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POLYMERIC MICELLES: A NOVEL APPROACH TO ENHANCE SOLUBILITY OF POORLY SOLUBLE DRUGS

Renu Tehlan* and Akshay Dahiya

University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali, Punjab, 140413, India.

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***Corresponding Author**
Renu Tehlan
University Institute of Pharma Sciences, Chandigarh University, Gharuan, Mohali, Punjab, 140413, India.

ABSTRACT

Almost 70% of synthetic substances are generally insoluble in water and in natural media and 40% of drugs with immediate – release and delivered orally, which are already marketed are found to be insoluble in water. After so many researches and advancements pharmaceutical industry has developed lots of novel ways to deliver drugs at different sites in body. Polymeric micelles are one of the novel approaches which has so many advantages while using as drug delivery method because of their biocompatibility, non-toxicity, nano-size, morphology, shell arrangement, stability. In this review we are going to study about how polymeric micelles are being used in oral drug delivery and in oncology by enhancing the solubility of water insoluble drugs also different methods of preparation of these micelles.

KEYWORDS: Polymeric micelles, novel drug delivery, solubility enhancement, biocompatibility.

INTRODUCTION

In recent years, the quantity of medication applicants with dissolvability issues has consistently expanded because of utilization of chemistry of drug combination and screening. Almost 70% of synthetic substances are generally insoluble in water and in natural media and 40% of drugs with immediate – release and delivered orally, which are already marketed are found to be insoluble in water (Lu and Park, 2013). The oral route is a simple, easy, widely used, ease to deliver the drug and having regularly increasing patient compliance. In oral dosage form, the solid drugs are most widely usable along with no of benefits (Hussain et al., 2017; Singh et al., 2020b). Solid drugs structures don't need sterility during formation, can be

acquired with generally basic and practical cycle, have high physicochemical dependability, are protected and simple to self-administer. It is grounded that disintegration is every now and again the rate-restricting advance in the gastrointestinal assimilation of a medication for solid doses formulations. Water solvency is a key boundary affecting organic action, plan and in vitro and in vivo biopharmaceutical properties (Bazzo et al., 2020), (Aldawsari and Singh, 2020). The improvement of oral formulations of ineffectively water-dissolvable Active pharmaceutical ingredients (APIs), Biopharmaceutical Classification System (BCS) class II and class IV water insoluble drugs, is one of the best current challenges and flow difficulties in pharmaceutics. For a strong measurement structure, the watery solvency and intestinal porousness are the two significant qualities of a medication item which oversee its bioavailability. BCS arrangement, a logical and crucial apparatus relates in vitro disintegration and in vivo bioavailability of medication item and is subsequently significant in drug advancement of oral items. Solvency upgrade procedures are needed for class II medications, where disintegration rate is frequently a restricting variable for bioavailability. Class IV medications are both disintegration and intestinal porousness restricted, so frequently considered as helpless contender for drug improvement (Singh et al., 2020a; Singh and Lal, 2014). Hence, class II and IV medications require exceptional consideration and contemplations regarding solvency and bioavailability enhancements. The innovative advancements in the drug business have improved a great deal and acquainted the novel ways with convey drugs proposed for various purposes into the body. Continuous attempts have been made to address this issue during the past 50 years, as apparent from straight forward pursuits in Web of Science; the quantity of papers coordinating with the hunt terms of 'insoluble medication' or 'ineffectively water-solvent medication' supposedly has expanded dramatically since 1960 (Yu et al., 2018). As per the Noyes–Whitney equation, the speed of disintegration of a drug is completely rely on its extent, diffusion constant, dispersion layer thickness, immersion dissolvability, the live of dissolve drug yet as volume of disintegration media. From these variables, effective extent, dispersion layer thickness and immersion dissolvability square measure those factors which will be modification by dynamic the formulation parameters (Lu and Park, 2013). With the nanocrystal approach, totally different forms of nanonization procedures have arisen as new nano platforms for the conveyance of inadequately solvent medications. Regular instances of those nano platforms incorporate nano emulsions and chemical compound micelles(Lu and Park, 2013). Over the most recent thirty years, polymeric micelles have arisen as a profoundly encouraging medication conveyance stage for therapeutic drugs. Mainly polymeric micelles are used to encapsulate

the small particles having high intensity and large toxicity index. Some of polymeric micelles are able to reach clinical stage either of them is in clinical stage or are marketed for human use. Still no of learnings or researches are required to improve the clinical data of these micelles (Hwang et al., 2020)(Lu and Park, 2013). Figure 1 is showing the systematic representation of polymeric micelles (Ghezzi et al., 2021).

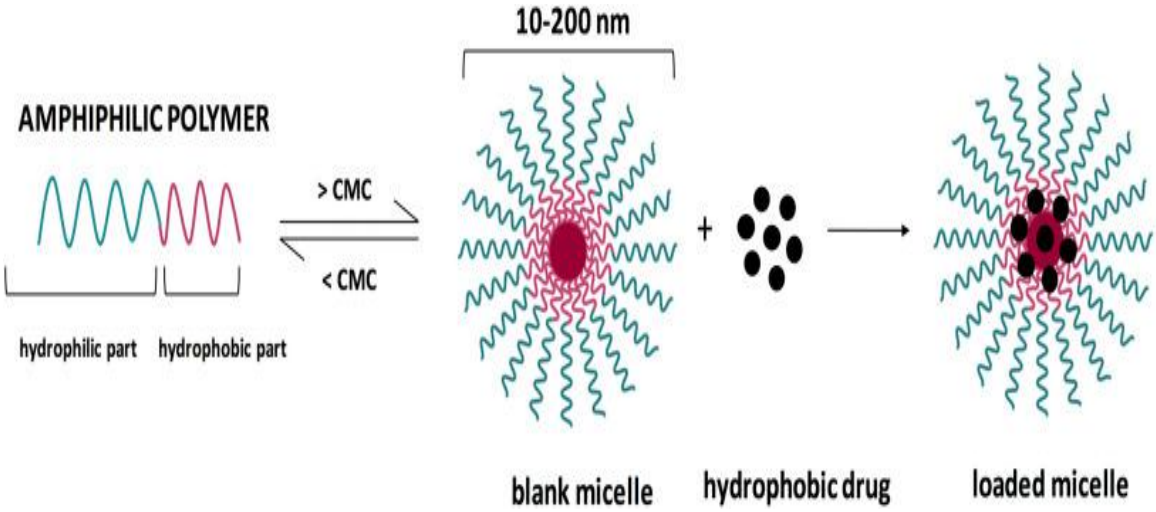

Fig. 1: Is showing the systematic representation of polymeric micelles(Ghezzi et al., 2021)

The micelles inside have a hydrophobic core and outside a hydrophilic surface. Micelles are comprised of 50 to 200 monomers (a normal number of monomers shaping micelle at some random time is named as the aggregation number). The radius of a round micelle is practically equivalent to the length of a completely expanded surfactant monomer, which generally is 1-3 nm, and accordingly micelles lie in the colloidal range (Mourya et al., 2011).

Critical micelle concentration (CMC)

CMC is a limit of concentration of surfactants upon which micelles start forming. By lowering the surface energy at the interface surfactants lower the strength of the system and remove the hydrophobic part from water, surface energy starts decreasing and aggregation take place which leads to the formation of micelles (Singh et al., 2015; Singh and Lal, 2016). Before reaching CMC, surface tension is inversely proportional to the concentration of surfactants after reaching CMC surface tension become independent of concentration of surfactants. Micelles formation take place over a sharp concentration range. CMC is generally present in the range of some ppm to tens of ppm (Rhein, 2007).

Polymeric micelles

Polymeric micelles (PMs) are nano-sized drugs having amphiphilic properties because of hydrophobic core and hydrophilic surface and poses a shell like structure which leads to their solubility in aqueous solution (Ghezzi et al., 2021). Different types of di, tri, unit copolymers are used in the formation of polymeric micelles (Yadav et al., 2019).

Polymeric micelles square measure utilized in completely different drug delivery systems attributable to their distinctive properties like biocompatibility, low poisonousness, core shell arrangement, micellar affiliation, morphology, nano size, and moderately high stability. they're utilized in treatment of various varieties of diseases like malignancy, in steroid treatment, respiratory illness antiviral (Mourya et al., 2011).

Direct disintegration, dissolvable projecting, or dialysis are different methods of micelles formation. This last specific property gives probably the most grounded contention for utilizing polymeric micelles for conveying against malignant growth drugs, the vast majority of which additionally have low fluid solvency. In spite of using polymer micelles as drug there is lot of work is going on in experimental way on these micelles with very few in clinical stages. Those immediately in clinical stages square measure incorporate stage II and stage IV investigations of paclitaxel-stacked compound micelles for cellular breakdown within the lungs (and repetitive bosom malignant growth, severally (Lu and Park, 2013).

Size

In case of any nano transporter size plays an important role so as in polymeric micelles it’s important to identify the size or to set the size of micelles while forming drug formulation (Duan and Li, n.d.)(Han, 2016)(Online et al., 2013)(Wang et al., 2015). For example, 30-100 nm sized micelles can easily accumulate in permeable tumors and they are plagued by these micelles (Cabral et al., 2011).

As an evident while considering the dissemination across the body fluid layer or the take-up into epithelial cells, as announced for other nano particle systems (Murgia et al., 2016)(Rossi et al., 2019) (Salatin et al., n.d.).

Because we do not have such broad information it is additionally critical to underline that, given their inclination, micelles can disassembly in the body fluid or in contact with epithelial

cells and, for this situation, the infiltration capacity is not dependent on size of micelles but upon the quality of unimers used and their interaction with body fluid.

Shape

With round shaped micelles sometimes pole like, worm-like or even circle like structures of micelles are also noticed (Owen et al., 2012) (Taylor et al., 2010) (Truong et al., 2014). The distinctions fit that the polymers are identified by their designs or (Owen et al., 2012) and to the qualities regarding temperature, pH and composition (Numan et al., 2020; Singh et al., 2016, 2020c).

Micelles morphology study is important because of their role in vivo as carrier system and their critical part in impacting course time, bio distribution and cell uptake (Truong et al., 2014). For example, filamentous micelles, because of their stretched shape, having slow clearance measure and a delayed flow time than circular micelles (Discher, 2017)(Oltra et al., n.d.).

According to recent researches the cross-sections, shorter filamentous micelles showed the deepest tumor penetration and the most efficient cellular uptake in comparison with spherical micelles and long filamentous micelles (2.5μm) (Ke et al., 2019).

Types of polymer used

Different types of polymers are used while forming polymeric micelles among them three types of polymers which are widely use are following:

- Di block copolymers, example: poly (ethylene glycol) (PEG)
- Tri block, example: poly (ethylene oxide)
- Unit block, example: stearic corrosive and G-chitosan (Yadav et al., 2019).

Method of preparation

Dialysis technique

- In this technique polymer and medication arrangement is dissolved in a natural dissolvable like dimethyl formamide in the expansion of limited quantity of water.
- Followed by the dialysis with the abundance of water for few hours and utilize a dialysis pack for the evacuation of natural solvent (Mourya et al., 2011)(Kim et al., 1999).
- Medication stacking needs 36hr of dialysis.

- To decrease this limitation, we can use another method which help to break the polymer and medication by lyophilization then by re-dispersion we will get the polymeric micelles.
- Arrangement of Morin hydrate (MH) compound nanomaterials is finished by exploitation qualitative analysis.
- The shell arrangement begins by utilizing 15mg of mucopolysaccharide poly (butyl cyanoacrylate) block polymer, that is lessened in 3mL of phosphate-cushioned saline at pH scale 7.4, at that time a mixture of MH in 0.5 mL dimethyl sulfoxide is value-added to the past chemical compound suspension with continuous combination at 150 rpm at 25℃.
- After this ultrasonicate of the last combination for 30min in Associate in an ice shower surface.
- At that time, by utilizing a qualitative analysis pack, the arrangement is dialyzed against Associate in an overabundance live of refined water for 12h followed by filtration and freeze (Press, 2014).

Oil-In-Water emulsion dissolvable vanishing technique

- Medication with the compound is jerky during a water-immiscible natural dissoluble like tetrahydrofuran, chloroform, acetone, or a mix of solvents like chloroform and alcohol.
- This solution is then step by step extra to the refined water beneath spirited mixing to border associate emulsion with associate inward natural stage and nonstop watery stage, that helps the compound to form like micelles.
- This emulsion is then unbroken hospitable air with mixing to evaporate all the natural solvent (Kedar et al., 2010).

Strong dispersion method

- In this technique, drug with the polymer are dissolved in the natural dissolvable solvent.
- Under decreased tension polymeric form is obtained by vanishing the dissolvable solvent.
- Medicated PMs are formed after the expansion of water to the preheated polymer matrix (Taillefer et al., 2000)(Zhang et al., 1996).

Micro phase separation method

- In this strategy the medication and compound are counteracted in (natural dissolvable) tetrahydrofuran.
- Under enticing mixed the solution is additional dropwise into water.

- PMs are formed sharply, and medications are present within the internal piece of the micelles.
- Natural dissoluble is taken out below diminished tension.
- Blue-colored PM arrangement is made (Neugebauer, 2020).

Direct dissolution

- Because of low medication stacking this technique is less popular for formation of polymeric micelles.
- To overcome this problem, the strategy or technique is use with expanding temperature and by dissipated film of drug before adding the copolymer (Mourya et al., 2011).
- This technique is used in formation of paclitaxel (PTX)- consolidating polymeric micelles.
- Self -interaction of amphiphilic copolymers in liquid medium.
- The PTX is present in the core of the micelles hydrophobic collaborations between the medication and the copolymer (Nakatomi et al., 2014).

Application of polymeric micelles in drug delivery

Micelles are worth useable for drug targeting, drug delivery, long circulation of drug. Because of their nano size and their hydrophilicity then are used in drug delivery across corneal obstructions and used in ocular drug delivery. These micelles are going high in research field because of their capacity to deliver hydrophobic medications and to dwell in the eye tissues turned (Mandal et al., 2017). Because of their hydrophobic property they widely use in anticancer field as they increase the permeability of medications across tumors. By forming the complex with ligands, will improving the focusing of malignancy tissues (Kedar et al., 2010).

In oral drug delivery

Most widely used route for drug delivery is the oral drug delivery route. The oral course of medication organization is broadly acknowledged by the specialists, is very much considered and perceived. From the patient's perspective, it is simple and effortless to regulate, and takes into account for administration by own, which is particularly helpful for constant treatment (Aldawsari and Singh, 2020; Hussain et al., 2017). Nonetheless, despite the fact that it is a generally used methodology and surely known, the detailing of medications for oral conveyance stays a multifaceted cycle, particularly for the inadequately water-dissolvable

medications. All together for retention of orally managed medication to happen, it should initially break down into its atomic structure. For an ineffectively dissolvable medication, the pace of disintegration might be so lethargic or the immersion solvency so low that there is fragmented or lacking arrival of medication, which at last prompts helpless bioavailability and low medication adequacy. Polymeric micelles can affect bioavailability by increasing the solubility of water insoluble drugs in GIT fluid. Because of the presence of drug in the shell of the micelles can prompt diminished measure of medication accessible for assimilation (Lu and Park, 2013).

Maintaining micelle stability

Every single drug which is delivered by oral route will face different climates in every part of GIT because it passes the GIT tract when given orally. The pH value of different sites or region in GIT is as, like, 1-2 (acidic) in stomach and 5-7 (basic) in small intestine (Daugherty et al., 1999). The liquid volumes in GIT tract changes with respect to the area. Such that in the fasted state, volume in both stomach and intestine is near 130ml and during eating conditions it will be 740ml. PMDDS advancement is that the micelle transporters should have the option to oppose fast and untimely separation upon weakening and openness to the different states of the GI tract (Iessman et al., 2005). Hydrophobic core of micelles is responsible for the low value of CMC. We can keep the shell shaping polymer at a similar chain length to maintain the low value of CMC (Peng, 2012).

Interactions with intestinal mucosa

Different trial techniques are there to know the interaction of micelles with viscus membrane. chemical compound micelles aren't proverbial to collaborate broadly speaking with cell films because of steric block from shell shaping chemical compound parts. Rather the greater part of the in vitro considers completed survey the impact of micelle embodiment on drug penetrability contrasted and un-exemplified drug permeability (Lu and Park, 2013). The intestinal mucosa is generally found to be impermeable to polymeric micelles. In every case, different pathways are there that helps to permit the vehicle of micellar transporter across the layer. Polymeric particle is wedged in its shell like structure by enterocytes or M cells through an endocytotic pathway depart by non-specific collaborations, chemical element bonds or van der Waal bonding square measure a lot of possible bonding found between the particle surface and therefore the cell (Norris et al., 1998). Micelles is assimilated through the cycle of bodily function, during which the cell surface structures invagination that

overwhelms the particle transporter. An approach typically examined in parentral medication conveyance is that compound micelles is assimilated through receptor-intervened pathway (Lu and Park, 2013).

In oncology

Hydrophobic nature of polymeric micelles helps water insoluble anticancer drugs in increasing their solubility. Second, exemplification is they may limit drug debasement and misfortune. The hydrophilic restrict opsonin adsorption. Because of nano size of micelles they empower shirking of rummaging by the mononuclear phagocytic framework in the liver and filtration between endothelial cells in the spleen. In the tumor area, with help of their nano size they help them to flee into the influenced tissue region by defective vasculature found at neoplasm web site, and in absence of bodily fluid waste in these sites, the micelles are often command there for a while to supply sufficient therapeutic impact, this can be called the enhanced permeability and retention (EPR) impact. By appending explicit ligands to advance PMDDS-cell explicit collaborations, we can adjust the shell of the micelles, results coming from exceptionally intense enemy of malignant growth specialists following up on typical cells. According to the above information, the advantage of utilizing polymeric micelles in malignancy treatment is incredible (Lu and Park, 2013).

Enhancements in solubility

When anticancer drugs combined with polymeric micelles it will leads to increase in solubility this is what we are going to discus in this section. Paclitaxel, whose solubility in aqueous phase is 0.3g/ml is referring as an antitumor agent was combine with the 1,2-distearoyl-sn-glycero-3phosphoethanolamine-N-methoxy micelles (Sawant and Torchilin, n.d.). Paclitaxel solubility increased by 38.9mg/ml with micelles. Nicotinamide subordinates, like N, N diethyl nicotinamide is amazing hydro tropes for paclitaxel. These subordinates with certain copolymers used to form micelles which show hydrotropic properties for paclitaxel. Micelles from these subordinates accomplish a surprisingly high medication stacking (37.4%, w/w) for micelle-based drug delivery. The stacking expanded relatively to the length of the hydrotropic portion. PEG-bPLA, micelles may simply fill to 27.6% (w/w) of paclitaxel beneath comparable conditions (Kim et al., 2010).

Improvement in stability

Drug strength increase by polymeric micelles by restraining drug corruption. For analyze in vitro release and stability camptothecin(CPT) fused into hydrophobic core of N- phthaloyl chitosan-grafted PEG methyl ether micelles by dialysis technique (Aminabhavi, 2007).

CONCLUSION

After so many researches and advancements pharmaceutical industry has developed lots of novel ways to deliver drugs at different sites in body. Polymeric micelles are one of the novel approaches which has so many advantages while using as drug delivery method because of their biocompatibility, non-toxicity, nano-size, morphology, shell arrangement, stability. In this review we had discussed about how to get polymeric micelles by using different methods. The effective nature of micelles in oral drug delivery and in oncology with maintenance of their solubility and stability.

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