the association of molecules, while the repulsive force prevents unlimited growth of the micelles to a distinct macroscopic phase (Bae and Kataoka 2009). The fabrication of polymer nano-micelle can be done by both physical and chemical methods. Chemical conjugation occurs by the formation of a covalent bond, such as an amide bond, between specific groups of the encapsulated compounds and the hydrophobic polymer of the core, while the physical entrapment of bioactive compounds is generally occurs by the dialysis or emulsification procedures in physical method (Bae and Kataoka 2009). Some examples of nano-micelles are:

resveratrol with poly-caprolactone (Lu et al. 2009), curcumin nano- micelles prepared by one-step solid dispersion method with monomethyl poly (ethylene glycol)-poly (ecaprolactone) (Gong et al. 2013), and so on.

Cyclodextrins (CDs), the natural nao-carriers have been widely used for nano-encapsulation of many different bioactive compounds to enhance their bioavailability, stability, and other functional properties. CDs are cyclic oligosaccharides consisting of 6, 7 or 8 glucopyranose units linked by a (1–4) glycosidic bond. Naturally, CDs have three cylindrical shapes of α-, β-, and γ- CD, but β-form is commonly used for encapsulation purpose. CDs are mainly used for water insoluble phenolics (Pinho et al. 2014). Some examples of CDs incorporated nano-encapsulations are: curcumin (Yallapu et al. 2010), quercetin (Borghetti et al. 2009), rutein (Calabro et al. 2005), resveratrol (Das and Kalita 2014), and hesperetin (Tommasini et al. 2005).

The other popularly used nano-carrier for the nutraceuticals including phenolics is casein, which is a flexible major milk protein (Holt and Sawyer 1993). The curcumin can be encapsulated with this type of nano-carrier (Esmaili et al. 2011). On the other hand, crystals with size in nanometer (nm) range are generally termed as nano-crystals can be used for nano-encapsulation of phenolics, where we can use water, aqueous solutions or non-aqueous media (e.g., liquid polyethylene glycol, oils) as dispersion media (Kakran et al. 2012).Furthermore, we can use some other technologies include: electro-spinning (mode: electricity for spinning) (Huang et al. 2003), electro-spraying (electro-hydrodynamic spraying) (Tapia-Hernández et al. 2015) and nano-spray drying (Mahdavi et al. 2014) for nano-encapsulation of phenolics. In **Table 1**, a number of polymeric-based nano-encapsulations of phenolics have been shown.

Table 1*. Some nano-encapsulations of phenolic drugs*

Compounds	Encapsulation-materials	Methods	Size (nm)	Activity	References
Catechin	β-cyclodextrin	Inclusion complex	67-470	↑ antioxidant activity	Krishnaswamy et al. 2012
	Chitosan/ poly (γ-glutamic acid)	Impel poly-electrolyte self-assembly	137-147	↑transport & antioxidant activity	Tang et al. 2013
Curcumin	Poly (lactic-co-glycolic acid) (PLGA)	Solvent evaporation	13-200	↑solubility, stability and antioxidant capacity	Kumari et al. 2010; Mathew et al. 2012
	Poly(butyl) cyanoacrylate (PBCA)/ chitosan	Polymerization	200	Inhibited hepatic carcinoma growth *via* an anti-angiogenic effect	Duan et al. 2010
	Protamine sulfate (PS) with bovine serum albumin (BSA)	Layer by layer	80	↑controlled release	Zheng et al. 2010
	Methoxypoly(ethylene glycol)- b-poly (ε-caprolactone-co-pdioxanone) [MPEG-P(CL-co PDO)] copolymers	Solid dispersion	29	↑bioavailability	Song et al. 2011
	Monomethyl poly(ethylene glycol)-poly(ε –caprolactone)	Solid dispersion	28.2	↑anti-tumor and anti-metastasis activity	Nabid et al. 2011
	Chitosan/tween 20	Nano-spray dryer	285	↑bioavailability	O'Toole et al. 2012
	1,4-diaminobutane (BDA) or 1,4-butanediol (BDO)	Emulsion diffusion	125	↑bioavailability	Souguir et al. 2013
	Sodium lauryl sulfate with poloxamer 188	Nanoprecipitation and sonication	126-474	↑stability	Moorthi and Kathiresan 2013
	BMS cocoons	Electro-spinning	30-150	↑controlled release	Elakkiya et al. 2014
Curcumininoid	Poly(butyl) cyanoacrylate/poloxamer 188	Solvent evaporation	178	↑solubility and controlled drug release	Mulik et al. 2009
Flavonoid	Plantacare 2000 ® UP	Milling and high pressure homogenization	413	↑dermal applicability	Al Shaal et al. 2011
	Casein	Self-assembly	109	↑drug delivery	Sahlan and Pramadewi 2012

Ferulic acid	Polyvinylpyrrolidone (PVP), sodium dodecyl sulfate (SDS) with sucralose	Electro-spinning	254	↑absorbance	Yu et al. 2010
	Whey protein concentrate (WPC) matrix with a commercial resistant starch	Nano-spray dryer	<1000	↑stability	Pérez-Masiá et al. 2015
Naringenin	B-casein	Self-assembly	10-100	↑solubility	Moeiniafshari et al. 2015
Oleoresin	Hydroxypropyl β-cyclodextrin	Inclusion complex	103.9	↑antimicrobial and antioxidant activity	Teixeira et al. 2013
Phytol	Triglycerides with a surfactant composed of soy phosphatidylcholine and sodium oleate	Phase inversion	130-250	↑permeability and antioxidant capacity	Islam et al. 2016b
Quercetin	Tween 80	High pressure homogenization	483	↑dissolution rate	Sahoo et al. 2011

Biological aspects of the nano-encapsulated phenolics

Catechin encapsulated with β-cyclodextrin within the range of 67-470 nm was found to increase the antioxidant capacity (Krishnaswamy et al. 2012), while with chitosan/ poly (γ-glutamic acid) (137-147 nm), there was an increase in transport and antioxidant capacity of this drug (Tang et al. 2013). Curcumin encapsulated with sodium lauryl sulfate with poloxamer 188 was evident to increase stability (Moorthi and Kathiresan 2013), while with methoxypoly(ethylene glycol)- b-poly (ε-caprolactone-co-pdioxanone) [MPEG-P(CL-co PDO)] copolymers, chitosan/tween 20 and 1,4-diaminobutane (BDA) or 1,4-butanediol (BDO) to bioavailability (Song et al. 2011; O'Toole et al. 2012; Souguir et al. 2013). However, curcumin when encapsulated with protamine sulfate (PS) with bovine serum albumin (BSA) and BMS cocoons, it caused an increase in controlled release of this drug (Zheng et al. 2010; Elakkiya et al. 2014). Furthermore, with poly (lactic-co-glycolic acid) (PLGA) (13-200), curcumin nano-encapsulation increased the solubility, stability and antioxidant capacity (Kumari et al. 2010; Mathew et al. 2012). Duan et al (2010) suggested that, curcumin encapsulation with poly(butyl) cyanoacrylate (PBCA)/ chitosan found to inhibit the hepatic carcinoma growth *via* an anti-angiogenic effect, where the nano-particle size was 200 nm. However, a better encapsulation was observed with monomethyl poly(ethylene glycol)-poly(ε – caprolactone) with an average particle size of 28.2 nm, which was evident to increase an anti-tumor and anti-metastasis activity in some human cancer cell lines (Nabid et al. 2011).

Curcumininoid encapsulated with poly(butyl) cyanoacrylate/poloxamer 188 by solvent evaporation method caused an increase in solubility and controlled release of the drug (Mulik et al. 2009). In some studies, flavonoid nano-encapsulation with plantacare 2000 ® UP and casein was evident to improve the dermal applicability and drug delivery (Al Shaal et al. 2011; Sahlan and Pramadewi 2012). On the other hand, ferulic acid encapsulated by polyvinylpyrrolidone (PVP), sodium dodecyl sulfate (SDS) with sucralose increased the absorption profile of this phenolic drug (Yu et al. 2010). However, whey protein concentrate (WPC) matrix with a commercial resistant starch significantly increased the stability profile of ferulic acid (Pérez-Masiá et al. 2015). B-casein was found to increase the solubility of naringenin (Moeiniafshari et al. 2015), while tween 80 (polysorbate 80) significantly increased the dissolution rate of quercetin (Sahoo et al. 2011). Teixeira et al (2013) demonstrated that, the nano-encapsulation of oleoresin with hydroxypropyl β-cyclodextrin significantly increased the antimicrobial and antioxidant capacity of this drug.

Nano-emulsion (both O/W and W/O) technology can be applied for phenolic drugs. In this context, the selection of solvent and surfactant plays an important role to control the droplet size, stability and overall activity (Gupta et al. 2016). In a recent study, Islam et al (2016b) found that the diterpenoid essential oil phyol when loaded into a carrier containing triglycerides with a surfactant composed of soy phosphatidylcholine and sodium oleate, it produced a fine nano-emlusion between the droplet size 130 and 250 nm. Interestingly, in comparison to the phytol (nano-free), this nano-emulsion significantly increased the drug permeability and

antioxidant capacity in a number of *in vitro*, *ex vivo* and *in vivo* test systems. Furthermore, resveratrol co-emulsified with labrasol or F68 was evident to improve drug transportation. The maximum plasma concentration and the bioavailability of resveratrol nano-emulsion were increased in 1098% and 560%, respectively. It also improved the cellular uptake in Caco-2 cells and lymphatic transport in rats (Zhou et al. 2015). Some currently used nano-emulsion methods and solvents along with the surfactants have been shown in **Table 2**.

Table 2*. Nano-emulsion preparation methods and the selection of solvents and surfactant observed in some literature*

Methods	Surfactant	Solvent	Droplet size (nm)	References
Phase inversion temperature	Brij 30	Tetradecane	80-120	Izquierdo et al. 2001
Solvent displacement	Pluronic F18	MCT's and Lipoid E-80 dissoved in ethanol	185-208	Chaix et al. 2003
High Pressure Homogenization	Tween 20	n-Hexane	-	Tan and Nakajima 2005
Spontaneous emulsification	Egg-lecithin	Ethanol	300	Fasolo et al. 2007
Ultrasound	Tween 80, Span 80, Sodium dodecyl sulfate	Sunflower oil	40	Leong et al. 2009
Rotor/Stator	Tween 20	n-Hexane	150	Silva et al. 2011

Conclusion

Doubtless, there has been a considerable interest in the development of nano-scale delivery systems for phenolics aiming to improve bioavailability, stability, and masking undesirable flavors. The techniques could focus on usage of modified delivery systems, formulations, biopolymers in the incorporation of phenolic-loaded systems in release and delivery systems in pharmaceutical products. However, more researches are necessary aspects of toxicity experiments, residual solvent analysis and analysis of biological fate during usages, digestion, absorption, and excretion of polymeric nanoparticles and nano-carriers.

Conflict of interest

None declared.

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