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Polymeric Micelles as Novel Nanocarriers for Improving Drug Solubility, Absorption, and Targeting Efficiency: A Review Article

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Abstract **Review Article**

A major problem for the formulation of safe, effective, and economic dosage forms is the formulation of molecules that have very low water solubility. Incomplete drug dissolution would at the end lead to decreased drug absorption that will finally affect drug bioavailability. Another aspect is the increasing need to target drug release. Targeted drug release, increases drug amount at the site of action improving drug efficacy and decreasing its side effects, this review article aims to focus on the interesting properties of polymeric micelles ranging from drug solubulilization to the capability of achieving drug targeting.

Keywords: Polymeric micelles, targeting, pH-responssive, immunomicelles, Pluronics.

INTRODUCTION

Pharmaceutical industry is considered as one of the fast growing industries worldwide. It's based on discovery, development and production of pharmaceutical drugs to be administered to either animals or humans to treat, vaccinate or alleviate the symptoms of the recipient. This industry contributes with over 12 billion dollars to the world-wide market economy with more expenditure towards biotechnological products, namely, peptides, DNA-based therapeutics and proteins.

Oral administration is the most common route to deliver the drug due to of the simplicity of administration, better patient compliance, patient acceptance and avoidance of pain especially chronic cases that require frequent administration [1]. Nowadays, more than 60% of the marketed products are orally administered. For the active pharmaceutical ingredient (API) to exert its pharmacological response, it has to dissolve first down to the molecule level; subsequently drug absorption through biological barriers takes place which usually occurs through passive diffusion. Because the biological membranes are lipid in nature, so, the rate at which drugs diffuses through membranes is directly connected to their lipid solubility. Usually the unionized form of the API is more lipid-soluble. Hence, this is the preferred form to be absorbed passively across biological membranes. Another reason for the difficulty of permeation of ionized moiety of the drug is the charge repulsion or attraction that occurs between drug molecules and charged lipid bilayer or due to the fact that ionized drug molecules are usually associated with water sheath making it bulky to be passively absorbed through the biological barriers. These are the reasons why lipid soluble drugs are readily absorbed while water soluble drugs are absorbed more slowly. Also, a point should be considered that highly lipid soluble drugs usually are characterized by poor water solubility. This process hinders drug dissolution leading to incomplete drug solubility which finally leads to incomplete drug absorption and decreased drug bioavailability.

According to biopharmaceutics classification system (BCS), drugs are divided to four categories according to their water solubility and permeability. Both BCS class II or BCS class IV suffers from low water solubility exhibiting low drug appearance in blood and subsequently minimal drug concentration at site of action. To solve this problem, the formulator tends to escalate the dose in an attempt to enhance drug abundance in blood in order to exert its pharmacological effect.

Another problem facing orally administered drug is lack of targetability. Drug targeting has always been of interest to the formulator and the patient. The direct release of the drug to target site improves drug efficacy by minimizing drug distribution to other tissues. Also, drug targeting decreases side effects

leading to better patient compliance and a superior pharmacoeconomics aspect. Feasibility of drug targeting is considered on the top of the advantages of nanoparticulate matter as carriers for drug delivery. This is in addition to ability to accommodate both hydrophobic and hydrophilic substances, and the capability of their administration through different routes, namely, oral, inhalation or nasal ones [2]. Among these systems, polymeric micelles (PMs) have gained remarkable attention as nanosized APIs delivery systems for low water solubility drugs. Kataoka *et al*. [3] had the initiative role in the early 1990s in the discovery of the pioneer properties of PMs through the formulation of doxorubicin-conjugated block copolymer micelles. In this article, we will go through the unique characters of those polymeric micelles and the interesting work fabricated using them.

1. Polymeric micelles structures

PMs are "self-assembled core-shell nanostructures (hydrophobic inner core is coated with a hydrophilic part) formed by amphiphilic block copolymers" [4]. At the beginning, the block surfactant molecules are found at air liquid interface. Increasing the polymer concentration after the saturation of the air-liquid interface, forces the polymer molecule to the rest of solution. At certain concentration in the bulk, the polymers start to form micelles. This concentration is commonly known as critical micelles concentration (CMC). Above the CMC, hydrophobic sections of block copolymers start to change their orientation and minimize exposure to water molecules, leading to the formation of a vesicular or core-shell micellar structure.

Most commonly used polymers to formulate PMs are either di-block or tri-block copolyerms. According to the length of the two or three copolymers, the ratio between the hydrophilic and the lipophilic parts (HLB) of the polymer changes. The resulting aggregates are lamellar, cylindrical, or spherical shape based on the relative molecular weight of those blocks [5]. If micelles are spherical they are composed of a hydrophobic inner milieu achieving a good circumstances to accommodate a hydrophobic drug and a hydrophilic part that facilitates aqueous solubility [6].

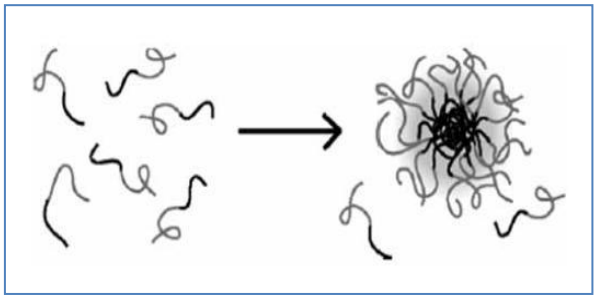

Fig-I: Model of PM Association[4]

Amphiphilic copolymers forming PMs are usually formulated from block copolymers. Block copolymers consists of similar segments along the line of the formed polymer [7]. They are classified to di-block or tri-block polymers. For diblock copolymers: they are A-B type, where A denotes a hydrophilicpart and B denotes a hydrophobic part. On the other hand, triblock copolymers are either ABA type consisting of two polymers or ABC type consisting of three polymers [7].

Pluronic® L121 and Pluronic® P123 are commonly used as block copolymers to formulate polymeric micelles. They are two di-block copolymer surfactant terminating in primary hydroxyl groups. Pluronic® L121 (L121) is a hydrophobic block copolymer (EO5–PO68–EO5) and Pluronic® P123 (P123) is a more hydrophilic copolymer (EO20–PO69–EO20). Their average molecular weights (Mwts) and HLB values are 4400 , 5750 and 1, 8, respectively.

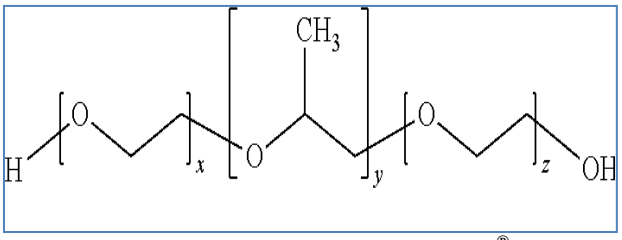

Fig-II: General Structure of Pluronics®[8]

2. Advantages of PMs

They provide several advantages including increasing drug solubility, targeting drug release and the capability to escape from reticule-endothelial system (RES) uptake and tumor targeting by improved absorption and retention effect [9]. Therefore, the micelles can enhance drug circulation time and stability. Also, the cylindrical and lamellar morphology can avoid being phagocytosed by macrophages [10].

It is worth mentioning that polymeric micelles have several advantages over other nanocarriers, as a smaller size if compared to liposomes offering PMs a superior benefit for percutaneous lymphatic uptake or extravasation from blood vessels into the tumor tissue[11].

Furthermore, Pluronics® molecules-one of the most famous used block co-polymers to formulate PMs-display important biological activities of their own. Also, being inert drug carriers, amphiphilic agents are seen as biological response modifiers [12]. Specifically, they can inhibit P-glycoprotein (P-gp) [13, 14] .

P-glycoprotein (P-gp) is a drug efflux protein found at the cellular surfaces hindering distribution and uptake of many APIs to the different body tissues, namely, brain, intestine and multidrug-resistant (MDR) tumors [15]. This process is characterized by the abundance of protein pump at the cellular surface. The pump acquires the required energy from hydrolysis of adenosine tri-phosphate (ATP) to transmit drug

molecules. The efflux takes place unidirectionally (from the cells into the extracellular space) and transfers only one molecule at a time [16].

Different mechanisms are be involved in the capability of Pluronics® to inhibit P-gp. For example, (1) Xiao *et al*. [16] declared that diblock copolymer poly (ethylene glycol)-poly (lactic acid) PEG-b-PLA micelles may inhibit P-gp function via inducing cell membrane depolarization and hence increasing membrane microviscosity ; (2) Wang *et al.* [17] encapsulated doxorubicin (DOX) in PEGylated phosphotidyl ethanolamine (PEG-PE) micelles, their results revealed that the nanocarriers possessed higher uptake in MDR cancer cells if compared to the marketed product. This was explained in the light of the reduction in P-gp expression modulated by PEG-PE block molecules ; and (3) Collnot *et al*. [18] went for the suggestion that ATPase inhibition is the reason behind the inhibitory mechanism of Pluronics on cellular efflux pumps. Inhibition of ATPase prevents ATP hydrolysis, which in turn prevent protein synthesis required for the normal functioning of those efflux pumps.

3. Polymeric micelles application for improvement of bioavailability

4.1. Increasing drug solubility

As mentioned earlier, BCS classifies different active pharmaceutical ingredients into four categories according to permeability and solubility. If the drug suffers from dissolution problems, it is expected that it ill posses incomplete absorption. Incomplete drug absorption will finally decrease drug bioavailability. PMs have been formulated to increase drug solubility in an attempt to increase drug abundance in blood.

Orientation of the co-polymer in water takes place such that the hydrophilic moieties are facing the external aqueous medium while the hydrophobic polymer sections are facing the interior of the formed micelle. This polymer orientation prepares the inner milieu of the formed micelle to take hydrophobic so they can present them in the nanorange to the GIT medium [19].

There is large number of attempts trying to solubilize low solubility drugs. Time *et al.* [20] have tried formulated stable curcumin polymeric micelles using polaxmers, the best formula was prepared using polaxamer P407 with particles size around 30 nm and a 88.1% entrapment efficiency. The PMs prepared maintained their initials properties up to 60 days in -80 ^{o}C.

Also Woraphatphadung *et al*. [21] tried to formulate meloxicam in polymeric micelles nanovesicular system. Meloxicam is class II BCS, it is practically insoluble in water. The synthesized PMs showed no toxicity in cell cultures indicating the safety of the final nanosuspension.

Additionally, it is known that drug release takes place from PMs by diffusion. Rate of drug release is controlled by the amount of block co-polymers used. Moreover, according to Camilleri *et al*. [19], dosage forms in general have limited presence time in the GIT. This increase the possibility of the formulated PMs to be excreted from the GIT before sufficient drug release or the release might occur outside the absorption window in the gastrointestinal tract.

Both griseofulvin [22] and risperidone [23] have been designed in PMs formulae in an attempt to increase their oral bioavailability via increasing the solubility of hydrophobic molecules. However, the formulated PMs exhibited release times exceeding the residence time in the small intestine. Hence, it is of due importance to take into consideration during the formulation of PMs systems the release pattern of the optimized formulation to prevent either drug precipitation on release or captivation in the developed nanocarrier.

4.1.1. pH-responsive PMs

Because of the above mentioned limitations of PMs, external stimuli are used to destabilize the micelles triggering drug release at the target organ. This would increase drug efficacy and concentration at the specifc tissues with decreasing its side effects. Various external stimuli were used like light [24], sound [25], and heat [26]. However, those external stimuli are used exclusively if the applied PMs are used near skin tissues. From this point, it is clear how difficult it is to deliver the drug to deeper blood tissues, for example liver or specific area in the small intestine.

All of these reasons necessitate the exploration of the capabilities to target PMs using differences in pHs in the physiological conditions. Blood pH is known to be around 7.4, in tumors it drops to 6.8, and reaches 5-5.5 in endosomes or lysosomes. Also the pH in the GIT changes from highly acidic in the stomach (pH~ 1.2) to neutral of slightly alkaline in the intestines (pH 6. 8-7.4). Such a variation in pH in different tissues inside the body could be the basis to promote drug permeation from PMs or even to target drug release to specific tissues.

4.1.1.2. Mechanism of enhancing or targeting drug release from pH-responsive PMs

In order for the formulated PMs should show pH responsiveness, the incorporation of polybasic or polyacidic polymers are required. Polybasic polymers usually contain amine groups in their structure. At high pHs, these groups remain unchanged and subsequently they are hydrophobic in nature. Dropping the pH to the acidic region, the amine groups are protonated and thus the molecules acquire a charged nature and become

hydrophilic. On the other hand, polyacidic polymers are loaded with acidic groups that such as carboxylic acids group. At low pHs, they remain unchanged and subseqeuntly hydrohphobic in nature. As pH increase, the carboxylic acids groups will donate a proton to the medium gaining a negative charge and thus they became hydrophilic in nature [27].

Thus, this "protonation" approach was used in order to destabilization the PMs. Incorporating molecules like L-histidine [28] or tertiary amino groups [29] were reported. PMs are formulated at pH higher than the pKa of the proton-acquiring groups, thus, the hydrophobic part exist as uncharged groups. Decreasing the pH less than the pKa ionizes of the polymers increasing its hydrophilicity triggering drug release through decreasing the stability of the formed PMs.

4.1.1.3. Polymers used to encounter pH-responsiveness

Acrylic based polymers are known for their possessing pH responsiveness. They are extensively used for oral route. Poly (methacrylic acid) retain a closed structure in low pH in the stomach, however, they swell in the following higher pHs through the intestine. Blends of those polymers can fine tune drug delivery to specific pH range [30].

Kim *et al.* [31] developed a hydrophilic polymer whose structure is PEG-b- (4-(2-vinylbenzyloxy)-N,N-(diethylnicotinamide)) (PEG-b-VBODENA), with hydrophilic moieties conferring ≤50 % of the whole molecular weight of the polymer. They worked on encapsulation of paclitaxel as a model drug in a hydrophilic polymer developed that thought to have pH sensitivity. Their results revealed that both drug encapsulation and release ere pH-dependant. PMs containing hydrophilic polymer release paclitaxel in 12 h utilizing intestinal simulated fluid, while the PMs release without the hydrophilic polymer was very slow and up to 24 h. thus, the incorporation of such polymer increased drug bioavailability and showed a pH-responsiveness indicating that increased pH of the intestine decreased the stability of the polymer used resulting in faster drug release in the intestine that their rate in the stomach.

On the other hand, Sant *et al*. [32] developed another pH-responsive polymer composed of poly ethylene glycol block- poly acrylic methacrylate. The resulting molecule characterized by having anchored carboxyl groups that for supramolecular micelles at pH of 4.7 or lower. Thus, these micelles become ionized as pH increases because of the donation of a proton from the carboxylic acids groups. Encapsulation of the two water-insoluble drugs, namely indomethacin and fenofibrate, in PMs prepared using the above mentioned polymer. The in-vitro drug release confirmed the responsiveness of the micelles to pH. Also, the in-vivo studies showed the ability of the developed nanocarriers to improve the drugs bioavailability that reached up to 156% in fenofibrate.

4.1.2. Mucoadhesive PMs

The fact that mucosal layers are highly viscoelastic in nature together with their rapid turnover phenomena, all this would present a barrier in front of drug permeation and residence in the GIT for a sufficient drug uptake. Thus, it was thought that formulating nanocarrier systems with mucoadhesive power would be a benefit [33]. Two reasons behind the willingness to develop muoadhesive PMs. First, mucosal adhesion allows the increase of the resident time spent by the formula in the GIT extending the window for drug release and permeation of the encapsulated drug. Second, mucoadhesive polymers swell if contacted the GIT medium increasing the exposed surface area and filling the cervices of the mucosal lining which finally leads to a high local amount of the encapsulated drug. Third, mucoadhesion is used to deliver the API to certain segment in GIT which finally leads to high local amounts of the drug promoting drug permeation and hence bioavailability.

4.1.2.1. Mechanism of enhancing or targeting drug release from mucoadhesive PMs

Mucoadhesion is a complex process and different steps are thought to be involved in its explanation. First, the mucoadhesive polymer spreads, gets wetted and starts to dissolve. Second, physical or mechanical engagement happens between the wetted polymer and the mucosal layer. And finally, a chemical interaction between the polymer and the mucosal layer occurs [34]. This chemical interaction can range from simple ionic, covalent or hydrogen bonds or van der Waals' interactive forces. And can extend to specific interaction between polymers anchored with targeting moieties (e.g. lectins) [35]or functional groups as thiols [36] with the mucosal layer.

Another point to be taken into consideration is the surface charge of the formulated mucoadhesive PMs. The mucosal surface with its negative charge would favor the attraction of positively charged formed PMs. So Prak *et al*. [37] used chitosan as a positively charged mucoadhesive polymer to increase drug residence in the site of absorption. It is worth mentioning that the attraction with the mucus layer may hinder drug absorption due to entrapment of the nanocarrier system in them. Thus studies declared that the permeation of negatively charged PMs is generally higher than positively charged ones. Crater and Carrier [38] demonstrated a 30 folds increase in drug diffusion of anionic moieties if compared to cationic ones. Therefore, it is of extreme importance to control the balance between drug absorption and mucoadhesion for a superior oral delivery.

The fate of the administered mucoadhesive PMs is either, mucoadhesion, direct absorption through biological layers or excretion as such.

4.1.2.2. Polymers Used to encounter Mucoadhesiveness

Polymers like carboxymethylcellulose, chitosan and alginate are among well-known mucoadhesive polymers. Positively charged class is extensively studied because of their longer resident time at the absorption site allowing all the released drug to be absorbed which in turn increases drug bioavailability. Chitosan is considered as a naturally occurring linear polysaccharide polymer decorated with d-gucosamine and N-acetyl d-glucosamine units [39]. It has a positive charge- a cationic polymer- which is generally regarded as safe, nontoxic, non-immunogenic and also biocompatible. It is postulated that the adhesive properties of chitosan is due to the electrostatic forces between the positively charged polymers and negatively charged mucous layer. Van Der Lubben *et al*. [40] formulated chitosan microparticulate for delivery of vaccines orally. Their results declared the ability of chitosan to transiently induce openings in the tight junctions between GIT cells improving the vaccine absorption.

Cellulose derivatives (methyl cellulose, hydroxyl propyl cellulose) and polyelectrolytes are being used for their mucoadhesive properties. Those polymers bind to the mucous layer using electrostatic interaction, hydrogen bond or van der Waals interactive forces or combination of interactions [41].

Another category of the mucoadhesive polymers is pluronics copolymers. It is thought that the mucoadhesion traits of Pluronic are originated form first: the carboxyl-mucin interaction, second: the capability of the polyether part of the pluronic to anchor the whole molecule to the mucosa. It is worthy to note that The mucoadhesive power of certain Pluronics –e.g. Pluronic F127- exceeded that obtained from carbopol- which is considered as the prototype of mucoadhesive polymers [42].

Ligands attached to mucoadhesive polymers could improve both their physical and chemical characteristics to obtain superior mucoahdesive pores. Krauland *et al*. [43] formulated insulin talets utilizing thiolated chitosan. Their results proved the ability of the thiolated molecules to deliver insulin orally because of the ability of the thiol moiety to induce mucoadhesion, improve permeation and protect the administered peptide from enzymatic degradation. Other ligands to be considered with targeting abilities are lectins. They are proteins which recognize and attach to sugar molecules. Sugar molecules are presented on mammalian mucous layer either the epithelial cells surface or deeper in mucosa. Through the attachment of the liganded lectins to the sugars presented at the cellular surface, they can both increase the nanocarrier resident at the cellular surface and also promote drug cellular uptake via mediated endocytosis.

5. Polymeric micelles application for achieving drug targeting

Targeted drug release has gained increased interest recently. It aims to amplify drug concentration in specific body tissues and decrease it in other tissues. Two strategies are involved in formulation of drug targeted carriers either passive targeting or active ones.

Four principle requirements are encountered to formulate a pioneering drug targeted system: The ability of the carrier system to retain, target and release the drug at specific site.

The ability to escape the hepatic metabolism that may degrade the drug so as to promote the drug abundance time in circulation and finally the absorption of the drug in the specific site within the time of effective drug functioning [44].

The interest is increasing in the utilization of PMs in drug targeting, most probably because of their nanoscopic size and core/shell architecture. The hydrophobic core is thought to stabilize micellarstructure and to accommodate a number of molecules ranging from drugs to DNA and proteins. From another point of view, the hydrophilic part will prevent the carrier from being recognized by the reticuloendothelialsystem (RES) and increasing the PMs circulation time [45].

5.1. Targeting by passive drug uptake

Several reports had pointed out to the idea that there are increased permeabilities of vasculture in some pathological conditions e.g: solid tumors or inflammation. In inflammation, the release of cytokines and inflammatory mediators lead to increased capillary permeability. It worth mentioning that, for solid tumors, several molecules released inside the body as vascular endothelial growth factor (VEGF) are recorded to enhance transcapillary permeation.

More than one polymeric micelle formulation is now under preclinical and clinical trials to gain market access. An interesting attempt is to entrap the drug paclitaxel in PEO-block poly aspartamide block PMs to increase drug solubility. Hamaguchi *et al*. [46] developed NK105 (PXT in PEO-b-poly(4-phenyl-1-butanoate)-L-aspartamide) micelles. the promising formula NK105 has shown 86-fold increase in the AUC of PXT in plasma, and 15-fold decrease in the volume of distribution compared to Taxol which has resulted in a 25-fold higher in drug AUC in tumor and stronger antitumor activity.

5.2. Targeting by active uptake

Active drug targeting depends on the selective uptake of the molecules by specific carriers due to the presence of certain functional groups leading to chemical interaction between the molecule and the carrier. Different mechanisms were suggested to encounter the active uptake and hence targeting of variable PMs.

5.2.1. Immunomicelles

Immunomicelles are formulated by chemically conjugating a monoclonal antibody or Fab fragments of specific antibodies to the hydrophilic part of the PMs. The abundance of either monoclonal antibodies or the Fab fragments on the outer part of PMs will allow it to react with tumor associated antigen providing a way for PMs Specific pick up. Several studies have reported to incorporate those antibodies from using murine polyclonal antibodies to one tissue factor (TF)-targeting Fab. However the attempt of Torchilin *et al*. [47] will remain the most interesting one. They worked on conjugation of monoclonal antibodies to the p-nitrophenyl carbonyl group of the hydrophilic segment of polyethylene oxide-phosphatidylethanol amine. The resulting PMs showed specific uptake by different cancer cells namely breast adinocarcinoma, murine Lweis lung carcinoma and T lymphoma.

5.2.2. Sugar modified PMs

Sugars have superior characters due to having specific receptors on the outer cell wall. This is why conjugation of PMs with sugars occur allowing active drug targeting. For an example, galactose and mannose have certain receptors namely asialoglycoprotein (ASGP) and Kupffer cell in the liver. An early attempt to formulate sugar decorated PMs were the work of Yasugi *et al.* [48], that succeeded in the attaching glucose and galactose to poly(ethylene glycol)-poly(D,L-lactide) block copolymer.

Another attempt is the work of Cho *et al*. who developed galactose anchored polyoxyetheylen-block-benzyl-block and encapsulated the drug paclitaxel in the formed polymer. The flow cytometry experiment demonstrated an enhanced uptake for galactose modified PMs in asialoglycoprotein expressing HepG2 cells.

CONCLUSION

Polymeric micelles will alwyas remain an interesting topic and will attract more researches because of their competitive properties if compared to other nanocarrier systems. They can achieve both enhancing drug absorption because of their solublization properties in addition to the capability of either the hydrophilic part or the hydrophobic one to accommodate targeting ligands. However, further work is required so these nano particles could gain a market access.

REFERENCES

1. Xu, W., Ling, P., & Zhang, T. (2013). Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. *Journal of drug delivery*.
2. Gelperina, S., Kisich, K., Iseman, M. D., & Heifets, L. (2005). The potential advantages of nanoparticle drug delivery systems in chemotherapy of tuberculosis. *American journal of respiratory and critical care medicine*, *172*(12), 1487-1490.
3. Yokoyama, M., Kwon, G. S., Okano, T., Sakurai, Y., Seto, T., & Kataoka, K. (1992). Preparation of micelle-forming polymer-drug conjugates. *Bioconjugate chemistry*, *3*(4), 295-301.
4. Aliabadi, H. M., & Lavasanifar, A. (2006). Polymeric micelles for drug delivery. *Expert opinion on drug delivery*, *3*(1), 139-162.
5. Lee, E. S., Oh, Y. T., Youn, Y. S., Nam, M., Park, B., Yun, J., ... & Oh, K. T. (2011). Binary mixing of micelles using Pluronics for a nano-sized drug delivery system. *Colloids and Surfaces B: Biointerfaces*, *82*(1), 190-195.
6. Rangel-Yagui, C. O., Pessoa Jr, A., & Tavares, L. C. (2005). Micellar solubilization of drugs. *J. Pharm. Pharm. Sci*, *8*(2), 147-163.
7. Francis, M. F., Lavoie, L., Winnik, F. M., & Leroux, J. C. (2003). Solubilization of cyclosporin A in dextran-g-polyethyleneglycolalkyl ether polymeric micelles. *European Journal of Pharmaceutics and Biopharmaceutics*, *56*(3), 337-346.
8. Kabanov, A. V., Lemieux, P., Vinogradov, S., & Alakhov, V. (2002). Pluronic® block copolymers: novel functional molecules for gene therapy. *Advanced drug delivery reviews*, *54*(2), 223-233.
9. Liu, Z., Liu, D., Wang, L., Zhang, J., & Zhang, N. (2011). Docetaxel-loaded pluronic p123 polymeric micelles: in vitro and in vivo evaluation. *International journal of molecular sciences*, *12*(3), 1684-1696.
10. Jhaveri, A. M., & Torchilin, V. P. (2014). Multifunctional polymeric micelles for delivery of drugs and siRNA. *Frontiers in pharmacology*, *5*, 77.
11. Qin, L., Zhang, F., Lu, X., Wei, X., Wang, J., Fang, X., ... & Liang, W. (2013). Polymeric micelles for enhanced lymphatic drug delivery to treat metastatic tumors. *Journal of Controlled Release*, *171*(2), 133-142.
12. Batrakova, E. V., & Kabanov, A. V. (2008). Pluronic block copolymers: evolution of drug delivery concept from inert nanocarriers to biological response modifiers. *Journal of controlled release*, *130*(2), 98-106.
13. Wei, Z., Hao, J., Yuan, S., Li, Y., Juan, W., Sha, X., & Fang, X. (2009). Paclitaxel-loaded Pluronic P123/F127 mixed polymeric micelles: formulation, optimization and in vitro characterization. *International journal of*

pharmaceutics, *376*(1-2), 176-185.
14. Han, L. M., Guo, J., Zhang, L. J., Wang, Q. S., & Fang, X. L. (2006). Pharmacokinetics and biodistribution of polymeric micelles of paclitaxel with Pluronic P123. *Acta Pharmacologica Sinica*, *27*(6), 747-753.
15. Amin, M. L. (2013). P-glycoprotein inhibition for optimal drug delivery. *Drug target insights*, *7*, DTI-S12519.
16. Srivalli, K. M. R., & Lakshmi, P. K. (2012). Overview of P-glycoprotein inhibitors: a rational outlook. *Brazilian Journal of Pharmaceutical Sciences*, *48*, 353-367.
17. Wang, J., Qu, H., Jin, L., Zeng, W., Qin, L., Zhang, F., ... & Liang, W. (2011). Pegylated phosphotidylethanolamine inhibiting P-glycoprotein expression and enhancing retention of doxorubicin in MCF7/ADR cells. *Journal of pharmaceutical sciences*, *100*(6), 2267-2277.
18. Collnot, E. M., Baldes, C., Wempe, M. F., Kappl, R., Hüttermann, J., Hyatt, J. A., ... & Lehr, C. M. (2007). Mechanism of inhibition of P-glycoprotein mediated efflux by vitamin E TPGS: influence on ATPase activity and membrane fluidity. *Molecular pharmaceutics*, *4*(3), 465-474.
19. Yorulmaz Avsar, S., Kyropoulou, M., Di Leone, S., Schoenenberger, C. A., Meier, W. P., & Palivan, C. G. (2019). Biomolecules turn self-assembling amphiphilic block co-polymer platforms into biomimetic interfaces. *Frontiers in chemistry*, *6*, 645.
20. Tima, S., Anuchapreeda, S., Ampasavate, C., Berkland, C., & Okonogi, S. (2017). Stable curcumin-loaded polymeric micellar formulation for enhancing cellular uptake and cytotoxicity to FLT3 overexpressing EoL-1 leukemic cells. *European Journal of Pharmaceutics and Biopharmaceutics*, *114*, 57-68.
21. Woraphatphadung, T., Sajomsang, W., Rojanarata, T., Ngawhirunpat, T., & Opanasopit, P. (2015). Polymeric Micelles for Enhanced Solubility of Meloxicam in Oral Drug Delivery. In *Advanced Materials Research* (Vol. 1060, pp. 7-11). Trans Tech Publications Ltd.
22. Pierri, E., & Avgoustakis, K. (2005). Poly (lactide)- poly (ethylene glycol) micelles as a carrier for griseofulvin. *Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials*, *75*(3), 639-647.
23. Ould-Ouali, L., Noppe, M., Langlois, X., Willems, B., Te Riele, P., Timmerman, P., ... & Préat, V. (2005). Self-assembling PEG-p (CL-co-TMC) copolymers for oral delivery of poorly water-soluble drugs: a case study with risperidone. *Journal of controlled release*, *102*(3), 657-668.
24. Chen, C. J., Jin, Q., Liu, G. Y., Li, D. D., Wang, J. L., & Ji, J. (2012). Reversibly light-responsive micelles constructed via a simple modification of hyperbranched polymers with chromophores. *Polymer*, *53*(17), 3695-3703.
25. Husseini, G. A., Velluto, D., Kherbeck, L., Pitt, W. G., Hubbell, J. A., & Christensen, D. A. (2013). Investigating the acoustic release of doxorubicin from targeted micelles. *Colloids and Surfaces B: Biointerfaces*, *101*, 153-155.
26. Tan, R., She, Z., Wang, M., Fang, Z., Liu, Y., & Feng, Q. (2012). Thermo-sensitive alginate-based injectable hydrogel for tissue engineering. *Carbohydrate Polymers*, *87*(2), 1515-1521.
27. Tang, H., Zhao, W., Yu, J., Li, Y., & Zhao, C. (2019). Recent development of pH-responsive polymers for cancer nanomedicine. *Molecules*, *24*(1), 4.
28. Lee, E. S., Shin, H. J., Na, K., & Bae, Y. H. (2003). Poly (l-histidine)–PEG block copolymer micelles and pH-induced destabilization. *Journal of Controlled Release*, *90*(3), 363-374.
29. Tang, Y., Liu, S. Y., Armes, S. P., & Billingham, N. C. (2003). Solubilization and controlled release of a hydrophobic drug using novel micelle-forming ABC triblock copolymers. *Biomacromolecules*, *4*(6), 1636-1645.
30. Yoshida, T., Lai, T. C., Kwon, G. S., & Sako, K. (2013). pH-and ion-sensitive polymers for drug delivery. *Expert opinion on drug delivery*, *10*(11), 1497-1513.
31. Kim, S., Kim, J. Y., Huh, K. M., Acharya, G., & Park, K. (2008). Hydrotropic polymer micelles containing acrylic acid moieties for oral delivery of paclitaxel. *Journal of Controlled Release*, *132*(3), 222-229.
32. Sant, V. P., Smith, D., & Leroux, J. C. (2004). Novel pH-sensitive supramolecular assemblies for oral delivery of poorly water soluble drugs: preparation and characterization. *Journal of Controlled Release*, *97*(2), 301-312.
33. Shaikh, R., Singh, T. R. R., Garland, M. J., Woolfson, A. D., & Donnelly, R. F. (2011). Mucoadhesive drug delivery systems. *Journal of Pharmacy and Bioallied Sciences*, *3*(1), 89.
34. Smart, J. D. (2005). The basics and underlying mechanisms of mucoadhesion. *Advanced drug delivery reviews*, *57*(11), 1556-1568.
35. Fu, L. L., Zhou, C. C., Yao, S., Yu, J. Y., Liu, B., & Bao, J. K. (2011). Plant lectins: targeting programmed cell death pathways as antitumor agents. *The international journal of biochemistry & cell biology*, *43*(10), 1442-1449.
36. Kausar, H., Munagala, R., Bansal, S. S., Aqil, F., Vadhanam, M. V., & Gupta, R. C. (2013). Cucurbitacin B potently suppresses non-small-cell lung cancer growth: identification of intracellular thiols as critical targets. *Cancer Letters*, *332*(1), 35-45.
37. Park, J. H., Saravanakumar, G., Kim, K., & Kwon,

I. C. (2010). Targeted delivery of low molecular drugs using chitosan and its derivatives. *Advanced drug delivery reviews*, *62*(1), 28-41.
38. Crater, J. S., & Carrier, R. L. (2010). Barrier properties of gastrointestinal mucus to nanoparticle transport. *Macromolecular bioscience*, *10*(12), 1473-1483.
39. Mizrahy S., Peer D. (2012). Polysaccharides as building blocks for nanotherapeutics. *Chemical Society Reviews*, 41(7):2623-40.
40. Van der Lubben, I. M., Verhoef, J. C., Van Aelst, A. C., Borchard, G., & Junginger, H. E. (2001). Chitosan microparticles for oral vaccination:: preparation, characterization and preliminary in vivo uptake studies in murine Peyer's patches. *Biomaterials*, *22*(7), 687-694.
41. Yadav, V. K., Gupta, A. B., Kumar, R., Yadav, J. S., & Kumar, B. (2010). Mucoadhesive polymers: means of improving the mucoadhesive properties of drug delivery system. *J. Chem. Pharm. Res*, *2*(5), 418-432.
42. Giuliano, E., Paolino, D., Fresta, M., & Cosco, D. (2018). Mucosal applications of poloxamer 407-based hydrogels: an overview. *Pharmaceutics*, *10*(3), 159.
43. Krauland, A. H., Guggi, D., & Bernkop-Schnürch, A. (2004). Oral insulin delivery: the potential of thiolated chitosan-insulin tablets on non-diabetic rats. *Journal of Controlled Release*, *95*(3), 547-555.
44. Mishra, N., Pant, P., Porwal, A., Jaiswal, J., & Aquib, M. (2016). Targeted drug delivery: a review. *Am. J. Pharm. Tech. Res*, *6*, 2249-3387.
45. Mahmud, A., Xiong, X. B., & Lavasanifar, A. (2006). Novel self-associating poly (ethylene oxide)-b lock-poly (ε-caprolactone) block copolymers with functional side groups on the polyester block for drug delivery. *Macromolecules*, *39*(26), 9419-9428.
46. Hamaguchi, T., Matsumura, Y., Suzuki, M., Shimizu, K., Goda, R., Nakamura, I., ... & Kakizoe, T. (2005). NK105, a paclitaxel-incorporating micellar nanoparticle formulation, can extend in vivo antitumour activity and reduce the neurotoxicity of paclitaxel. *British journal of cancer*, *92*(7), 1240-1246.
47. Torchilin, V. P., Lukyanov, A. N., Gao, Z., & Papahadjopoulos-Sternberg, B. (2003). Immunomicelles: targeted pharmaceutical carriers for poorly soluble drugs. *Proceedings of the National Academy of Sciences*, *100*(10), 6039-6044.
48. Yasugi, K., Nakamura, T., Nagasaki, Y., Kato, M., & Kataoka, K. (1999). Sugar-Installed Polymer Micelles: Synthesis and Micellization of Poly (ethylene glycol)− Poly (d, l-lactide) Block Copolymers Having Sugar Groups at the PEG Chain End. *Macromolecules*, *32*(24), 8024-8032.