Liposome Encapsulation: A Promising Approach to Enhanced and Safe Mefenamic acid Therapy

Qais B. Jarrar, Zuraini Ahmad, Arifah Abdul Kadir, Zainul Amiruddin Zakaria and Muhammad Nazrul Hakim

***Abstract* — Mefenamic acid (MEF) is a non-steroidal anti-inflammatory drug (NSAID) characterized by low bioavailability with relative high toxicity. Despite the efforts which have been paid to enhance its bioavailability, its inherent toxicity remains the limiting factor for its medical uses. Designing MFE as a prodrug of ester derivatives can attenuate gastrointestinal (GI) toxicity, but shows no advantages in term of therapeutic efficacy. Liposomes have a dual action and would be a promising tool to enhance MFE bioavailability and reduce its gastric and systemic adverse reactions. This review covers the pharmacological and toxicological aspects of MFE and provides substantial trend to enhance its clinical therapy.**

***Keywords* — Bioavailability, Mefenamic acid, Proliposome, Phospholipids, Toxicity**

I. Introduction

Oral therapeutic agents are usually intended to be used in pharmaceutical preparations that generate good patient compliance with safe and reproducible plasma concentrations. Nevertheless NSAIDs, including MFE, are characterized by poor aqueous solubility and low dissolution rate, and accordingly their bioavailability and therapeutic efficacy would be affected (Derle et al., 2008). In addition, the doses elevating practice, that are usually indicated for enhancing their therapeutic efficacy in treatment of certain diseases, can increase the incidence of gastrointestinal and systemic toxicities (Lanza *et al.*, 2009). NSAIDs are widely ingested either by medical prescription or over the counter. Despite a steady decline of MFE use in last decades, it remains frequently ingested for pain syndromes and some gynecological disorders (Cimolai, 2013). However, clinical trials as well as animal toxicity studies have shown that MFE therapy was implicated in a series of complications on different biological systems. It is capable to interrupt the gastric tolerability and can sometimes result in serious conditions on the liver, kidney and other vital organs (Cimolai, 2013; Hunter et al., 2011). In addition, this drug shows no preferable clinical indication in comparison with other members of NSAIDs. Pharmacologist have therefore argued for decades that, since there is a wide range of effective and less toxic agent, there is no reason for continuing to prescribe MFE (Künzel et al., 2007). These facts together have hampered the long scale development of MFE and shift the interest toward other NSAIDs (Cimolai, 2013).

Liposome encapsulate technology is among the most important strategies for delivery of problematic and hydrophobic drugs. Over the last decades, liposomes (the lipid based nanoparticles) were extensively studied as preferable drug carriers due to their several unique properties. Liposomes are capable to incorporate hydrophilic and hydrophobic drugs together with good biocompatibility, low toxicity, lack of immune system activation, and can deliver of bioactive compounds to the site of action. Liposomes were also proven to enhance pharmacokinetics of several drugs, improve oral bioavailability and potency as well as reduce GI tract and systemic toxicities (Allen & Cullis, 2013; Samad et al., 2010). These advantages together can bring the life back to many other withdrawal agents and afford new respect to the drugs that show suboptimal behaviors.

II. Historical Background

Mefenamic acid is anthranilic acid derivative which belong to old NSAIDs family known as fenamates. The drug was initially described as anti-inflammatory agent until it became available for public use as early as 1963. The pharmaceutical marketing of MFE was flourished in 1990s and being one of the most prescribed NSAIDs. However, MFE uses were dramatically declined at the era when other NSAIDs were discovered. This was coincided with the emergence of some allegations regarding MEF toxicity. Such allegations started after Wender et al. (1967) reported that MEF therapy might be associated with the incidence of allergic diarrhea and thus it should not be recommended for more than two weeks of treatment. The caution of MEF use in clinical therapy was increased with the emergence of some evidence showing relationship of GI tract toxicity with MFE therapy.

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Qais B. Jarrar and Zuraini Ahmad are with the Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor MALAYSIA.

Arifah Abdul Kadir is with the Department of Pre-clinical Studies, Faculty of Veterinary Medicine, Universiti Putra Malaysia, Serdang, Selangor MALAYSIA.

Zainul Amiruddin Zakaria is with the Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia and Halal Product Research Institute, Universiti Putra Malaysia Serdang, Selangor MALAYSIA.

Muhammad Nazrul Hakim is with the Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Halal Product Research Institute, Universiti Putra Malaysia Serdang, and Sports Academy, Universiti Putra Malaysia, Serdang, Selangor MALAYSIA. (E-mail: nazrulh@upm.edu.my).

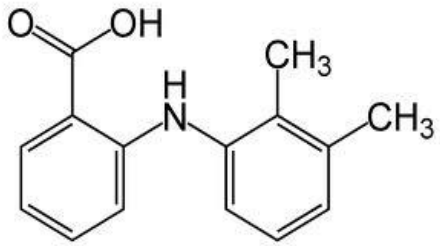

Fig. 1. Mefenamic acid chemical structure

III. PHARMACOLOGY OF MFE

Clinical indications: Mefenamic acid demenostrated a number of advantages in the clinical therapy but at different degrees of efficacy (Kunkulol Rahul et al., 2013; Roy, 1983; Keinänen et al., 1978). Considerable attentions have been given to the drug as antipyretic agent in pediatric therapy. According to comparative clinical study on 124 pediatric patients, MFE (4 mg/kg) was found to be more effective for treating fever and equally tolerable than paracetamol (15 mg/kg) (Kunkulol Rahul et al., 2013).The antipyretic activity of MFE is even greater than its antirheumatic effect (Keinänen et al., 1978). This drug was also licensed in a clinical therapy for management of primary dysmenorrhea and menorrhagia and for relief postoperative pain, soft tissue injuries and other musculoskeletal painful conditions (Ebadi, 2008; Namavar Jahromi et al., 2003; Hall et al., 1987; Hart & Huskisson, 1984). In general, the analgesic activity of the drug in treatment of various pain syndromes seems to be superior to acetylsalicylic acid but mostly equivalent to other NSAIDs. However, studies on MFE have recently demonstrated several unique pharmacodynamics on various biological systems which may expand its clinical utilities (Table I) (Cimolai, 2013).

TABLE I: SUMMERY OF CLINICAL AND POTENTIAL USES OF MFE

Primary clinical indications:	
Gynecology	Premenstrual tension, Menorrhagia, Primary dysmenorrhea, secondary dysmenorrhea
Pain syndrome	Acute pain: Headache and pain associated with menstrual cycle, musculoskeletal injuries and after dental surgeries.
Fever	Pediatric fever
Potential utilities:	
Patent ductusarteriosus in newborns, Chronic bronchial asthma, Alzheimer's disease, Urticaria and cancer	

Pharmacokinitics and Bioavailability: pharmacokinetic data of the drug is presented in (Table II). Pharmaceutically, MEF is belong to class 2 which characterizes by slow dissolution rate, and thus require more time to be dissolved in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract. This may suggest that drug dissolution rate plays a critical role on MFE bioavailability and its therapeutic efficacy. Diseases like diabetes, fasting, food and water intake may be other limiting factors (Qamar et al., 1997; Hamaguchi et al., 1986). Pharmaceutical efforts have recently paid in order to improve MFE bioavailability. These efforts included enhancing drug dissolution rate through the conventional methods such as reducing particle size, complexation with cyclodextrine and freeze drying techniques (Table III).

TABLE II: PHARMACOKINETIC DATA OF MFE

Pharmacokinetic data		
Percentage absorption (%)		80%
Doses (mg)		250-500
Peak concentration (C max) (mg/L)		2-6
Time to peak concentration (t max) (h)		2-4
Half-life (t1/2) (h)		2-4
Site of metabolism		Mainly liver (oxidation via cytochrome mono-oxygenase P450TB, CYP2C)
Metabolites		3-hydroxymethyl metabolite (most common) and 3-carboxyl metabolite
Glucuronides		Acyl glucuronides from mefenamic acid and its two major oxidized metabolites
Protein binding		90%
Enterohepatic circulation		Probably occur in minor portion
Volume of distribution (L/kg)		1.06
Excretion	urinary	Conjugate metabolites (most common)
	faecal	MEF (in case of incomplete absorption) or in the form of unconjugated 3-carboxymefenamic acid
	glandular	Breast milk excretion (0.04–0.033 mg/l).

TABLE III: PHARMACEUTICAL METHODS FOR ENHANCING MFE BIOAVAILABILITY

Method	Advantages	References
Solid dispersion in a super disintegrant, primojel (PJ) or in a combined carriers of PJ and polymer polyvinyl pyrrolidine (PVP)	Increase mefenamic acid dissolution rate by 2.61- 4.11 folds	Sambasiva *et al*.,2011
Complexation with Hydroxy propyl-β-Cyclodextrin	Increase mefenamic acid dissolution rate by 11.20 folds	Nagabhushanam *et al.*,2011
Solid dispersion in Starch citrate	Increase mefenamic acid dissolution rate by 4.74 folds	AmaravathiVikram *et al*.,2012
Solid dispersion in a super disintegrant, crospovidone (CP), or in a combined carriers of CP and polymer polyvinyl pyrrolidine (PVP)	Increase mefenamic acid dissolution rate by 2.26- 3.64 folds	Nagabhushanam and Sudha Rani, 2011
Solid dispersion in PEG4000	Increase mefenamic acid dissolution rate by 4 folds	Dexit *et al.*, 2011 [a]
Freeze drying inducing microparticles	Simple method with high dissolution rate	Dexit *et al.*, 2011 [b]

Pharmacodynamic activity: Mefenamic acid, an anthranilic acid derivative, is a potent non-selective NSAIDs that inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (Chavez & Dekorte, 2003; Yao et al., 2005). It is thought that their analgesic, anti-inflammatory and antipyretic actions are mainly attributed to their capability to inhibit COX-2 whereby block the conversion of arachidonic acid (AA) to prostaglandins that mediate inflammatory response as well as contribute in fever and pain sensation (Wahbi et al., 2005).The anti-inflammatory action of MFE may also attributed, in part, to their capability to inhibit lipooygenaseenzyme, another key enzyme involved in the AA cascade, leading to block the production of inflammatoryleukotrienes (ILs) (Fig. 2).Some studies showed evidences on the effectiveness of MFE to inhibit the secretion of 1L-1 β, 1L-6 and endotoxin (Chiou et al., 1993; Walton et al., 1993).

Some reports indicated that MFE are able to inhibit membrane-associated processes that promote synthesis of anti-inflammatory eicosanoids. This drug also can suppress molecules adhesion by inducing the shedding of a family of surface adhesion receptors in neutrophils knowing as L-selectin (Gómez-gaviro et al., 2000). It has been shown that MFE could exert powerful actionin inhibiting transient receptor potential channel, member-3 (TRPM3) mediated gene transcription (Lesch et al., 2014). This may suggests that MFE is capable to deactivate TRPM3 channels and disturb its function in sensing noxious heat and secretion of inflammatory cytokines (Vriens et al., 2011).

In animal studies, the anti-inflammatory activity of this drug was demonstrated by Carrageenan-induced rat paw edema and subcutaneous cotton pellet models (Afsara et al., 2013; Winder et al., 1961).

On the otherhand, its antinoceciptive activity was demonstrated by formalin-induced paw licking and acetic acid-induced writhing models (Alipour et al., 2014).

Potential pharmacodynamics: Mefenamic acid is known to affect various types of membrane channel in smooth muscles possessing multiple effects on outward K^+ currents (Teramoto et al., 2005). Effects on gastric, uterine, urethra and trachea smooth muscles have been reported (Teramoto et al., 2005; Hidalgo et al., 1998; Anderson et al., 1979).

Mefenamic acid has recently showed substantial role as anti-proliferative and neuroprotectiveagent. At high doses, MEF can modulate growth and behavior of cancer cell via mechanism independent of its ability to inhibit COX-2. Among NSAIDs, it has the heights inhibiting effect on the proliferation of two human cancer cells(Chang and Huh-7 cells) by inducing apoptosis through enhancing caspace-3 activity (Woo et al., 2004). Another mechanism suggested by August et al. (1994), demonstrated that MFE inhibits the production of hyaluronic acid in fibroblast at concentration not toxic for normal cell.

Mefenamic acid promotes neuronal cell survival by different mechanism. It can inhibit destabilization of mitochondria by reducing the accumulation of reactive oxygen species and nitric oxide, inhibiting the leakage of mitochondrial proteins such as cytochrome c and up regulating the antiapoptic protein Bcl-XL (Joo et al., 2006).

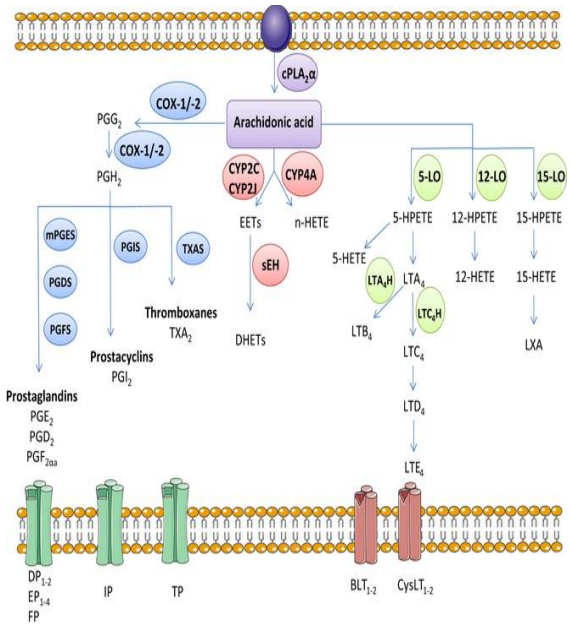

Fig. 2. Schematic overviewof main enzymes involved in the arachidonic acid cascade. BLT, LTB4 receptor; COX, cyclooxygenase; cPLA2α, cytosolic PLA2 α; CYP, cytochrome P450; CysLT, cysteinyl LTs receptor; DHET, dihydroxyeicosatrienoic acid; DP, PGD2 receptor; EET, epoxyeicosatrienoic acid; EP, PGE2 receptor; FP, PGF2 receptor; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid; IP, PGI2 receptor; mPGES, microsomal prostaglandin E2 synthase; LO, lipoxygenase; LT, leukotriene; LX, lipoxin; PG, prostaglandin; sEH, soluble epoxide hydrolase; TP, TXA2 receptor; TXAS, thromboxane synthase(cited from Meirer*et al.*, 2014).

IV. TOXICITY OF MFE

Mefenamic acid canexert its toxicity on the biological systems via diverse toxicodynamics. It is capable to affect cellular stability and permeability. This drug can alter the function of ion channels and transport systems, disturb enzymes activity and their biosynthesis as well as interact with drugs pharmacokinetics and displace biological mediators from their target actions (Cimolai, 2013). According to material safety data sheet of MFE by Pfizer Drug Company (2008), the target organs toxicity are liver, kidney and GI tract. However, toxicity may also involve blood, pancreas and central nervous system and others.

Gastric mucosal lesion: It is thought that NSAIDs including MFE can induce gastric mucosal lesion by different mechanisms, such as by cyclooxygenase dependent action via blocking the production of **gastroprotective prostaglandin** and by local cyclooxygenase independent action. Direct toxic effect of NSAIDs is mainly attributed to their ability in disrupting the active phospholipids layer on the surface of mucosa, and thus increases the sensitivity of epithelium to acid-induced injury (Wallace, 2008). Acidic NSAIDs are capable to destabilize the hydrophobicity of epithelial membrane and reduce its ability to repel the polar substances which result in trapping and accumulation of charged NSAIDs within the cytoplasm of epithelial cells. Trapped drugs exert their cytotoxicity by affecting expression and production of proteins, enzyme activity and uncouple oxidative phosphorylation (Wallace, 2008). Like other NSAIDs, MEF has shown to induce apoptosis in guinea-pig gastric epithelial cells by decreased caspase-3-like activity (Ashton & Hanson, 2002). NSAIDs can also disrupt mechanism of repairing damaged epithel1ial cells and diminish their proliferation by avoid epithelial growth factor to bind its receptor (Fujiwara et al., 1995). NSAIDs can also activate nuclear transcription factor which regulates adhesion molecules and promote leukocyte adherence to the vascular endothelium leading to impairment of mucosal blood flow and inducing endothelial injury (Pawlik et al., 2002). In addition, the rehepaticcirculation of some NSAIDs, including MEF, renders epithelial cells to be a target for drug repeated exposures causing further damage in GI tract (Reuter et al., 1996). Mefenimic acid therapy was implicated in some cases of gastritis, enteritis and colitis as well as gastrointestinal ulceration with or without bleeding. Bjarnason et al. (1993) demonstrated that incidence of nonspecific colitis may more common in fenemates therapy. The elderly and those taking long-term NSAID therapy appear to be at highest risk (Grant & MacConnachie, 1995; Gibson et al., 1992). Hall et al. (1983) reported two cases of acute colitis after treatment with mefenamic acid: (1) Gastrointestinal tract adverse reaction was seen in 69 year old man who took intermittent doses of MEF for eight months and presented with chronic diarrhea, bowel actions and weight loss**.** (2) Anotherelderly woman developed gastritis, duodenitis, and bleeding duodenal ulcer after two weeks starting MFE therapy. Experimental animal study also revealed that continuous daily treatment of MFE (30 mg/kg) was capable to induce gastric ulcer among rats (Afsara et al., 2013).

Hepatotoxicity: Mefenamic acid can exert its hepatotoxicity by either direct action or alter its biological functions. During inflammatory conditions, MFE is more proxidant and exerts oxidative stress that can mediate idiosyncratic hepatotoxicity (Tafazoli et al., 2005). This agent is metabolized inside the body to reactive acyl glucuronides that can form covalent adduct with plasma and hepatic protein producing cell mediated toxicity (Boelsterli et al., 1995). The histopathological findings of a sub-acute toxicity study indicated that MFE was capable to induce hepatocellular necrosis, massive degeneration and inflammation on mice (Somchit et al., 2004). Significant elevation of mice serum level of alanine aminotransferase was also observed in the same study as an indicator of hepatic damage. One in-vitro comparative study showed that MFE was more cytotoxic on rat hepatocytes than other ten NSAIDS (diclofenac, indomethacin, flurbiprofen, piroxicam, sulindac, ibuprofen, ketoprofen, naproxine, tolmetetin and acetylsalicylic acid) (Jurima-Romet et al., 1994). The hydrophopicity of the MFE may contribute, in part, in provoking its ability to inhibit triiodothyronine (T3) uptake by H4 hepatocytes (Chalmers et al., 1993). Other evidences showed the capability of MFE to inhibit liver enzymes such as sulphotransferase and CYP1A2 enzyme (Karjalainen et al., 2008; Pacifici, 2004).

Renal toxicity: Number of evidences indicates that MEF is capable to impair renal function. This may attributed mainly to its ability to block the biosynthesis of renal prostaglandins which play an important role in the maintenance of renal blood flow, and avoiding the incidence of pre-renal azotemia and ischemia (Somchit et al., 2014; Schölkens & Steinbach, 1975). Sever, reversible and acute non-oliguric renal failure has been reported in a number of clinical cases following MFE therapy (Onay et al., 2009; Brunner et al., 1985; Woods & Micheal, 1981). Segasothy et al. (1995) reviewed the renal profile of patients with various type of arthritis and found evidence of chronic renal papillary necrosis associated with MFE treatment. Renal papillary and glomerular necrosis, massive degeneration, inflammation and tubular atrophy confirmed by elevation of plasma and urinary uronic acid and plasma creatinine measurement, were also detected in rat model after short treatment of MFE (Somchit et al., 2014; Thanh et al., 2001).

Hematological alterations: Among NSAIDs, MFE has the potential to cause acute and reversible hemolytic disorders by its ability to induce drug dependent antibodies which react against blood components mainly red blood cells and platelets (Garratty, 2010). Serological findings suggested a possible

relation between MFE hemolytic autoimmune anemiathrompocytopenia together with leucopenia, agranulocytosis and neutropenia (Balasubramanian & Sumanth, 2010; Homberg, 1999).

V. Liposmes in Drug Delivery System

Liposomes are spherical nanoparticles composed of phospholipids in a structure that is very similar to the cell membrane lipid bilayer.

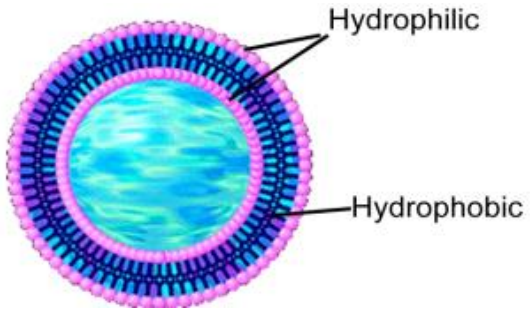

Fig. 3. Phospholipid

Liposomes tend to act as enclosed system keeping a part of the surrounding medium into their inner aqueous core (Blume, 2008). Interestingly, they exhibit several unique properties where their structure, chemical composition and colloidal size can be well controlled by the preparation methods. With this respect, liposomes have included in a wide variety of applications including pharmacology and medicine (Kim, 2013; Bergstrand, 2003). Over the last few decades, liposomes have been used exclusively in drug delivery researches aspromising tool for targeting and enhancing the efficacy of various therapeutic agents as well as in reduction their adverse reactions. Recently, different methods have been developed to prepare talented NSAIDs, but some are costly and practically inapplicable. However, using commercial liposomes knowing asproliposomes may take advantages as being simple, cost effective and stability controlled method for drugs encapsulation in the pharmaceutical industry. Proliposomes are dry phosphlipid(s) contained powders mixed with drug(s) and hydrated to produce a multi-lamellar liposomal suspension (Shaji & Bahatia, 2013). The produced suspensions can be optimized by adjusting the preparative parameters such as type of proliposomesused, drug(s) concentration and hydration time (Chiong et al., 2011). Prolipo^{TM}Dueproliposomes contained 50% unsaturated soybean PCs in which was suspended in controlled amount of food grade hydrophilic medium, was the most frequent and effective proliposomes for NSAIDs encapsulation. Table IV shows different types of liposome and their role in improving the pharmacological and toxicological profile of some NSAIDs.

TABLE IV: TALENTED NSAIDS OF DIFFERENT LIPOSOME FORMULATIONS

	Drug	Liposomal type	Experimental model(s)	Observed effect(s)	Reference (s)
1	Indomethacine	Large unilamellar vesicles	Carrageenan induced paw edema and adjuvant arthritis (rat, Intra-peritoneal)	Increase anti-inflammatory activity, less ulcer index	Srinath et al. (2000)
2	Piroxicam	Pro- lipo duo	In vitro evaluation of cytoprotective and anti-inflamatory activities of liposomal piroxicam formulation in lipopolysaccharide-stimulated RAW 264.7 macrophages	Reduce cytotoxicity and enhancing anti-inflammatory responses in vitro	Chiong et al. (2013)
3	Diclofenac sodium	Lipogelosome	Antigen-induced arthritis (Rabbit, Intra-articular)	Reduce side effects, increase retention of drug at inflammatory site	Türker et al. (2008)
4	Ketoprofen	L-α-phosphatidylcholine vesicles	Writhing and tail flick test (mouse, intra-peritoneal)	prolonged antinociceptive and analgesic activity of the drug	Tarţău et al. (2012)

Improving Bioavailability: There are several proposed mechanisms in which liposomes can enhance the bioavailability of poor water soluble drugs including enhancement of drug solubilisation, promotion of lymphatic transport, prolongation of gastric residence time, enhancement of gastrointestinal membrane permeability, reduction of metabolism and efflux activities and modification of drug release (Kalepu et al., 2013).

A. **Enhancement of drug solubilisation:** Lipid content of liposome enhance the solubilisation by dual mechanism: (1) facilitating the formation of crude emulsion by stimulating gallbladder contractions and enhancing biliary and pancreatic secretions, of bile salts, phospholipids and cholesterol a long with the gastric shear movement Shah et al., 1994). (2) Esters moiety from liposomes rapidly hydrolyzed by pancreatic lipase to form lipolytic products. The later interact with bile salts and phospholipids forming different miceller species which solubilize the hydrophopic drug and prevent its precipitation (Pouton, 2006).

B. **Promotion of lymphatic transport:** Lipidic molecules of the lipid-based vehicles can provoke the production of chylomicrons in the enterocytes which in turn increases drug transport into lymphatic in the enterocytes (Fig. 4) (Tso & Balint, 1986).

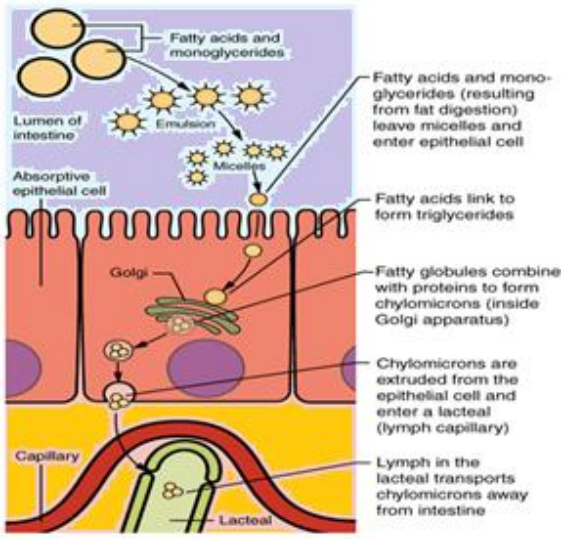

Fig. 4. Absorption of Lipid

C. **Prolongation of gastric residence time:** presence of lipids in the GI tract evokes sluggishness in gastric emptying leading to increase residence time of the coadministered lipophilic drug in the small intestine and enhance its dissolution at the site of absorption (Nakae, 1999).

D. **Enhancement of gastrointestinal membrane permeability:** liposomes can enhance the permeability by its capability to alter the physical barrier function of gut wall or by penetrating intact via pinocytosis, diffusion or endocytosis (Rejman et al., 2006).

E. **Reduction of metabolism and efflux activities:** Certain lipids and surfactants have been shown to reduce the activity of efflux transporters and P-glycoprotein efflux pump in the GI wall leading to increase the amount of drug absorbed (Kopecka et al., 2014).

F. **Modification of drug release:** Liposome encapsulation can protect loaded drugs from enzymatic degradation and provide sustain release pattern (Niu et al., 2011; Van slooten, 2001).

Reducing toxicity: The liposomal carrier system is expected to reduce the side-effects of delivered drugs due to sustained release of the drug and provide sufficient cellular uptake due to its nano-dimensions as well as alter drug pharmacokinetic behaviors (Ramana et al., 2010; Trevaskis et al., 2008). In addition, the low toxicity of liposomes coupled with a good biocompatibility, biodegradability, lack of immune system activation all make liposomes an attractive system for drug delivery (Chrai et al., 2002).

Gastroprotective mechanism of liposomes: Phospholipid is the main constituent of liposomes. This fact suggests, in part, the gastroprotictive mechanisms of liposome against mucosal injuries induced by some loaded NSAIDs. Exogenous phospholipids can increase the hydrophopocity of mucus membrane where forming electrostatic bond with the cell membrane and lay their fatty acid into lumen. Maintain the hydrophopicity of gastric mucosa is a critical of importance to ensure its integrity (Kivinen et al., 1992).

VI. CONCLUSION

During the last few decades allegations has been raised regarding MEF toxicity. These allegations have hampered its medical uses and delay its long scale development. MEF toxicity studies showed results which is not agreeable at their end points with different conclusions. While some toxicologist think MEF therapy should not exceed two weeks, others find the drug equally tolerable to paracetamol. In addition MFE toxicity assumed from just few clinical cases with a frequency is similar to those seen during treatment with other NSAIDs. This fact suggest that NSAIDs induced toxicities depend on different predisposing factors such as patient age, drug dose, disease states, concomitant medications, and dehydration therapy (Marcia, 2000; Whelton, 1999; Mann et al., 1993), and thus it is not strange that ibuprofen, the safest NSAIDs, can induce toxicity even after single dose treatment (Diaconescu et al., 2013). Further comparative studies are quiet required to elucidate the gap on MEF toxicity. Despite recent pharmaceutical studies has contributed, in part, to enhance MEF bioavailability, drug toxicity is remain the limiting factor for its medical uses. Incorporation of esters into the chemical structure of the drug may attenuate its GI tract toxicity. However, the current evidences demonstrated that these ester derivatives are subjected to efflux mechanisms on GI tract in which limit drug bioavailability (Wiwattanawongsa et al., 2005; Kwon et al., 2004). On the otherhand, Liposome drug carriers have dual action; it would be a promising tool to improve bioavailability together with reducing gastric and systemic toxicities. Without clear answer for MEF toxicity, utilizing of MFE as anti prolilative and neuroprotictive agent or in cases required high doses or long term therapy is quiet unreasonable. Liposome encapsulation is helpful to expand indications in such cases.

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