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Applications of Lipid Core Nanocapsules: Novel Drug Delivery System

S. Thamrook[1]*, SS. Subhi[1], SK. Savitha[2], M. Mathan[3]

[1]Mpharm, Department of pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, kerala-695 124, India.
[2]Assistant Professor, Department of pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, kerala-695 124, India.
[2]Doctorate in Pharmaceutics, Department of pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, kerala-695 124, India.

Abstract:

Nanoparticles is a drug delivery systems have particle sizes in the range of 10−1,000 nm. Depending on the strategies and methods and materials used for preparation, completely different supramolecular structures is obtained. In general, when composed of an oily core surrounded by a polymer shell, they are known as nanocapsules. These systems have several advantages, including controlled and sustained release of the drug, allowing a more effective and less toxic treatment than when conventional options are used, and promoting increased efficacy. Several studies have evaluated the administration of nanocapsules by completely different routes, namely oral, ocular, cutaneous, vaginal and parenteral, demonstrating the versatility of the systems. Lipid-core nanocapsules (LNCs) are a very specific kind of nontoxic polymeric nanocapsules in which the oily core is formed by an organogel composed of capric/caprylic triglyceride and sorbitan monostearate. The core chemical composition permits these nanocapsules to regulate drug penetration in numerous tissues. A variety of nanosystems such as nanostructured lipid carriers, nanosuspensions and nanocrystals have been developed nowadays.

Keywords: Lipid core nanocapsules(LNC), Nanosuspensions, Nanocapsules

INTRODUCTION:

One of those extensively studied nanoplatforms is the polymeric nanoparticles that can significantly alter the drug pharmacokinetics and body distribution. While free drug distributes in all tissues and organs, the encapsulated drug distribution is imparted by the characteristics of the carrier. Polymeric nanoparticles are colloidal systems that have received much attention owing to their potential use as drug carriers and their ability in controlling the release of encapsulated drugs. Recent interest has been focused on developing nanoscale biodegradable delivery vehicles capable of controlling the release of drugs[1,2]. These nanoplatforms are supposed to obtain a higher effect with minimal toxicity due to the controlled delivery of the drug to the targeted site and to the decrease in its systemic distribution, as well as to protect the encapsulated drugs from early in vivo metabolization and elimination, improving their pharmacokinetic profile The term “polymeric nanoparticles” refers to vesicular or matricial colloids containing polymer as a domain in the system[3,4]. Nanocapsules are vesicular carriers constituted of an oil core surrounded by a polymeric wall. Recently, we developed a new kind of nanocapsules, named lipid core nanocapsules, that square measure composed by a dispersion of sorbitan monostearate and medium chain triacylglycerol, within the core, engulfed by poly(s-caprolactone), an acylic polyester as polymeric wall.[5,6] Different from nanospheres composed by polymer or lipid nanospheres, a dispersion of sorbitan monostearate and biodegradable polymer, those lipid core nanocapsules are vesicular structures due to the presence of oil as raw material. Polymer carriers represent one of the dominant classes of nanocarrier platforms capable of efficiently encapsulating and delivering a variety of drugs, peptides and proteins increasing stability and/or decreasing toxicity. However, the qualitative composition of nanoparticles could influence either the drug in vitro release kinetic or the in vivo drug effect[7,8].

PREPARATION METHODS FOR LIPID CORE NANOCAPSULES

1. Interfacial deposition of preformed polymer

The LNC were prepared by interfacial deposition of the preformed polymer method. The organic phase of the formulations containing the PCL polymer (1%), medium chain triglycerides (1.65%), drug (0.2%), and sorbitan monostearate (0.38%) were dissolved in acetone (67 ml) for 1 hr at 40°C. The organic phases were poured into the corresponding aqueous phases containing polysorbate 80 (0.76%) and ultrapure water (134 ml). After stirring for 15 min, the organic solvent was evaporated under reduced pressure with the aid of a rotary evaporator to the desired volume of formulation (25 ml) with temperature control (40°C)[9,10].

2. Nanoprecipitation method

The LNC were prepared using the nanoprecipitation method first developed by Fessi et al. (1988, 1989). Polymer and drug were dissolved in acetone at 30°C using a water bath. The organic solution was then added drop wise, using a syringe, at the rate of 5 ml min−1 into the aqueous phase containing the hydrophilic surfactant under moderate magnetic stirring, at 25°C. The aqueous phase immediately turned milky with bluish opalescence due to the formation of the nanocapsule suspension[11]. The acetone was then evaporated at 40 ◦C under reduced pressure, using a rotavapor for approximately 30 min. Finally, the nanocapsule suspension was concentrated to final volume of 35 ml by removal of water under the same conditions[12,13].

3. Emulsion diffusion method

The drug, the oil, and the polymer were dissolved in saturated ethyl acetate at 50°C. The resultant organic solution was poured into saturated water containing stabilizer and stirred with a rotor-stator device (Ultraturraxss T25) at 8,000 rpm during 5 min in a cylindrical vessel. The emulsion O/W was formed at 20°C

(7 51C). The dispersed droplets were converted in nanocapsules by addition of a large volume of water (4 times the emulsion volume) in order to induce the solvent diffusion. After the water addition on the emulsion and mixing at 300 rpm, the nanocapsules were formed. The solvent and part of the water were removed by evaporation under reduced pressure to get a purified and concentrated suspension[14].

APPLICATIONS OF LIPID CORE NANOCAPSULES (LNCs)

The LNC has several applications as a drug carrier. They have application in cancer treatment, food materials, nutraceuticals, ethyl alcohol absorption and as self healing material.

Water-soluble compund shells being created to deliver a protein, apoptin into cancer cells. The macromolecule goes into the nucleus of the cancer cells where as feat healthy cells alone. The capsules are 100 nm in size. Active targeting of cancer cells is also being researched. Through active targeting, the nanocapsules forms ligands that bind to malignant cells for cell delivery. This methodology is particularly useful for those drugs that are not as permeable through the cell membrane[15].

Nanoencapuslation in foods involves the changing of textures, flavorings, colorings, and stability. Nutraceuticals are substances that are placed in food to enhance nutrition. The increased bioavailability of these substances is relative to the size of the nanocarrier. The smaller the nanocarrier, the better the delivery properties and the solubility of the nutraceuticals the nanocarrier is able to enter the bloodstream easier if smaller. The LNCs are used for encapsulation for nutraceuticals[16].

Relatively new analysis involves the encapsulation of enzymes within a non-toxic polymer shell. The catalyst crammed nanoshell has wll-tried in workplace mice to soak alkyl group alcohol from the blood, therefore resulting in reduced blood alcohol levels. It has been concluded that the particles act as organelles, which proposes other benefits to enzyme therapies. This discovery is introducing different studies, like encapsulation strategies for hair loss[17].

For materials like in microelectronics, polymeric coatings, and adhesives, nanocapsules can decrease damage caused by high masses. The healing of cracks within these materials is alleviated by dispersing nanocapsules within the polymer. The healing substances embody dicyclopentadiene (DCPD), which is prepared on site within the material by sonication. The nanoencapsulated material is primarily blended inside the host material by creating an oil-in-water self-healing epoxy. The blended material is then agitated inside the host material to form particles which then bond to the host material[18].

LNC AS A DRUG CARRIER

1. CURCUMIN[19]

For glioma treatment

Curcumin has been thought-about the one in every of the foremost promising natural compounds for the treatment of various forms of maladies as well as cancer and neurodegenerative diseases. Previous studies demonstrated that curcumin can inhibit the growth of several glioma cell lines through a variety of mechanisms involved in cell cycle progression (induction of p21 and p53, inhibition of cyclin D1), invasiveness (blocking of secretion of MMPs), anti/proapoptotic response (decreases in bcl-2, bcl-xL, and caspases activation), autophagy and modulation of survival pathways such as JAK/ STAT3, EGFR, PI3K/Akt, and NFkappaB[20,21]. Also studies shows that curcumin is selectively cytotoxic to tumor cells, but it spares normal neural cells such as astrocytes and neurons. Curcumin was obtained from in vitro models of cell growth in variable drug concentrations, which are almost impossible to reach under in vivo conditions. Particularly in cases of cancer, despite the promising results in cultured cancer cell lines at low concentrations, curcumin blood levels do not reach these concentrations via dietary consumption in humans because of its poor solubility, restricted tissue layer absorption and first-pass metabolism, evidencing a niche between basic findings and clinical applications of this drug. Several authors have designed drug delivery systems, such as solid lipid nanoparticles , phospholipid and cyclodextrin complexes and polymeric nanoparticles, aimed at enhancing the bioavailability and therapeutic potential of curcumin[22,23].

Among the numerous benefits that nanoparticles possess, it is important to highlight the demonstrated ability of these carriers in increasing the delivery of drugs to the brain, this being a promising strategy for the treatment of diseases affecting the central nervous system. The exact mechanism whereby nanoparticles enhance the transport of drugs across the brain blood barrier (BBB) is unclear. Previous studies have reported that the polysorbate 80 coating is a suitable strategy for brain delivery aimed at improving the receptor-mediated endocytosis of nanoparticles at the level of the BBB[24,25].

Curcumin loaded lipid-core nanocapsules (C-LNCs) is prepared to improve the antiglioma activity of this polyphenol. C-LNC showed nanotechnological properties like nanometric mean size (196 nm), 100 percent encapsulation potency, polydispersity index below 0.2, and negative zeta potential. The in vitro discharge assays shows a controlled discharge of curcumin from lipid-core nanocapsules. In C6 and U251MG gliomas, C-LNC promoted a biphasic delivery of curcumin: the primary peak occurred early with in the treatment (1–3 h), whereas the onset of the second part occurred after 48 h. In C6 cells, the cytotoxicity of C-LNC was comparable to non-encapsulated curcumin only after 96 h, whereas C-LNCs were more cytotoxic than non-encapsulated curcumin after 24 h of incubation in U251MG. Induction of G2/M arrest and autophagy were dicovered in C-LNC likewise in free curcumin treatments. In rats bearing C6 gliomas, C-LNC (1.5 mg/kg/day) diminished the neoplasm size and malignance and prolonged animal survival as compared to same dose of non-encapsulated drug. In addition, serum markers of tissue toxicity and histologic parameters were not enhanced. Considering overall, the nanoencapsulation of curcumin in LNC is an important strategy to improve its pharmacological efficacy in the treatment of gliomas[26].

2. CIPROFLOXACIN[27]

For cystic fibrosis

Ciprofloxacin is a broad spectrum 5 fluoroquinolone antibiotic and effective against P. aeruginosa and S. aureus. Intravenous and oral application of ciprofloxacin are already established in CF therapy, however systemic administration involves as well systemic side effects. Ciprofloxacin is mainly limited to adult patients, due to safety concerns regarding a long term use in children. In contrast to oral or intravenous application, administration via inhalation delivers the antibiotic directly to the site of infection. This leads to a higher local concentration and lower systemic side effects[28,29]. Ciprofloxacin applied as dry powder inhaler is currently investigated in clinical studies and its efficacy in chronic P. aeruginosa infections has already been shown. By using inhaled ciprofloxacin, dose and systemic side effects can be reduced and pediatric therapy might benefit from this antibiotic[30,31]. However, even if the antibiotic is locally distributed in the lungs, it still has to overcome the mucus as biological barrier to reach its site of action. In infected lungs of CF patients bacteria are located inside the mucus, which significantly impedes the successful treatment of pulmonary infections by inhaled drug. Mucus is a gel consisting of water, mucins (glycoproteins), non-mucin proteins. In cystic fibrosis bacterial colonization is even favored due to a reduced mucociliary clearance. Inside highly viscous and immobile mucus pathogens are protected from antibiotics and immune response. Besides a potential deactivation of antibiotics inside the mucus, effective antimicrobial therapy suffers from limited diffusion of drugs through mucus. For an effective inhalative antibacterial therapy in cystic fibrosis, advanced drug delivery systems protecting the drug and facilitating the transport to the site of action are required[32,33].

A promising approach is to use nanoparticles as carriers to protect the drug from deactivation and increase mobility. An advanced carrier system with advantageous properties for drug delivery are lipid core nanocapsules (LNC), which are composed of a lipid core, covered by a polymeric wall. LNC can efficiently be loaded with poorly soluble drugs, such as ciprofloxacin free base, since its lipid core structure is formed by an organogel composed by sorbitan monostearate and a liquid lipid. In addition, active ingredients encapsulated in LNC are protected from chemical and light induced degradation. LNC also exhibit decreased side effects, high pharmacological responses and the capability of crossing biological barriers[34,35].

3. BUDENOSIDE[36]

For ulcerative colitis

Inflammatory bowel disease (IBD) is a relapsing, progressive, chronic inflammatory disease of bowel mucosa that is more localized to the colon and characterized by both long-term and short-term inflammation. The “IBD” term is used to describe both ulcerative colitis (UC) and Crohn’s disease (CD). Both diseases are thought to be a result of dysregulated mucosal response in the bowel function[38,39]. Both UC and CD usually extend over many years and it is sometimes impossible to differentiate between them. Treatment lines for IBD are more complex and include many categories of drugs such as 5-aminosalicylates, antibiotics, thiopurines, methotrexate, biological treatment as TNF-α antibodies, and especially corticosteroids which have more effect on the active phase. In contrast, systemic absorption of corticosteroids is usually associated with higher levels of adverse effects and complications on long-term treatment[40,41]. Prednisolone is the most commonly applied corticosteroid member for the treatment of IBD but higher dose is required for this purpose (up to 40–60 mg/day), and many side effects are reported at this dose. In addition, the use of traditional dosage forms has many limitations such as extensive first pass metabolism, side effects due to drug absorption from upper gastrointestinal tract (GIT), and only small amounts of the active drug reach the inflamed areas of the colon. This results in lower therapeutic efficiency and higher side effects. Budesonide (BSD) is a potent non-halogenated corticosteroid and it was approved by FDA for the management of ulcerative colitis. BSD offers many advantages over prednisolone and solve many problematic issues related to corticosteroid therapy as the drug possesses potent efficacy, being given at a lower dose of 9 mg/day as a single dose, lower systemic absorption, and fewer side effects[42].

Drug delivery to the inflamed bowel is of an increased interest as drug delivery systems in the form of nanoparticles (NP) have the ability to protect drug against the environmental conditions of GIT. Also, in this case, NP are able to passively target inflamed area, increase drug deposition at the diseased site, prolong the desired pharmacological drug effect, and lower the side effects of the drugs. Studies shows that nanocapsules loaded with budesonide showed mean particle size in the nanoscale range with good stability . In vitro drug release studies showed that the initial rapid and unwanted releasewas greatly affected by composition variables like polymer nature, polymer concentration, and oil nature. Optimized formulations showed lower initial release of 10% at first 2 h, and higher rapid release of 72% at the end of ileum and colon. In vitro release studies were confirmed by the activity of BSD-loaded nanocapsules in animal studies as the prepared formulations showed higher improvements in disease activity index[43,44].

4. CLOTRIMAZOLE[45]

For vulvovaginitis

Clotrimazole is a broad-spectrum low toxic antifungal imidazole derivative that can be used topically to treat fungal infections, especially in the vaginal tract. Vulvovaginitis is a sexually transmitted disease caused by Candida species and is considered a recurring gynecological problem. It is estimated that 75% of women suffer from candidiasis at least once in their lives, while 40–50% experience at least two episodes. For the management of vulvovaginitis, clotrimazole is usually administered by the vaginal route as a cream, gel, ovules and pessaries, once daily at bedtime. However, this type of treatment is associated with some drawbacks such as

mucosal irritation, leakage of the formulation and low residence time at the vaginal cavity. Clotrimazole is a poorly water-soluble drug, which affects its local absorption. Bioadhesive formulations such as tablets, gels and nanostructured carriers as liposomes, cyclodextrins and microemulsion were developed in order to increase the residence time of the dosage form and to enhance local bioavailability.

Although there are studies showing that incorporation of clotrimazole into nanosized systems. The raised interest in nanoparticles is because of their properties, as they can control drug release and transport to specific sites of action, with a consequent increase in therapeutic efficacy and a reduction of side effects. In addition, these systems are able to protect the drug against enzymatic, chemical/photochemical or immunological degradation. Considering these advantages, the development of LNC prepared from a bioadhesive polymer could be considered a promising strategy for the vaginal delivery of clotrimazole, since such nanocarriers are able to prolong drug release, improve bioavailability, protect the mucosa from the topical irritant effects of the drug and enhance residence time in the vaginal cavity.

5. METHOTREXATE

For rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common autoimmune disease, and it affects 1% of the world's population.1 The disease affects the synovial membrane of joints, and, if not properly treated, leads to joint destruction and incapacity, loss of work productivity, and poor quality of life. RA is associated with a high prevalence of comorbidities, such as cardiovascular diseases, in affected individuals[47]. A reduced life anticipation in RA sufferers compared with the conventional population has been rumored. Although the mechanism for the disease etiology remains unclear, both genetic background and environmental factors have been associated with the loss of tolerance and rising autoimmunity. In the previous decade, the long prognosis of RA greatly improved following the introduction of extremely effective medications, such as methotrexate (MTX) and biologic agents, as well as treatment adjusted to target low disease activity or remission. MTX is the keystone of RA and alternative rheumatic treatments. Despite the importance of MTX for RA and alternative inflammatory conditions, it ought to be noted that 8%–16% of patients should discontinue the drug because of side effects, such as hepatic, gastrointestinal, hematological and pulmonary problems. The clinical responsiveness of RA patients to MTX treatment is another vital issue. Approximately 26 percent of patients treated with MTX should stop the drug because of deprived response and high toxicity.

Different nanocarriers, that are used as drug carrier systems, have the potential to attain the treatment goals of rheumatic conditions. Different approaches have been tested to overcome the issues and to concentrate MTX at inflammatory sites[48]. In this line of investigation, it is well known that the intravenously administered nanoparticles over 100 nm can concentrate mainly at inflammatory sites because of their particle size, which enables the nanocarriers to only cross defective capillary vessels, thereby avoiding the liver, spleen, and bone marrow. These findings may maximize the therapeutic index to scale back adverse effects and improve drug profit. MTX-LNC prepared in a liquid dose form that reduce proinflammatory and T-cell-derived cytokines on activated mononuclear cells resulting from RA patients, even in functional MTX-resistant conditions, and whether the MTX-LNC are able to diminish inflammation at lesser doses than an MTX solution in an experiment of inflammatory arthritis[49].

6. HESPERETIN[50]

For chronic venous insufficiency

Chronic venous insufficiency is characterized by chronic reflux disorder of blood from the peripheral to the central vein, with resulting venous hypertension and resulting changes in the skin. Nonsurgical treatments relied on the use of compression therapy, and more recently a variety of flavonoids have been exposed to have positive effects. Flavonoids are a big group of phenolic compounds that are widely distributed in plants.1 Hesperetin (Hst), 5,7,3′-trihydroxy-4′-methoxyflavanone, is a natural bioflavonoid found abundantly in citrus fruits with promising antioxidant and antiinflammatory properties. Studies have shown that citrus flavonoids will exert antiatherogenic and vasculoprotective effects by modulating the expression of molecules associated with inflammation, preventing the formation of foam cells, reducing the area of atherosclerotic plaques, improving the lipid profile, inhibiting the adhesion of monocytes to the endothelium and modulating cell migration. Hst via the inhibition of L-type voltage-gated Ca2+ channels and the enhancement of voltage-gated K+ channel currents of the myocytes has a direct vasorelaxant effect. Hst may also have antiplatelet effects via the inhibition of arachidonic acid-induced monoamine neurotransmitter secretion. Thus, its antiplatelet effects make Hst a good candidate in the treatment of chronic venous insufficiency (CVI).

The clinical use of Hst has been limited due to its low solubility in water and poor in vivo bioavailability. The poor bioavailability of hydrophobic drugs demands the use of high doses to overcome subtherapeutic levels in plasma. To solve this limitation, New formulations have attracted the textile sector and inspired the development of fabrics containing medication or active ingredients for topical delivery in a diversity of uses, including the treatment of CVI and other conditions. The drug is released in response to a skin stimulus, like sweating, friction or skin enzymes. For the treatment of CVI a new fabric containing Hesperetin-loaded LNCs, which would be effortless and easy to use and therefore pick up adherence to therapy.

7. LUTEIN[51]

In food industry

The preference for natural foods and ingredients containing functional properties has increased due to interest for health and life quality. Carotenoids are natural

colorants associated with beneficial health effects due to antioxidant activity and, in this context; carotenoids have received particular attention. Lutein is the second prevalent carotenoid in human blood plasma (β-carotene is the first one), and this carotenoid is abundantly present in vegetables such as kale and spinach. Besides to vegetables, flowers can also be a source of lutein to the production of dietary supplementation. However, commercial production of lutein is restricted to only a few species, and only the marigold flowers (Tagetes) are commercially cultivated as a source of this carotenoid. Lutein is a hydroxylated carotenoid and a potent antioxidant that actively protects tissues from damage caused by reactive species. In addition to preventing age-related macular degeneration, the use of lutein through diet has been strongly related to the decrease of diseases such as arteriosclerosis, cataracts, diabetic retinopathy, cancer and other diseases. Although of these important biological activities, lutein is an unstable molecule with low bioavailability due to their insolubility in aqueous media. The stability of lutein varies widely based on processing and storage, and factors such as temperature, oxygen availability, light exposure, water activity, moisture, acidity, metals, peroxides and lipoxygenase.

New technologies are continuously introduced in an attempt to increase the stability of carotenoids such as microencapsulation, which can prevent or reduce the oxidation of bioactive compounds present in foods, and additionally enable the dispersion of powders in water. Another possibility to stabilize the 5 carotenoids is the application of delivery systems with diameters less than 1 micrometer such as nanoemulsions, nanoparticles and nanocapsules. Lutein loaded to LNC improve the stability and improve the possibility of use in food industry.

CONCLUSIONS

From this above review we can conclude that lipid core nanocapsule is a most efficient drug delivery. These LNC have used as a carrier in different drugs, with its novel nature it can be used in different medications. This new kind of nanocapsules has the advantage of dispersing lipophilic drugs in their core presenting higher loading capacity than the parent nanocapsules obtained with pure oil cores. Moreover, this approach showed a rational design to develop high performance nanocarrier platform with potential application in nanomedicine.

REFERENCES

1. Venturini, C G, Jäger, E Oliveira, CP, Bernardi A, Battastini A M O. Formulation of lipid core nanocapsules. Colloid Surf A Physicochem Eng Aspects 2011;375:200–208.
2. Owens ED, Peppas AN, Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles, Int J Pharm 2006;307: 93–102.
3. Kumari A, Yadav SK, Yadav SC, Biodegradable polymeric nanoparticles based drug delivery systems, Colloid Surf B 2010;75:1–18.
4. Couvreur P, Barratt G, Fattal E, Legrand P, Vauthier C, Nanocapsule technology: a review, Crit Rev Therap Drug Carrier Syst 2002;19:99–134.
5. Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudziski WE, Biodegradable polymeric nanoparticles as drug delivery devices, J Control Rel 2001;70:1–20.
6. Rao GCS, Kumar MS, Mathivanan N, Rao MEB, Nanosuspensions as the most promising approach in nanoparticulate drug delivery systems, Pharmazie 2004;59:5–9.
7. Reis CP, Neufeld RJ, Ribeiro AJ, Veiga F, Nanoencapsulation II. Biomedical applications and current status of peptide and protein nanoparticulate delivery systems, Nanomed Nanotechnol Biol Med 2006;2:53–65.
8. Jager A, Stefani V, Guterres SS, Pohlmann AR, Physico-chemical characterization of nanocapsule polymeric wall using fluorescent benzazole probes, Int J Pharm 2007;338:297.
9. Jaguezeski, Gündel AM, Favarin SS, Gündel FR, Souza A, Baldiss CF, Lowdose curcumin loaded Eudragit L100 nanocapsules in the diet of dairy sheep increases antioxidant levels and reduces lipid peroxidation in milk. J Food Biochem 2012 p.12942.
10. Coradini, Lima K, Oliveira FO, Chaves CM, Athayde PS, Carvalho ML, Beck LM. Co-encapsulation of resveratrol and curcumin in lipid-core nanocapsules improves their in vitro antioxidant effects. Eu J Pharm Biopharm 2014;88:178–85.
11. Khayata, Abdelwahed N, Chehna W, Charcosset MF. Preparation of vitamin E loaded nanocapsules by the nanoprecipitation method: From laboratory scale to large scale using a membrane contactor. In J Pharm 2012;423:419–27.
12. Fessi H, Puisieux, Devissaguet F, Ammoury JP, Benita NS. Nanocapsule formation by interfacial polymer deposition following solvent displacement. Int J Pharm. 1989;55:25–28.
13. Fessi H, Puisieux F, Devissaguet JP. Nanocapsule formation by interfacial polymer deposition following solvent displacement. Int J Pharm 1988;55:R1–R4.
14. Guinebretière S, Briançon S, Lieto J, Mayer C, Fessi H. Study of the emulsion-diffusion of solvent: preparation and characterization of nanocapsules. Drug Deve Rese 2002;57:18–33.
15. Zhao, Muxun H, Biliang G, Zhen J. Degradable polymeric nanocapsule for efficient intracellular delivery of a high molecular weight tumor-selective protein complex. NanoToday. 2013;8:11–20.
16. Ezhilarasi P, Karthik P, Chhanwal N, Anandharamakrishnan C. Nanoencapsulation Techniques for Food Bioactive Components: A Rev Food Biopro Techn 2012;6:628–47.
17. LiuYang D, Juanjuan Y,Liang S. Biomimetic enzyme nanocomplexes and their use as antidotes and preventive measures for alcohol intoxication. Natur Nanotech 2013;8: 187–92.
18. Blaiszik BJ, Sottos NR, White SR. Nanocapsules for self-healing materials. Compos Sci Tech 2008;68: 978–86.
19. Zanotto-Filho A, Coradini K, Braganhol E, Schröder R, de Oliveira CM. Curcumin-loaded lipid-core nanocapsules as a strategy to improve pharmacological efficacy of curcumin in glioma treatment. Eu J Pharm Biopharm 2013;83:156–67.
20. Ohgaki P, Kleihues, Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendrial gliomas, J Neuropathol Exp Neurol 2005;64 479–89.
21. Soni D, King JA, Kaye AH, Hovens CM, Genetics of glioblastoma multiforme: mitogenic signaling and cell cycle pathways converge, J Clin Neuro sci 2005;1:21–5.
22. Roesler R, Brunetto AT, Abujamra AL, de Farias CB, Brunetto AL, Schwartsmann G, Current and emerging molecular targets in glioma, Expert Rev Anticancer Ther 2010;10: 1735–51.
23. Brennan C, Momota H, Hambardzumyan D, Ozawa T, Tandon A, Pedraza A, Holland E, Glioblastoma subclasses can be defined by activity among signal transduction pathways and associated genomic alterations, PLoS ONE 2009;4 e7752.
24. Anand P, Nair HB, Sung B, Kunnumakkara AB, Yadav VR, Tekmal RR, Aggarwal BB, Design of curcumin-loaded PLGA nanoparticles formulation with enhanced cellular uptake, and increased bioactivity in vitro and superior bioavailability in vivo, Biochem Pharmacol 2010;79:330–38.
25. Zanotto-Filho A, Braganhol E, Schroder R, de Souza LH, Dalmolin RJ, Pasquali MA, Gelain DP, Battastini AM, Moreira JC, NFiB inhibitors induce cell death in glioblastomas, Biochem Pharmacol 2011;81:412–24.
26. Zanotto-Filho A, Braganhol E, Edelweiss MI, Behr GA, Zanin R, Schroder R, Simoes-Pires A, Battastini AM, Moreira JC, The curry spice curcumin selectively inhibits cancer cells growth in vitro and in preclinical model of glioblastoma, J Nutr Biochem 2012;23:591–601.

27. Torge A, Wagner S, Chaves PS, Oliveira EG, Guterres SS, Pohlmann AR. Ciprofloxacin-loaded lipid-core nanocapsules as mucus penetrating drug delivery system intended for the treatment of bacterial infections in cystic fibrosis. Int J Pharm 2017;527(1-2):92–102.
28. Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis: strategies that increase life expectancy and improve quality of life. Am J Respir Crit Care Med 2011;183: 1463-71.
29. Ahlgren HG. Clinical outcomes associated with Staphylococcus aureus and Pseudomonas aeruginosa airway infections in adult cystic fibrosis patients. Bmc Pulm Med 2015 p.15.
30. Høiby N. Understanding bacterial biofilms in patients with cystic fibrosis: current and innovative approaches to potential therapies. J Cyst Fibros 2002;1:249-54.
31. Forier K. Lipid and polymer nanoparticles for drug delivery to bacterial biofilms. J Control Release 2014;190:607-23.
32. Marks MI. Clinical Significance of Staphylococcus Aureus in Cystic Fibrosis. Infection 1990;18:53-56.
33. Wagner S. Novel Strategies for the Treatment of Pseudomonas aeruginosa Infections. J Med Chem 2016;59:5929-69.
34. Principi N, Esposito S. Appropriate use of fluoroquinolones in children. Int J Antimicrob Ag 2015;45:341-6.
35. Antoniu SA. Inhaled ciprofloxacin for chronic airways infections caused by Pseudomonas aeruginosa. Expert Rev Anti Infect Ther. 2012;10:1439–46.
36. Qelliny MR, Aly UF, Elgarhy OH, Khaled KA. Budesonide-Loaded Eudragit S 100 Nanocapsules for the Treatment of Acetic Acid-Induced Colitis in Animal Model. Pharm Sci Tech 2019;20.
37. Rathbone MJ. Rathbone MJ, Controlled release in Oral drug delivery, Springer; 2013. p. 415.
38. Philip AK, Philip B. Colon targeted drug delivery systems: a review on primary and novel approaches. Oman Med J 2010;25:79–87.
39. Coco R, Plapied L, Pourcelle V, Jerome C, Brayden DJ, Schneider YJ. Drug delivery to inflamed colon by nanoparticles: comparison of different strategies. Int J Pharm. 2013;440:3–12.
40. Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. Gut 2004;53:v1–v16.
41. Hanauer SB, Robinson M, Pruitt R, Lazenby AJ, Persson T, Nilsson LG, Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. Gastroenter. 1998;115:525–32.
42. Hua S, Marks E, Schneider JJ, Keely S. Advances in oral nanodelivery systems for colon targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue. Nanomed Nanotechnol Biol Med 2015;11:1117–32.
43. Walker BR, Colledge NR. Davidson's principles and practice of medicine e-book: With STUDENT CONSULT Online Access, Elsev Heal Sci 2013.
44. Wiener C, Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's principles of internal medicine, selfassessment and board review. McGr Hil Profes 2008.
45. Santos SS, Lorenzoni A, Ferreira LM, Mattiazzi J, Adams AI. Denardi LB, Cruz, L. Clotrimazole-loaded Eudragit RS100 nanocapsules: Preparation, characterization and in vitro evaluation of antifungal activity against Candida species. Mater Sci Eng: C, 2013;33:1389–94.
46. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205–19.
47. Boechat Nde O, Ogusku MM, Boechat AL, Sadahiro A. Interaction between smoking and HLA-DRB1*04 gene is associated with a high cardiovascular risk in Brazilian Amazon patients with rheumatoid arthritis. PLoS ONE. 2012;7: e41588.
48. Chan ES, Cronstein BN. Molecular action of methotrexate in inflammatory diseases. Arthritis Res 2002;4:266-73.
49. Chan ES, Cronstein BN. Methotrexate – how does it really work? Nat Rev Rheumatol 2010;6:175–8.
50. Menezes P, Frank LA, Lima B, Carvalho Y, Serafini M, Quintans-Junior, Araujo, Hesperetin-loaded lipid-core nanocapsules in polyamide: a new textile formulation for topical drug delivery. Int J Nanomed Volume 2017;12:2069–79.
51. Brum AA,Santos, PP, Silva MM, da Paese, Guterres SS, Costa, T. M. H, Lutein-loaded lipid-core nanocapsules: Physicochemical characterization and stability evaluation. Colloid Surf A: Physicochem Eng Asp 2017;522:477–84.