

CHAPTER II

LITERATURE REVIEW

2.1 Value addition to chicken meat through n-3 PUFAs supplementation

n-3 PUFAs are a bioactive compound, have considered as beneficial functions such as prevent rheumatism, inflammation, psychiatric and neurodegenerative illnesses, dyslexia, depression, type 2 diabetes, coronary heart disease, atherosclerosis, and Alzheimer's disease (Calder, 2013), boots muscle activity (Jeromson et al., 2015) and decreased expression factors which regulate muscle protein breakdown in the older adults (McGlory et al., 2019). Recommendation for intake n-3 PUFA for adult male and non-pregnant or non-lactation female around 250 mg EPA+DHA/day (FAO, 2010). By the way, there is not necessary to gain these fatty acids from only marine source but also found in functional meat production in livestock which raising with n-3 PUFA source including fish oil and algal oil. Chicken production is suitable for developing meat rich in n-3 PUFA because it takes less time to raise and could accumulate fatty acids more than other species due to muscle type of chicken has less breakdown of fatty acids (Smet & Vossen, 2016). Besides, the slow-growing chicken had higher amounts of long-chain fatty acids in the breast meat compared to the fast-growing rate of chicken breast (Jayasena et al., 2013).

As mentioned above, fatty acid sources can be found in fish oil, containing 13 to 24.56% DHA (Suseno et al., 2014; Mizambwa, 2017), from linseed oil which is content α -linolenic acid (ALA) equal to 57.8% (Shingfield et al., 2011). ALA is the primary fatty acid of EPA and DHA synthesized. However, because the animal body is limited in these essential fatty acids production. Thus, it necessary to directly supplement these fatty acid sources in the diet. Mostly choose fish oil as the main ingredient.

Korat chickens are classified as slow-growing chickens and are suitable for creating a career for farmers. With the value of nutritional and good texture that suitable to produce healthy chicken meat. According to Hang et al. (2018) has

studied n-3 PUFA accumulation in the Korat chicken with tuna oil supplementation. The result found that supplement with 4% tuna oil was able to adjust the meat composition of fatty acids as n-3 PUFA enriched meat. Nonetheless, with this n-3 PUFA ingredients, n-3 PUFA might be oxidized during storage because these fatty acids are sensitive to lipid oxidation (Chang & Nickerson, 2018) and the fishy smell from the sea fish in the chicken meat was not favorable to consumers (Gonzalez et al., 2006).

2.2 Accumulation of n-3 PUFAs in chicken tissue

There have been numerous researches about the accumulation of fatty acids in animal body. For the chickens were found in many parts of the body, especially in the liver tissue (Moran et al., 2018; Tolba et al., 2019) due to this is the first pass metabolic organ when the nutrient absorption occurs. Moreover, Keegan et al. (2020) found that an important level of n-3 PUFAs enrichment occurred in the liver, adhering fat, and skin followed by breast and thigh meat. Thus, feed formulation required higher n-3 PUFAs supplementation to achieve the recommended levels for n-3 PUFA-enriched meat. However, some n-3 PUFAs were also lost during the process, which might affect large-scale production.

Therefore, the key process for functional chicken production that should be paid attention is about fat accumulation mechanism. Because it affects the consumption of n-3 PUFA sources to achieve n-3 PUFA meat recommended while they accumulate to unnecessary organs as well. The enhancement of utilization of n-3 PUFA might be reduced with nanotechnology (Khosa et al., 2018) which can better optimize the utilization of these bioactive compound.

2.3 Application of lipid nanotechnology for functional meat production in Korat chickens

Lipid-based nanocarriers have been widely used in various applications to transport drugs, bioactive compounds, vitamins, peptides, proteins, antibodies, and RNA (Tagami and Ozeki, 2017). These nanoparticles are suitable for both injection and oral administration, as their synthesis involves biocompatible and biodegradable

materials that are safe for cells. Additionally, the surface of these nanoparticles can be engineered for specificity, allowing targeted delivery to specific organs or organelles (Khosa et al., 2018).

In the field of animal production, nanotechnology has been successfully applied to enhance the delivery of drugs, mineral supplements, and even in ovo feeding techniques (Gangadoo et al., 2016). For n-3 PUFAs enriched Korat chicken meat production, lipid-based nanocarriers offer promising potential by improving the stability, bioavailability, and targeted absorption of n-3 PUFAs in the gastrointestinal tract. This approach could enhance the nutritional value of chicken meat while minimizing potential losses due to lipid oxidation or inefficient absorption.

2.4 Lipid based nanocarriers become attractive formulation in livestock

2.4.1 lipid based nanocarriers

Lipid-based nanocarriers, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), are widely used as drug delivery systems through various administration routes, such as injection and oral delivery (Table 2.1). Composed of biocompatible and biodegradable materials, these carriers enhance drug bioavailability and can be made from natural or synthetic ingredients (Das and Chaudhury, 2011). They are commonly employed to deliver active compounds, including antioxidants, nutrients, peptides, proteins, antibodies, and RNAs, with surface modifications enabling targeted delivery (Tagami and Ozeki, 2017; Khosa et al., 2018). Oral drug administration is favored for its patient compliance, cost-effectiveness, and ease of management, but around 40% of drugs face challenges with this route due to their hydrophobic nature and poor bioavailability (Poonia et al., 2016). Lipid nanocarriers such as SLNs and NLCs have attracted significant research interest for addressing these limitations. By encapsulating drugs, these carriers improve permeability across the gastrointestinal membrane, making them promising vehicles for oral drug delivery.

Table 2.1 Lipid based nanocarriers apply to several applications.

Nanoparticle carrier	Application	Ingredient		References
		Lipid	Surfactant	
Nanostructure lipid carriers	Oral delivery	Monostearin Soybean oil	- Soya lecithin - PEG-40 - DSPE-PEG	Zhang et al. (2011)
Nanostructure lipid carriers	Oral delivery	Trilaurin Labarafac CC	- PC - PEG-40	Li et al. (2016)
Phospholipid complex-based	Tumor targeting injection	-	- Soybean phosphatidylcholine - DSPE-MPEG - DSPE-PEG-FA	Xie et al. (2017)
Liposome	Skeletal muscle targeting	-	- DSPC - Bio-PEG-DSPE - Cholesterol - OX26 antibody	Schnyder et al. (2004)
Liposome	Blood–brain barrier targeting	-	- Soybean phospholipids - Glucose-derived cholesterol	Xie et al. (2012)

PEG, PEGylated; DSPE-MPEG, 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]; DSPE-PEG-FA, 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[folate(polyethylene glycol)-2000]; PC, Phosphatidylcholine; DSPC, Distearoylphosphatidylcholine.

For the oral drug administration route which have several advantages like patient compliance, cost-effectiveness, easy management, and most accepted route for drug administration (Poonia et al., 2016) whereas 40% of drugs were not appropriate for oral delivery due to their hydrophobic nature and poor oral bioavailability. So, these drugs need improvement to enhance permeability across the gastrointestinal membrane (Poonia et al., 2016). Encapsulation drugs in lipid

nanoparticles such as SLN and NLCs become depicting huge interest of researchers for employing them as a promising vehicle for oral delivery.

These lipids based nanocarriers occur properties which suitable to deliver the drug or bioactive compound for disease prevention such as improving bioavailability (Wang et al., 2015a), avoid reticuloendothelial system which involves clearance of lymphocyte, plasma cell or macrophage (Manjunath et al., 2005), control drug release, bypass first hepatic metabolism, and suitable to produce on a large scale (Ali Khan et al., 2013). According to Wang et al. (2015b) has studied lipid based nanocarriers to improve absorption of phytoestrogen compound, biochanin A, which is a poor absorption molecule. As a result of the study found that NLCs improve the oral bioavailability of this compound, and the higher bioavailability of biochanin A enhances cytotoxicity against. As reported by Tian et al. (2017b) who studied improving curcumin bioavailability with the formulation of these lipid based nanocarriers and evaluated in oral administration found that increase curcumin absorption and residence time in plasma whereas decreased clearance from the reticuloendothelial system.

2.4.2 Difference between SLN and NLCs

Lipid-based nanocarriers enhance the oral bioavailability of lipophilic molecules but differ in formulations, resulting in unique properties. Solid lipid nanoparticles (SLNs), derived from nanoemulsions, are composed solely of solid lipids. They offer benefits such as well-defined lipid crystals, controlled drug release, low toxicity, good biocompatibility, and enhanced bioavailability (Yuan et al., 2013; Lin et al., 2017). However, SLNs face limitations, including low drug-loading capacity, restricted drug release, particle aggregation, and core leakage during storage (Khan et al., 2015).

To address these issues, nanostructured lipid carriers (NLCs), the second-generation lipid nanoparticles, were developed. NLCs combine solid and liquid lipids, resulting in nanostructures that improve drug-loading capacity, modulate drug release, and enhance stability during storage (Tamjidi et al., 2013). The inclusion of liquid lipids introduces imperfections in the crystalline matrix, increasing entrapment efficiency of active ingredients (Mendes et al., 2013; Hsu et al., 2019). The differences

between SLNs and NLCs, highlighting their distinct advantages and challenges, are summarized in Table 2.2.

Table 2.2 Comparison between properties of solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLCs).

Properties	SLNs (developed since early 1990s)	NLCs (developed since early 2000s)
Drug encapsulation efficiency	Lesser drug encapsulation efficiency due to formation of highly ordered crystalline arrangement	Higher drug encapsulation efficiency as blend of solid lipids and liquid lipids forms disordered structure providing higher space for drug loading Also due to high solubility of drug in liquid lipids
Shelf-life storage	Drug expulsion takes place during storage due to polymorphic transition of high-energy modification formed during fabrication to low-energy modification during storage	No polymorphic transition takes place and drug expulsion is prevented
Release rate	Slower release as mobility of drug in crystalline form is less	Faster release as mobility of drug in crystalline form is high

Source: Poonia et al. (2016).

2.4.3 Encapsulated for increased utilization of bioactive compound and other substances

Almost bioactive compound and some substance include vitamin are low bioavailability because their limitation such as low oral bioavailability, susceptible to oxidation and poor solubility, for example. As a result, these molecules were improved the stability and enhance absorption by encapsulation (Table 2.3). Therefore, this is a useful technology to enhance utilization of the substances.

Table 2.3 The results of encapsulation bioactive compound and other substances.

Substance	Benefits / Limitation	Key finding	References
ALA	- Helps enzymes turn nutrients into energy - Poor water solubility and antioxidant stability	The antioxidant evaluation of ALA-loaded microemulsion demonstrated enhanced about 80% compared with that of ALA in oil solution	Chen et al. (2017)
Free DHA	- Induce apoptosis in cancer cell - Sensitive to pH fluctuations and oxidation	Liposomal DHA reduce cell growth and induce apoptosis in human breast cancer cell lines more effectively than free DHA	Skibinski et al. (2016)
Fish oil	- Supports heart and cardiovascular health - Susceptible lipid oxidation	Encapsulation fish oil improve their stability from lipid oxidation.	Chang and Nickerson (2018)
β -carotene	- Anti-cancer and Anti-oxidant - Low oral bioavailability, Poor solubility and Instability	Nanoencapsulated form reduced particle size and larger surface area, enhance permeability and bioavailability	Mahalakshmi et al. (2020)
Curcumin	- Strong antioxidant activity - Poor water-solubility and chemical stability	Curcumin loaded nanoparticles exhibited higher antioxidant and radical scavenging activities than curcumin solutions	Huang et al. (2016)
Astaxanthin	- High antioxidant activity - Hydrophobic molecule, and sensitive	Nanostructured lipid improve stability of astaxanthin in beverage	Tamjidi et al. (2018)

2.5 Lipid nanocarriers for n-3 PUFAs enrichment in functional meat from Korat chickens

A significant body of research has explored the use of lipid-based nanocarriers for oral administration. These studies have assessed the permeability and efficacy of lipid-based nanocarriers through various models, including in vitro cell cultures, in situ intestinal segments, and in vivo studies. The findings demonstrate the exceptional ability of these nanocarriers to enhance the bioavailability of biochemical compounds and drugs.

This study aims to utilize lipid-based nanocarriers to enhance the delivery of bioactive compounds, specifically n-3 PUFAs derived from fish oil, for the production of functional meat in Korat chickens. The differential processes involved in lipid digestion, absorption, and transportation between traditional n-3 PUFA supplements and those encapsulated in lipid-based nanocarriers.

The review emphasizes the ability of lipid-based nanocarriers to traverse the intestinal tract and the mechanisms by which they are transported via enterocytes. Understanding these processes offers valuable insights into how lipid-based nanocarriers can improve the nutritional profile and functionality of poultry meat.

2.5.1 Lipid digestion and absorption in chicken

Lipid digestion, as summarized in Table 2.4, begins in the duodenum of the intestinal tract with the assistance of accessory organs. The pancreas produces enzymes, such as pancreatic lipase, while the liver secretes bile containing bile salts, phospholipids, and the pigment-protein bilirubin. These components act as emulsifiers, breaking lipids into a digestible form. Triglycerides are then hydrolyzed into fatty acids, monoglycerides, and diglycerides, which are absorbed by enterocytes through various pathways depending on the fatty acid chain length or molecular size.

Once absorbed, long-chain fatty acids are reassembled into triglycerides, which combine with lipoproteins and fat-soluble vitamins to form chylomicrons. In mammals, these chylomicrons are absorbed into the lymphatic vessels, whereas in poultry, they are transferred as portomicrons into the portal vein (Ravindran et al., 2016). Portomicrons, synthesized in intestinal cells, average around 150 nanometers

in diameter and subsequently enter the bloodstream (Griffin et al., 1982; Hermier, 1997).

Additionally, lipid-based nanocarriers provide alternative pathways for delivering lipid cargo through the gastrointestinal tract, as further detailed in Table 2.4 and the discussion below.

2.5.2 Cargo transported with lipid based nanocarriers through gastrointestinal tract

2.5.2.1 Lipid based nanocarriers stability in GI tract

The literature review demonstrates the property of lipid based nanocarriers on stability in the GI tract shown in the Table 2.5. Oral administration route has shown that lipid nanoparticle might be degraded by an enzyme in the intestinal lumen such as phospholipase A2 (Fricker et al., 2010) because their compose with phospholipid as nanoparticle surfactant might be led to less stability in the harsh physiological condition in GI tract (Wang and Luo, 2019). Moreover, mucus upper enterocyte cells are entangled and cross-linked adhesively to create a filter which able to defense large particulates that difficult to permeate the mucus mesh spacing (approximately 200 nm) (Cone, 2009; Yildiz et al., 2015). Therefore, nanoparticles for oral delivery need to modify their surface with a polymer such as PEGylating which potentially avoids the nanoparticles by enzyme activity in the GI tract and free mucins in the lumen (Zhang et al., 2014a) present in the Table 2.6.

Table 2.4 Summarized the possibility to improve functional meat production by applying lipid based nanocarriers in chicken.

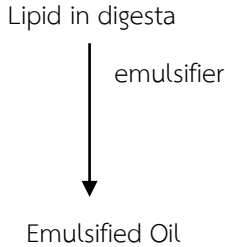
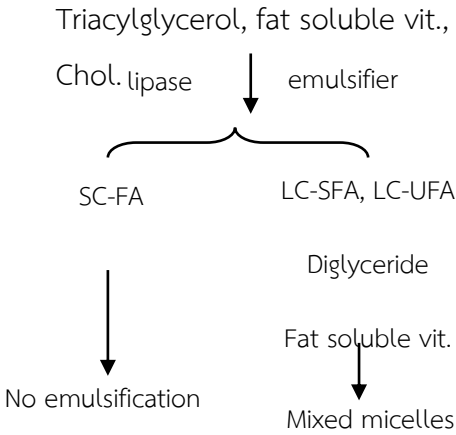
Process	n-3 PUFA in normal source		n-3 PUFA in lipid-based nanocarrier	
	Process	Description	Process	Description
Emulsion		In duodenum content bile such as bile salt and phospholipid to help emulsify oil which able to be digested by lipase.	Lipid-base nanocarriers	Lipid-base nanocarriers able to maintain their structure pass GI tract but some might degrade by PLA2.
			Targeting Lipid-base nanocarriers	
Digestion process		Lipases hydrolyze triacylglycerol to glycerol and fatty acid, which absorbed depend on their chain length. SC-FA and monoglyceride uptake via passive diffusion. For LC-FA and another hydrophobic molecule was absorbed via mixed micelles.	Lipid-base nanocarriers	- Modified lipid-base nanocarriers with PEGylated protect nanocarrier from degradation of intestinal enzyme. - Which lipid-base nanocarriers maintain their structure constantly, their will absorb by enterocyte endocytosis.
			Targeting Lipid-base nanocarriers	

Table 2.4 (continued).

Process	n-3 PUFA in normal source		n-3 PUFA in lipid-based nanocarrier	
	Process	Description	Process	
Absorption & Rebuild				
	SC-FA, Monoglyceride LC-UFA, Fat soluble vit., Cholesterol esters, Diglyceride, Triglyceride	After absorbed into enterocyte, Fatty acids and glycerol rebuild to triglyceride.	Clathrin, Caveolae (>200 nm - 1 μm), Transcytotic vesicles, Enterocyte	- Possible transcytosis pathways of lipid-base nanoparticles - For enterocyte cell, 2 endocytosis (Clathrin and Caveolae) pathways different protein function, depend on particle size of nanoparticle.
Transportation				
	SC-FA, fat soluble vit., Triglyceride, esterified chol., chylomicrons, Enterocyte cell, Portal vein, Portomicrons	- SC-FA directly transfer to portal vein via blood vessel - Triglyceride combined with hydrophobic molecule, lipoprotein, and phospholipid to form chylomicrons, and secreted to the portal circulation which are term as portomicrons (mean diameter of about 150 nm).	Clathrin, Caveolae, Blood vessel, Lymphatic vessel	- Sorting molecule size and localized into suitable circulation - Lipid-base nanoparticles might transcytosis into blood vessel of poultry by both transcytosis pathways.

Table 2.4 (continued).

Process	n-3 PUFA in normal source		n-3 PUFA in lipid-based nanocarrier	
	Process	Description	Process	Description
Synthesize & accumulation				
<pre>graph TD PV[Portal vein] --> Liver[liver] PV --> C[Circulation] Liver --> EFS[endogenous fat synthesis] EFS --> LP[lipoprotein] LP --> PL[phospholipid] C --> VT[Various tissue] VT --> FD[Fat deposits]</pre>		• Portomicrons were transferred into liver to synthesized lipoprotein and required molecule for another tissue or send to various tissue for fat deposition.	<pre>graph TD LV[Lymphatic vessel] --> APM[Avoid first pass metabolism in] APM --> TL[Thoracic lymph duct] TL --> LSC[Left subclavian] LSC --> SBC[Systemic blood circulation] SBC --> RES[RES] SBC --> TO[Target organ]</pre>	
Reference		Reference		
Griffin et al. (1982); Hermier, (1997); Ravindran et al. (2016)		Casteleyn et al. (2010); Beloqui et al. (2013); Trevaskis et al. (2015); Ravindran et al. (2016); Wang and Luo (2019)		
Abbreviates: PLA2, phospholipase A2; SC-FA, short chain fatty acid; LC-SFA, long chain saturated fatty acid; LC-UFA, long chain unsaturated fatty acid; FABP, fatty acid binding protein; RES, Reticuloendothelial system				

Table 2.5 Unmodified surface of lipid based nanocarrier influence on particle size in gastrointestinal fluid study.

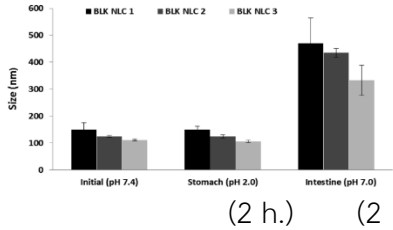
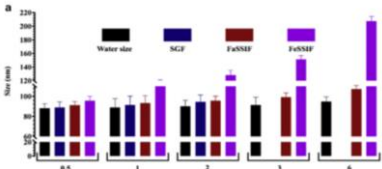
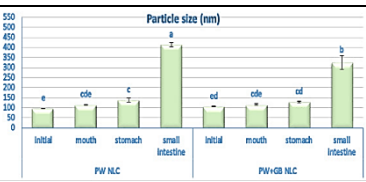
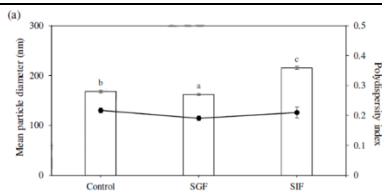
Nanocarriers	In vitro digestion	Keys finding	References
• NLC	 Size (nm) Initial (pH 7.4) Stomach (pH 2.0) Intestine (pH 7.0) (2 h.) (2 h.)	Particle size changed when stimulated with SIF condition (from 200 to 400 nm, approximately)	Aditya et al. (2013)
	 Size (nm) 0 1 2 3 4 Water SIF FeSSIF FeSSIF+P	Particle size change when stimulated with FeSSIF condition (from 100 to 200 nm, approximately)	Alam et al. (2018)
	 Particle size (nm) Initial mouth stomach small intestine Initial mouth stomach small intestine PW-NLC PW-GB NLC	Particle size of NLCs change while incubated with small intestine phase ($p < 0.05$) (from 140 to 400 nm, approximately)	Soleimania et al. (2020)
• NLC	 Mean particle diameter (nm) Polydispersity index Control SGF SIF	The particle size of vitamin-D NLCs avoid degraded in SGF but particle size change in SIF condition ($p < 0.05$)	Park et al. (2017)

Table 2.5 (continued).

Nanocarriers	In vitro digestion	Keys finding	References
• Niosomes	In vitro digestion steps Before digestion Oral phase Gastric phase Small intestinal phase	Particle size (nm) 196.6b 172.4b 175.7b 539.8a	• Particle size changed by stimulated with intestinal enzyme (P<0.05) Hunthayung et al. (2019)

Abbreviates: NLC, Nanostructured lipid nanocarriers; SASS, Simulated artificial saliva solution; SGF, Simulated gastric fluid; SIF, Simulated small intestinal fluid; FaSIF, Fasted state simulated intestinal fluid; FeSIF, Fed state simulated intestinal fluid.

Table 2.6 Modified surface of lipid based nanocarrier improved stability in gastrointestinal fluid study.

Nanocarriers	Treatment	Key findings	References
• Polymeric coat lipid-base nano carriers	• SLNs • p-SLNs-10%	• SLN changed particle size after incubated with SIF (from 280 nm to 472 nm, approximately) • Coat SLN prevent aggregation in SIF condition (from 150 nm to 156 nm)	Yuan et al. (2013)
	• PEG-LNs • CLNs	• PEG improve penetration of LNs. (339.8 nm to 409.2 nm, PEG-LNs) (up to 1,526.1 nm, CLNs)	Zhang et al. (2014a)
	• biotinylated liposomes • conventional liposomes	• Cargos were better protected enzyme degradation by biotinylated liposomes encapsulated in both of SGF and SIF condition	Zhang et al. (2014b)
	• Uncoated • PEG-NLCs • PVA-NLCs	• Particle size of uncoated NLCs changed (from 245 nm to 318 nm, approximately) • Coated NLCs more stability	Chanburee & Tiyafoonchai (2017)

Abbreviates: NLC, nanostructure lipid carrier; PEG, poly(ethylene glycol); PVA, polyvinyl alcohol; SLN, solid lipid nanoparticles; LNs, lipid nanoparticles; CLNs, conventional lipid nanoparticles.

2.5.2.2 Permeability of lipid based nanocarriers in enterocyte

After passing the enzyme condition of nanocarriers, the nanocarriers which can stable degraded by hydrolysis were absorbed by intestinal cells both of plain and modified surface nanocarriers, but the efficiency of permeability is differently. For a clear understanding of absorption both unmodified lipid based nanocarriers and modified lipid based nanocarriers able to study from intestine permeability were present in Table 2.7 and Table 2.8.

The permeability of lipid based nanocarriers in enterocyte cell was present in Table 2.7. In a summary, the modified surfactant of nanoparticle improve nanoparticle across the intestinal membrane. According to Zhang et al. (2011), Yuan et al. (2013) and Li et al. (2016) shown that PEGylation nanoparticle higher permeates intestinal membrane more than drug suspension and plain lipid based nanocarriers because of PEGylated nanoparticles less interaction with mucin and more resistance digestion enzyme led to increase transport across enterocyte cell. Moreover, the increase of oral bioavailability (Zhang et al., 2014a) mean PEGylation nanoparticles was absorbed and maintain their structure into blood circulation. By the way, exceed pegylated on nanocarriers surface is difficult to transport nanocarriers pass intestinal membrane (Li et al., 2016).

As well as the result of research were present in Table 2.8 indicated that lipid based nanocarriers with modified surface led to more stable in the GI environment and absorbed by the intestinal cell. Moreover, targeting nanocarriers which specific with transporter or receptor in the enterocyte membrane, was absorbed better than unmodified nanocarriers. This phenomenon indicated the possibility to increase the utilization of bioactive compounds by enhancing penetrate enterocyte cells by using the substrate as a ligand, which is a common nutrient including galactose, L-carnitine, folic acid, and other molecules

Table 2.7 Lipid based nanocarriers modified surface with PEG improve nanoparticle permeability in intestinal membrane.

Type	Carriers	Physicochemical characteristic			Determination	Keys finding	Reference
		PS	ZP	PDI			
Nanostructure lipid carriers	- Suspension	-	-	-	Diffusion chamber method	PEGylating NLCs significantly higher permeate intestinal membrane more than drug suspension (p <0.05)	Zhang et al. (2011)
	- NLC	125.9 nm	-28.49	0.23			
	- PEG-40-NLC	89.7 nm	-16.43	0.17			
	- DSPE-PEG-NLC	91.2 nm	-15.34	0.18			
Solid lipid nanoparticles	- SLN	280.2 nm	-24.50	0.34	In Vitro	p-SLN able to diffuse through the mucus barriers, permeate deeply into villi.	Yuan et al. (2013)
	- p-SLN-10%	192.1 nm	-20.30	0.32	Everted Gut Sac		
Lipid nanoparticle	- CLNs	191.4 nm	-	0.30	Ex vivo evaluation of nanoparticles–mucin binding	Pegylated LN less interaction with GI free mucin and more resistance digestive enzyme.	Zhang et al. (2014a)
	- PEG-LN	186.7 nm	-	0.20			
Nanostructure lipid carriers	- NLC	136.4 nm	-59.00	0.12	In situ permeability studies	pNLC 20% was 2.04-, 1.80- and 1.76-fold higher than NLC, pNLC-40% and pNLC-80%, respectively (p <0.01).	Li et al. (2016)
	- pNLC 20%	130.5 nm	-53.96	0.12			
	- pNLC 40%	130.8 nm	-58.34	0.21			
	- pNLC 80%	133.3 nm	-50.47	0.30			

Abbreviate: PS, Particle size; ZP, Zeta-potential; PDI, polydispersity index; NLC, nanostructure lipid carrier; PEG, polyethylene glycol; SLN, solid lipid nanoparticles; LNs, lipid nanoparticles; CLNs, conventional lipid nanoparticles.

Table 2.8 Targeting modified surface nanoparticle improve intestinal permeability.

Nanoparticle	Carriers	Ligand	Target transporter/receptor	Intestinal penetration	Reference
NLC	- CT-NLCs (cell-penetrating peptide-coated) - 126.7 nm	Basic amino acids such as arginine, lysine, and leucine,	These peptides are capable of internalizing electrostatically	• The CT-NLCs in the duodenum and jejunum were 3.0- and 3.3-fold higher than those of the tripterine solution and approximately 1.5 times higher than another NLCs.	Chen et al. (2012)
	TCA 20%-NLC - 131.6 nm	taurocholic acid (TCA)	bile-acid transporter	• TCA 20%-NLC were taken up maximum absorption by ileum	Tian et al. (2017a)
	NAPG-100 NLC - 89.2 nm	Thiol group	Disulfide bond	• NAPG-100 NLC could improve the intestinal absorption	Tian et al. (2017b)
	GPS-SGC-NLCs - 146.7 nm	sodium glycocholate	Bile salt transporter	• Enhance permeability and bioavailability	Yang et al. (2019)
Liposome	FA-liposome - 309.4 nm	Folic acid (FA)	folate receptors	• Enhance oral bioavailability 1.4– 2-times compare plain liposome	Ling et al. (2009)

Table 2.8 (continued).

Nanoparticle	Carriers	Ligand	Target transporter/receptor	Intestinal penetration	Reference
Polymeric nanoparticles	LC-PLGA NPs - 218.1 nm	L-carnitine	Na ⁺ -dependent carnitine transporter (OCTN2)	• LC-PLGA NPs improves the absorption of the drug in the small intestine	Kou et al. (2017)
	RES-GNPs - 108.4 nm	Galactose	sodium glucose-linked transporter 1 (SGLT1)	• RES-GNPs could enhance the permeability of RES in all investigated intestinal segments	Siu et al. (2018)
	Dipeptide-PLGA NPs - 165.6 nm	L-valine-valine	oligopeptide transporter 1 (PepT1)	• Modified NPs had better absorption than those of DTX solution and unmodified NPs	Du et al. (2018)

2.5.3 Transportation of lipid based nanocarriers to target organ

The oral bioavailability has been studied from in vivo pharmacokinetic tests shown in Table 2.9. Pharmacokinetic parameter including C_{max} is maximum concentration of drug achieves in blood after absorption, T_{max} is maximum time of maximum concentration of drug and area under the curve (AUC) is drug bioavailability.

Table 2.9 Nanoparticles surface modification on in vivo pharmacokinetic studies.

Nanoparticles	Carriers	Results	References
		In vivo pharmacokinetic	
Solid lipid nanoparticles	- SLN	- p-SLN, higher drug in plasma after absorbed	Yuan et al. (2013)
	- p-SLN-10%	- improve drug bioavailability and Prolong blood circulation time	
Nanostructure lipid carriers	- NLC	- Drug loaded DSPE-PEG NLCs absorbed into the blood circulation	Zhang et al. (2011)
	- PEG-40-NLC	- Higher bioavailability and prolongs blood circulation	
	- DSPE-PEG-NLC		
	- PEG-NLC	- High oral bioavailability	Wang et al. (2015b)
		- High absorb drug through plasma	
	- NLC	- Drug loaded pNLC 20% more absorbed into the blood circulation	Li et al. (2016)
	- pNLC 20%	- Prolong blood circulation time	
	- pNLC 40%		
	- pNLC 80%		
	- NLC	- TCA 20%-NLC reabsorbed from small intestine and high concentration in blood (C _{max})	Tian et al. (2017a)
	- TCA ¹ 20%-NLC	- Prolongs blood circulation (AUC)	
	- TCA 50%-NLC	- Decreased clearance of curcumin	
	- TCA 100%-NLC		
Lipid nanoparticle (LN)	- Conventional LN	- PEGylate LN higher plasma concentration of drug (C _{max})	Zhang et al. (2014a)
	- PEGylate LN	- Enhance bioavailability of drug	

Table 2.9 summarized that modified surface by PEGylation increase drug concentration in the blood higher than nonmodified surface was observed higher Cmax value which means after drug absorbed through intestinal membrane then directly transport to blood circulation system or bypass hepatic first-pass metabolism. Moreover, Joshi et al. (2014) describe nanocarriers were absorbed through M cell of Peyer's patches associate lymphatic vessels that avoid metabolism in the hepatic cell. AUC value observed in each research found that higher in PEGylation nanocarriers result in high drug bioavailability (Zhang et al., 2011; Tian et al., 2017a) because this polymer reduce elimination by the reticuloendothelial system also prolongs drug or bioactive compound in blood circulation. In addition, plain lipid based nanocarriers present in blood circulation still rapidly disappeared by clearance from the reticuloendothelial system (RES) (Kim et al., 2018). As the report by Yuan et al. (2013) described polyethylene glycol (PEG) is sterically stabilizing particles, avoiding phagocyte from macrophage and clearance from the reticuloendothelial system and prolong blood circulation time, etc.

The distribution of drug-loaded nanocarriers to target organ by oral delivery as shown in Table 2.10 demonstrate that nanocarriers effectively transfer drug and enhance drug distribution to target organ by surface modification of nanocarriers specific with transporter (Tunki et al., 2019) or receptor (Qin et al., 2016; Krishna et al., 2019) or even design for enhancing penetration of barrier cells including blood-brain barriers (Das and Lin., 2005). The drug distribution study found that tagged nanocarriers with ligand significantly increase drug content in the brain compare drug suspension ($P < 0.05$) (Krishna et al., 2019), enhance cancer cell growth inhibition ($P < 0.01$) (Qin et al., 2016) and were observed to hepatic cell better than plain nanocarrier (Tunki et al., 2019).

The literature reviews present possibility to improve utilization of n-3 PUFA source for producing functional meat by this perspective to reduce accumulation in non-necessary organ including liver by synthesizing n-3 PUFA source as nanoparticle with targeting might have the ability to transfer n-3 PUFAs across intestinal membrane, bypassing first-pass metabolism and stability from clearance in blood circulation until uptake by the cell.

Table 2.10 Targeting of nanoparticles and drug distribution in target organ via oral delivery.

Nanoparticles	Ligand	Key findings	References
Polymeric NPs	- / Brain	Drugs-loaded NPs modified surface with tween 80 and PEG was more absorbed via orally administration, across blood brain barriers and enhance drug release in brain tissue.	Das and Lin (2005)
Polymeric NPs	ApoE3 / Brain	After absorbed, drug-loaded NPs significantly increase drug content in brain when compare with pure drug which accumulate mostly in liver ($P<0.05$).	Krishna et al. (2019)
Polymeric NPs	IgG Fc portion (FcRn) / Breast cancer	- Modified surface NPs able to transfer efficiently in intestinal cell line ($P<0.01$) - Targeting NPs more entered systemic circulation ($P<0.05$) and enhance inhibition breast cancer growth ($P<0.01$).	Qin et al. (2016)
Solid lipid nanoparticles (SLN)	Galactose/ Hepatic cell	- Pharmacokinetic test of SLN modified with galactose present statistically highly significant prolong blood circulation compare with drug suspension ($P<0.001$) - The real time biodistribution studies, targeting SLN were observed in liver even after 48 h of incubation whereas plain SLN were detected in lungs.	Tunki et al. (2019)

The present study decides to modify nanocarriers surface with Glucose due to it was studied as ligand-specific with C2C12 cell which represents skeletal muscle cell in mammalian (Yeh et al., 2014). Although this ligand was not studied in an animal model in term of oral route but the research had studied galactose which classified as a monosaccharide group as a ligand of lipid base nanocarriers and indicated effectively penetrate enterocyte cell (Siu et al., 2018, present in Table 2.8). This means that galactose take the part of ligand was absorbed by sodium-glucose co-transporter (SGLT1) which is involved endocytosis pathways. Along with glucose was also adsorbed via SGLT1 (Poulsen et al, 2015), GLUT 2, GLUT 5 and GLUT 7 (Byers et al., 2017). The research to date inadequate to support all the GLUT in the property of nanoparticle absorption. However, the researcher had studied ability of GLUT 2 and found that this transporter able to transfer substrate via endocytosis pathways was noticed in enterocyte cells (Grefner et al., 2015) and proximal tubules of the kidney (Cohen et al., 2014).

2.6 Understanding transcytosis mechanisms in nanoparticle transfer and intracellular vesicle dynamics

2.6.1 Transcytosis pathways in nanoparticle delivery

The nanoparticles absorptions are involved endocytosis pathways. These pathways involve several proteins that related with sorting nanoparticles in the cell, which has an effect on potential of nanoparticles. Moreover, the mechanism was studied by using inhibitors or fluorescence to demonstrate the generally knowledge about nanoparticles transportation and the characteristics of intracellular vesicle, respectively. Nevertheless, there are several pathways was risen in the enterocyte cell before delivery the nanoparticles into blood circulation. In addition, the endocytosis is an important phase to transfer nanoparticle successfully via the process of transcytosis which do not degrade the nanoparticle in the cell before translocated into the bloodstream. Therefore, the entire process should be studied to determine the dominant process during the transcytosis and responding of cell for further development of the suitable nanoparticle.

The pathways involved transcytosis of nanoparticles include endocytosis, intracellular trafficking and exocytosis. That is exhibit the process to move nanoparticles without any changed in enterocyte cell. Therefore, the studied should focus on how the cell act when treat with nanoparticles. According to Siu et al., 2018 demonstrate that monosaccharide functioned as a ligand is participated in the Clathrin-mediated endocytosis. This process contains a specific protein group to absorb nanoparticles when ligand-receptor/transporter interaction (Nel et al., 2009) is shown in Figure 2.1. However, the researcher said that the process is often classified as an associate with the lysosome, which is the organelles would cause the breakdown of molecules to get the smallest unit (Settembre & Ballabio, 2014). That was not expected for the delivery of the substance to the target by ingestion whereas were preferred for intracellular release of cargo in target cell.

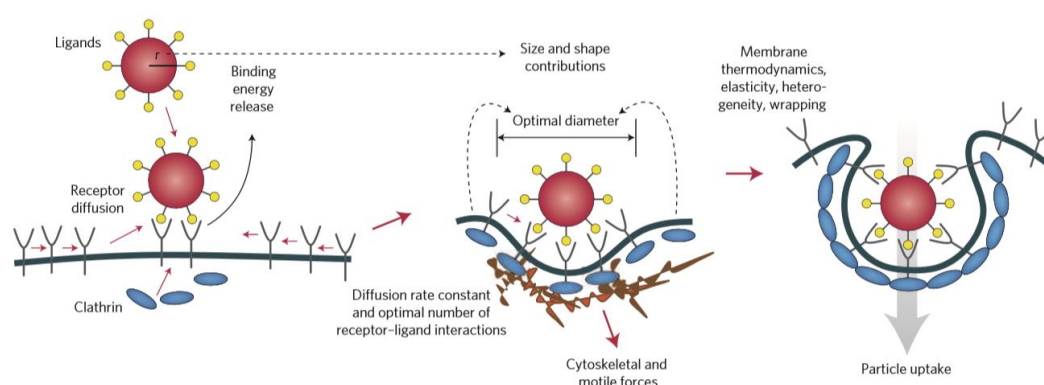


Figure 2.1 Nanoparticle wrapping at the surface membrane.

Source: Nel et al. (2009).

However, according to research by Wang et al. (2021). there are two directions involved in the use of glucose to deliver substances via blood brain barriers include Clathrin-mediated endocytosis and micropinocytosis. Then, the intracellular trafficking of nanoparticles go through exocytosis by lysosomal exocytosis, as shown in Figure 2.2. As the result, indicated possibility of transmitted nanoparticle by this route.

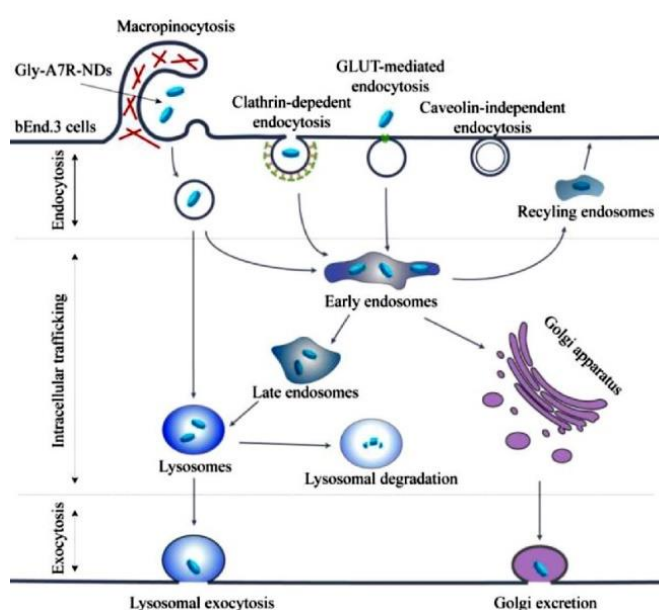


Figure 2.2 Diagram representation of the transcytosis pathways of glycosylation in barrier cells.

Source: Wang et al. (2021).

2.6.2 Protein involved nanoparticle adsorption by enterocyte cell

As mentioned in the previous paragraph, it is important to identify the complete processes involved in nanoparticle transportation because intracellular mechanisms occur through several pathways that facilitate nanoparticle translocation. Thus, determining the entire pathways is key to proving the flow of nanoparticles. Moreover, attention should be paid to the biological responses that may be related to nanoparticle toxicity (Matysiak et al., 2016). Proteomics has been used to identify and quantify cellular responses following nanoparticle treatment. By using proteomic techniques, the entire proteome can be examined to visualize unpredicted responses (Nath Roy et al., 2017). This approach provides a relative and quantitative analysis of protein composition, architecture, and dynamics associated with nanoparticles in various biological environments (Juling et al., 2017). The results of determining nano-bio interactions using proteomics, as shown in Table 2.11, identified proteins related to nanoparticle translocation and cellular responses in the cells.

The present study aims to determine the mechanisms of proteins related to n-3 PUFA transportation in nanoparticle form. This is to prove the ability of nanocarriers to penetrate the enterocytes of Korat chickens. Finally, the information will be used to generate a suitable nanocarrier prototype for large-scale functional meat production.

Table 2.11 The studied of nanoparticles transcytosis and cellular responded by proteomics.

Nanoparticles	Aims / Cell type	Keys finding
• Carboxyl-functionalized polystyrene nanoparticles • 100 nm	• Protein involved transverse nanoparticles • Caco-2 cell (model for gut-blood transition)	• Nanoparticles were transcytosis by related with protein includes RhoB and Rab3 represent the early or late endosomes and exocytosis, respectively, successfully transcytoses in apical-to-basal direction. • Nanoparticles involved Lamp1, a marker for lysosomes limit in 100 nm.
Source: Reinholz et al. (2018)		
• Dendrimer • 185 nm	• Cellular entry and trafficking Nanomaterials • HeLa cells	• Clathrin-coated pits (CCPs) formation such as clathrin (CLTC), adaptor proteins (AP2A1 and DAB2) involved in early stage of endosome.
Source: Wang et al. (2015c)		
• Surfactant-coated silver nanoparticles (polyoxyethyl ene glycerol) • 11.1 nm	• Nanoparticle protein corona and cellular reaction. • Caco-2 cell	• 54 proteins were identified as differentially regulated by silver nanoparticle, located in the cytoplasm and the cell membrane. • The protein play an important role in silver nanoparticles-induced cytotoxicity (ATP5H, COX5B, PRDX5, CYB5A and NDUFS7).
Source: Juling et al. (2017)		

Table 2.11 (continued).

Nanoparticles	Aims / Cell type	Keys finding
• Silver Nanoparticles • 100 nm	• Investigate the molecular mechanisms underlying the cellular responses that might be triggered	• 717 proteins were regulated by exposure to 100 nm AgNPs (378 down-regulated and 339 upregulated) • The 100 nm nanoparticles provided indirect effects via serine/threonine protein kinase (PAK), mitogen-activated protein kinase (MAPK), and phosphatase 2A pathways. • The 20 nm nanoparticles induced direct effects on cellular stress, including generation of reactive oxygen species and protein carbonylation.

Source: Verano-Braga et al. (2014)

2.7 References

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