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REVIEW

Polymers influencing transportability profile of drug

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Abstract Drug release from various polymers is generally governed by type of polymer/s incorporated in formulation and mechanism of drug release from polymer/s. Single polymer may show one or more mechanisms of drug release out of which one mechanism is majorly followed for drug release. Some of the common mechanisms of drug release from polymers were, diffusion, swelling, matrix release, leaching of drug, etc. Mechanism or rate of drug release from polymer or combination of polymers can be predicted by using different computational methods or models. These models were capable of predicting drug release from its dosage form in advance without actual formulating and testing of drug release from dosage form. Quantitative structure–property relationship (QSPR) is an important tool used in prediction of various physicochemical properties of actives as well as inactives. Since last several decades QSPR has been applied in new drug development for reducing the total number of drugs to be synthesized, as it involves selection of the most desirable compound of interest. This technique was also applied in predicting in vivo performance of drug/s for various parameters. QSPR serves as a predictive tool to correlate structural descriptors of molecules with biological as well as physicochemical properties. Several researchers have contributed at different extent in this area to modify various properties of pharmaceuticals. The present review is focused on study of different polymers that influence the transportability profiles of drugs along with application of QSPR either to study different properties of polymers that regulate drug release or in predicting drug transportability from different polymer systems used in formulations.

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Contents

Introduction

Delivery of drug/s to target site at a specific concentration for a specific time can be successfully achieved by the use of suitable polymer/s. Therefore, selection of proper polymer system is a critical step involved in formulation of drug into dosage form. Type of polymer/s incorporated in formulation majorly decides the mechanism and rate of drug release. Single polymer may show one or more mechanisms of drug release, such as diffusion, swelling, matrix release, leaching of drug, etc.; out of which any one mechanism is majorly followed for drug release. Several computational methods or models are available to predict the mechanism and/or rate of drug release from a polymer or a combination of polymers. Such models will assist in prediction of drug release in advance without actual formulation of drug into suitable dosage form. QSPR is an important tool used in the prediction of various physicochemical properties of actives as well as inactives.

Commonly, physicochemical properties of polymers and release mechanism for polymer compositions were considered in designing any formulation. However, several excipients especially polymers have shown pharmacological interaction with physiological components such as membrane situated efflux pumps. Such interactions could lead to altered drug bioavailability. Membrane situated efflux pump inhibitors were generally preferred to increase the substrate drug concentration inside the cell. These inhibitors are classified majorly into two groups: polymeric inhibitors and small molecule inhibitors (SMIHs). SMIHs include first, second and third generation agents. First generation SMIHs, such as quinine and verapamil have been majorly preferred in several disorders because of their pharmacological activity in addition to efflux pump inhibitory property (Beck et al., 1988; Tsuruo et al., 1981). Second and third generation SMIHs have been specifically developed to inhibit efflux pump along with circumvention of pharmacological interactions associated with first generation SMIHs (Woo et al., 2003; Asperen et al., 1997; Bardelmeijer et al., 2000). However, SMIHs mediated risk of accumulation, toxicity and anti-targeting cannot be completely ignored. Hence, to overcome pharmacological interactions associated with actives, several pharmacologically inactive compounds have been successfully investigated for efflux pump inhibitory activity. These inactives include polymeric materials like Tween 80 and pluronic 85 (Friche et al., 1990; Alakhov et al., 1996).

A number of polymers are known to interact with membrane components that alter membrane transportability of several drugs. This is more useful in cancer treatment, where polymers inhibit membrane situated efflux pumps to improve drug delivery inside the cell. Thorough understanding of interaction between polymeric inhibitors and efflux pump is very essential for developing better polymeric inhibitors with higher safety, efficacy and specificity. It has been reported that polymeric inhibitors may interact with or inhibit efflux pumps in several ways such as [a] bypassing of drug efflux system by drug-polymer conjugate (dendrimers); [b] inhibitor form conjugates with ATP that results into ATP depletion [poloxamer unimers (Batrakova et al., 2001b), Myrj, Brij, dendrimers]; [c] inhibitors interfering with ATP-binding sites resulting in site depletion for ATP binding [TPGS 1000 (Collnot et al., 2007), dendrimers]; [d] blockage of trans-membrane situated drug binding sites by polymeric inhibitor (thiomers) (Bernkop-Schnurch and Grabovac, 2006); [e] interactions between membrane and polymeric inhibitor that alters the integrity of membrane lipids [polyethylene glycol (PEG), thiomers, pluronics (Batrakova et al., 2001b), Myrj, Brij, dendrimers]. Jette et al. (1998) have reported that SMIHs usually inhibit the efflux pump by either modifying or completely blocking efflux pump-drug binding sites. In previous studies, several polymeric compounds with structural variations have been established for their efflux pump inhibitory activity.

It has been observed that different membrane transporters are continuously involved in transport of materials across the biological membranes. Juliano and Ling (1976) have identified a membrane glycoprotein responsible for drug resistance in colchicin drug resistant cells and specified it as ''P-glycoprotein''. Nature, localization and mechanisms of such transporters have been previously discussed independently by Thiebaut et al. (1987) and Cordon-Cardo et al. (1990). Additionally, the role of such transporter proteins in drug development and drug delivery have been discussed earlier by several researchers (Girardin, 2006; Majumdar et al., 2004; Varma et al., 2006). P-glycoprotein (PGP) is a transporter protein located in apical membranes of epithelial cells which acts as an efflux pump. It has been reported that these ATP dependent transporter proteins are capable of active transport of several structurally diverse compounds outside cell, such as anticancer agents (Tsuji, 1998), immunosuppressants (Goldberg et al., 1988), steroid hormones (Yang et al., 1989), calcium channel blockers (Yusa and Tsuruo, 1989), beta-adrenoreceptor blockers and cardiac glycosides (Karlsson et al., 1993; Lannoy and Silverman, 1992). Cancer cell shows resistance to multiple drugs (multidrug resistance cell) due to over expression of such transporter proteins acting as efflux pumps. Additionally, these transporter proteins are also present in healthy tissues, such as kidney, placenta, liver, brain, testis and intestine (Thiebaut et al., 1987; Cordon-Cardo et al., 1990). Leveque and Jehl (1995) have reported that these transporter proteins take part in

detoxification process in addition to other mechanisms where they influence pharmacokinetic processes. Choudhuri and Klaassen (2006) have identified breast cancer resistant proteins and multidrug resistant proteins (MRPs) 1 and 2 acting as efflux pumps in the same way as PGP. Therefore, inhibition of efflux pump is much essential step to enhance the transport of anticancer agents (efflux pump substrates) into multidrug resistance cells and improve drug delivery. This is a prerequisite in cancerous cells where presence of abundant number of efflux pumps (PGPs) results in lowered concentrations of anticancer drugs inside multidrug resistance cells and hence, therapeutic efficiency of such drugs get reduced or diminished totally.

Recently, pharmaceutical research is majorly concentrating on formulating a drug into suitable dosage form that will bypass the efflux pump transport system or developing novel therapeutic molecules that will not act as efflux pump substrates (Mazel et al., 2001; Raub, 2006). As well as on development of efflux pump inhibiting agent to overcome multiple drug resistance in cancerous cells (Varma et al., 2003). Several researchers have demonstrated an increase in oral bioavailability of efflux pump substrates when co-administered with efflux pump inhibitors (Woo et al., 2003; Banerjee et al., 2000). Local treatment of gastrointestinal carcinoma is an important example involving combination of efflux pump inhibitors with cancer therapy and oral drug delivery. Apart from blood brain barrier (BBB), efflux transporters are also responsible for limited drug transport to brain (Pardridge, 1998). It has been observed that co-administration of BBB located efflux pump inhibitors with pump substrates results in enhanced transport of later through BBB (Batrakova et al., 2001a).

Polymers are mainly classified into two main classes, namely natural and synthetic polymers based on their origin. Both natural and synthetic polymers have influenced the transportability profiles of drug/s across biological membranes through interaction with various membrane components. Such polymer-membrane component interactions and their influence on physiological performance of drug are discussed briefly with examples in following section.

Natural polymers

Several researchers have reported the use of natural polymers as efflux pump inhibitors. Jodoin et al. (2002) and Honda et al. (2004) have observed polyphenols of green tea and compounds of grapefruit juice as natural polymeric efflux pump inhibitors. Polysaccharides are the naturally occurring polymers with ability to inhibit efflux pump. However, some polysaccharides such as starch, cellulose, hyaluronic acid and chitosan are not able to inhibit efflux pump. Carreno-Gomez and Duncan (2002) have patented the use of polysaccharides, dendrimers and surfactants as efflux pump inhibitors for the oral delivery of antitumor, antineoplastic, antibiotic, antiviral, antifungal and antidepressant drugs. It has been revealed with experimental data that anionic gums (polysaccharides), dextran and sodium alginates possess ability to inhibit efflux pump. Natural gum polysaccharides include xanthan gum, gellan gum, guar gum, agar, traganth etc. Carreno-Gomez and Duncan (2002) have reported PGP efflux pump inhibitory activity of xanthan gum that resulted in an enhanced accumulation of PGP substrates vinblastin and doxorubicin inside gut cells. However, enhanced serosal transport has been observed with vinblastin but not with doxorubicin (Carreno-Gomez and Duncan, 2002). Gellan gum has shown efflux pump inhibitory activity with increased serosal transport of vinblastin but with unchanged tissue level. However, gellan gum has increased both accumulation and serosal transport of doxorubicin. Dextran has also shown concentration dependant effects on efflux pump (Carreno-Gomez and Duncan, 2002). Carreno-Gomez and Duncan (2002) have also investigated efflux pump inhibitory activity of alginates such as flavicam and ascophyllum. It has been observed that flavicam enhanced the cell accumulation and serosal transport of doxorubicin in everted gut sac cells. However, cell accumulation of vinblastin remains unaffected (Carreno-Gomez and Duncan, 2002). Ascophyllum has shown increase in cell accumulation of both vinblastin and doxorubicin in everted gut sac cells. However, increase in serosal transport of only vinblastin and not of doxorubicin has been observed. Additionally, use of ascophyllum (250 mg/kg) resulted in 1.7 folds increase in blood level (biodistribution) of radioactive labeled vinblastin with respect to control after oral gavage in rats (Carreno-Gomez and Duncan, 2002).

Hori et al. (1978) have studied the effect of free fatty acids as membrane components on the permeability of various drugs across lipid bilayers derived from egg phosphatidylcholine membranes and intestinal lipid membranes. In this study, free fatty acids such as lauric, stearic, oleic, linoleic and linolenic acid have been incorporated into the bilayer lipid membranes derived from egg phosphatidylcholine. This study concludes with enhancement in permeability coefficients of several anionic-charged acidic drugs such as *p*-aminobenzoic acid, salicylic acid and *p*-aminosalicylic acid across phosphatidylcholine membranes. Although the permeability of *p*-aminobenzoic acid through intestinal lipid membranes was higher than that of phosphatidylcholine membranes, a decrease in the permeability coefficient of *p*-aminobenzoic acid on addition of fatty acids to intestinal lipid membranes has been observed (Hori et al., 1978).

Synthetic polymers

Use of synthetic polymers as efflux pump inhibitors has been revealed previously. Several copolymers of PEG such as polyethylene oxide glycol, polyoxyethylene glycol have been investigated for efflux pump inhibitory activity. Johnson et al. (2002) have reported the efflux pump inhibitory activity of PEG 400 (1–20%) with decrease in the basolateral to apical transport of digoxin through stripped rat jejunal mucosa. Shen et al. (2006) have investigated the efflux pump inhibitory activity of various concentrations (0.1–20% v/v or w/v) of PEG 400, 2000 and 20,000 and reported that the secretory transport of rhodamine 123 (RHOD 123) get suppressed independent of PEG molecular weights in isolated rat intestine. Additionally, improved absorption of RHOD 123 has been reported from solution formulations prepared using different concentrations of PEG 20,000. Hugger et al. (2002) have reported an increase in permeation of efflux pump substrates doxorubicin and paclitaxel through Caco-2 cell monolayers in presence of PEG 300. This was attributed to changes in the microenvironment of Caco-2 cell membranes by modifying fluidity of the polar head group regions by PEG 300. It has been observed that apical to basolateral transport of paclitaxel increases with an increase in PEG 300 content and vice versa (Hugger et al.,

2002). Choi and Jo (2004) have observed an increase in PEGylated paclitaxel uptake than unmodified paclitaxel following oral administration and concluded with improvement in absorption of PEGylated water soluble prodrug due to partial bypass of PGP efflux and CYP3A metabolism. Additionally, efflux pumps inhibitory activity of several polymeric surfactants such as PEG based detergents have been revealed previously by various researchers. Amongst them Tween 80 and D-Alpha-Tocopheryl Poly(ethylene glycol) Succinate 1000 (TPEGS 1000) were the most potential candidates. Varma and Panchagnula (2005) have observed an improvement in the oral bioavailability of PGP substrate paclitaxel (BCS class IV) with use of TPEGS 1000 as the solubilizing agent. This effect was attributed to improved paclitaxel solubility and PGP inhibition by TPEGS 1000. Effect of TPEGS alkyl-chain length on its efflux pump inhibitory activity have been investigated by Collnot et al. (2006) and concluded TPEGS 1000 as the most potent efflux pump inhibitor amongst all the tested ten different TPEGS derivatives. Amongst all polysorbates, Tween 20, 40 and 80 have been reported as the most potent efflux pump inhibitors. Friche et al. (1990) have investigated efflux pump inhibitory activity of Tween 80 and observed an enhancement in accumulation of daunorubicin in resistant Ehrlich ascites tumor cells. Shono et al. (2004) have reported a decrease in efflux ratio of RHOD 123 in the presence of Tween 80 when studied with excised rat intestinal mucosa. Additionally, Zhang et al. (2003) have reported an improvement in absorption of PGP substrate, digoxin in rats with use of Tween 80.

Polyoxyethylene stearates (Myrj) and alkyl-Polyethylene oxide surfactants (Brij) have also shown efflux pump inhibitory activity. Lo (2003) have investigated the relationship between the multidrug resistance modulating effect of pharmaceutical excipients and their hydrophilic–lipophilic balance (HLB) values in Caco-2 cells and rat intestine. In this study, efflux pump inhibitory activity of polyoxyethylene 40 stearate has been proved by enhancement in intercellular accumulation of epirubicin in Caco-2 cells (Lo, 2003). Additionally, Foger et al. (2006) have demonstrated 2.4 folds increase in oral bioavailability of PGP substrate RHOD 123 in rats from tablets containing polyoxyethylene 40 stearate.

Poloxamers (pluronics) are amphiphilic copolymers consisting of ethylene oxide (EO) and propylene oxide (PO) segments arranged in alternative manner. Chain length of EO and PO is found to affect the size and lipophilicity of pluronics. Pluronics mediated efflux pump inhibition was found to be more promising in BBB drug delivery and cancer therapy. Batrakova et al. (2001b) have reported that efflux pump inhibitory activity of pluronics was mediated by ATPase inhibition followed by ATP depletion and its effect on membrane fluidization. Miller et al. (1997) have revealed the concentration dependent efflux pump inhibitory effect of pluronic 85 in brain microvessel endothelial cell monolayers using RHOD 123 as model drug. Furthermore, it has been demonstrated that the efflux pump inhibitory effect of pluronics get reduced when its concentration reaches toward critical micelle concentration (CMC). Banerjee et al. (2000) and Jagannath et al. (1999), in separate studies have demonstrated the PGP efflux pump inhibitory activity of CRL-1605 copolymer to improve tobramycin and amikacin oral uptake. Kabanov et al. (2003) have discussed the different mechanisms behind efflux pump inhibitory activity of pluronics and its role in delivery of efflux pump substrates across BBB. Batrakova et al. (1999a) have performed in vitro permeation studies using polarized bovine brain microvessel endothelial cells and demonstrated that pluronic P85 increases permeability of several efflux pump substrates such as doxorubicin, paclitaxel and etoposide across BBB. Additionally, Batrakova et al. (2001a) have reported that pluronic P85 was responsible for prolongation of residence time and improved concentration of digoxin in the brain of wild type mice. In cancer therapy, polymers have been used commonly to overcome multidrug resistance either by inhibition of efflux transporter proteins or by evading efflux pump transport system. Kabanov et al. (2002) have thoroughly reviewed the importance of pluronics in cancer therapy. Alakhov et al. (1999) have observed that several types of cancers can be efficiently treated in vivo by using doxorubicin and pluronic formulation. In separate studies, Venne et al. (1996) and Batrakova et al. (1999b) have revealed PGP inhibition as the mechanism behind inhibitory activity of pluronics, where an increase in doxorubicin content has been observed in PGP expressing cells but not in non-PGP expressing cell lines. Additionally, several researchers have demonstrated no increase in non-PGP substrates accumulation inside resistant cells with use of pluronics (Batrakova et al., 1998, 2001a; Miller et al., 1997). Furthermore, it has been reported that pluronics can also inhibit MRP 1 and 2 types of efflux pumps.

Targeted design of efflux pump inhibitors is quite difficult due to the presence of numerous binding sites on efflux pump, such as PGP contains four different drug binding sites (Dey et al., 1977; Pascaud et al., 1998; Shapiro et al., 1999; Lugo and Sharom, 2005). Additionally, development of polymeric inhibitors of interest for specific efflux pump is yet again more complex due to the involvement of other factors such as unspecific interactions with the cell membrane in efflux pump inhibition. Various mechanisms involved in interaction between polymeric inhibitors and efflux pumps have been summarized in Table 1.

Pavlov et al. (2009) have studied the interaction of copolymers of EO and dimethylsiloxane with model biological membranes and cancerous cells, where an enhancement in permeability of model membranes in the presence of copolymers has been observed. It has been observed that Pluronic L61 at its low nontoxic concentrations showed a decrease in the concentration of doxorubicin by a factor of 30, which is toxic to cancerous cells.

The most important function of cell membrane is to control the material transport into and out of the cell. Interruption in this function due to loss of membrane integrity leads to generation of transient pores in the membrane structure causing cell necrosis. Therefore sealing of porated membrane is an important phenomenon, which can be accomplished in a natural way or with use of several surfactants.

Maskarinec et al. (2005) have studied the membrane sealing property of several polymers such as poloxamers, poloxamine, etc. Industrial use of poloxamer copolymers as emulsifying, wetting, thickening, coating, solubilizing, stabilizing, dispersing, lubricating, and foaming agent has been already proved (Chu and Zhou, 1996). Additionally, poloxamers can also be used to restore the membrane integrity attributed to its ability of interacting with the lipid bilayers and sealing the structurally damaged membranes.

Several researchers have indicated the use of poloxamer 188 as membrane sealing agent due to its medical safety record

Table 1 Mechanisms behind interaction between polymeric inhibitors and efflux pump.

Sr. No.	Mechanism of interaction	Polymeric inhibitor
1.	Bypass of drug efflux system by drug-polymer conjugate	Dendrimers*
2.	Inhibitors form conjugates with ATP that result in ATP depletion	Poloxamer unimers[42], Myrj, Brij, Dendrimers*
3.	Inhibitors interfering with ATP-binding sites resulting into site depletion for ATP binding	TPGS 1000[69], Dendrimers*
4.	Blockage of trans-membrane situated drug binding sites by polymeric inhibitor	Thiomers[68]
5.	Interactions between membrane and polymeric inhibitor that alters the integrity of membrane lipids	PEG, Thiomers, Pluronics[42], Myrj, Brij, Dendrimers*

* Possibly by mentioned mechanism as exact mechanism is not clear.

(Lee et al., 1992; Padanilam et al., 1994; Merchant et al., 1998; Frim et al., 2004; Marks et al., 1998, 2001; Hannig and Lee, 2000a). Additionally, poloxamine 1107 has also shown membrane sealing capability (Palmer et al., 1998; Hannig et al., 2000b; Greenebaum et al., 2004; Terry et al., 1999). These polymers selectively get inserted in the damaged portions of the membrane where low lipid packing density with respect to intact cell membrane density has been observed. However, as soon as the membrane lipid packing density is improved or membrane integrity is restored, the inserted polymer is ''squeezed out'' of the lipid film signifying the cell free of the inserted polymer. Maskarinec and Lee (2003) and Weingarten et al. (1991) in separate studies have reported the high surface pressure as a possible mechanism for poloxamer 188 squeezing out of lipid monolayers. It has been concluded that poloxamer aids to improve the local lipid packing density in the damaged bilayers of the membrane and can be used as a membrane sealant for therapeutic purposes.

D'Emanuele et al. (2004) have demonstrated an improvement in apical to basolateral transport of propranolol (PGP substrate) with use of generation 3 polyamidoamine dendrimers through Caco-2 monolayers attributed to bypass PGP transport system instead of inhibition. This was supported by no more improvement in propranolol transport in the presence of recognized PGP inhibitor such as cyclosporine A. Furthermore, it has been observed that conjugation of dendrimer with efflux pump substrates is not essential but presence of former may lead to enhancement in substrate transport. This was supported by increased vinblastine and doxorubicin accumulation in presence of generation 3 dendrimer with use of gut sacs (Carreno-Gomez and Duncan, 2002).

Werle and Hoffer (2006) have demonstrated the ability of thiomers (thiolated polymers) to inhibit efflux pump. Several other researchers have revealed the dependence of inhibitory activity of thiomers on presence of thiol groups (Bromberg, 2001; Bromberg and Alakhov, 2003; Luessen et al., 1994, 1997). Foger et al. (2007) have revealed an improved uptake of the saquinavir (efflux pump substrate) in presence of thiomer-glutathione system. These studies indicate that thiomer is a potential candidate to improve transport of substrates of different efflux pumps such as MRP and PGP. Iqbal et al. (2010) have improved the PGP inhibitory properties of PEG by covalent attachment of thiol moieties. PEG was grafted with polyethylenimine and subsequently thiolated with γ-thiobutyrolatone. This novel thiolated PEG-g-polyethylenimine co polymer has been further evaluated for the transport of RHOD 123 as PGP substrate across freshly excised rat intestinal mucosa. Thiolated co polymer (at 0.5% w/v) has shown profound effect on absorptive transport of RHOD 123 compared to other tested compounds, where it has increased RHOD 123 transport up to 3.3-folds than control (RHOD 123 without inhibitor). In addition to PGP inhibition, Foger et al. (2007) have observed that thiolated polymers can also inhibit intestinal efflux pumps (MRP) that have resulted in modulation of drug absorption. It has been observed that thiomers are promising candidates for inhibition of efflux transporters such as PGP and MRP that affect the delivery of various drugs to target site. Greindl et al. (2009) have evaluated the thiolated poly(acrylic acid) as MRP2 inhibitor to modulate MRP2 efflux pump substrate absorption using freshly excised rat intestinal mucosa mounted in Ussing-type chambers. An increase up to 3.8-fold in area under curve in the plasma concentration time plot of sulforhodamine 101 (MRP2 substrate) in presence of poly(acrylic acid)-cysteine solution compared to buffer control has been reported.

Chen and Schluesener (2010) have studied the effect of multi-walled carbon nanotubes on transportability of several compounds, such as fluorescein diacetate, carboxyfluorescein diacetate, RHOD 123 and doxorubicin across rat astrocytes cell membrane. These compounds are either prosubstrates or substrates of multidrug transporter proteins. It has been observed that cellular uptake of doxorubicin get inhibited significantly in presence of multi-walled carbon nanotubes attributed to mode of loading of doxorubicin. However, cellular uptake of other drugs remains unaffected. After an efflux period, a notable high retention of fluorescein diacetate, carboxyfluorescein diacetate and RHOD 123 within cells exposed to multi-walled carbon nanotubes have been reported. Quinton and Philpott, (1973) have studied the effect of several cationic polymers such as poly-L-lysine, protamine and histone on rabbit gall bladder epithelial cells to explore possible functions carried out by anionic sites in the membrane. All tested cationic polymers have shown similar changes in membrane structure as examined by bathing the tissue in number of Ringer's solutions containing cationic polymers at different concentrations. These changes include loss of rigidity by microvilli, an apparent increase in membranes permeability, etc. It has been observed that fixed anionic sites in the membrane played major roles in stabilizing epithelial membrane structure as well as maintaining both the anatomical form and physiological integrity of the cell (Quinton and Philpott, 1973).

ATP-binding cassette (ABC) transport proteins reported to mediate the transport of several structurally diverse compounds through cell membranes. These compounds include amino acids, ions, peptides and variety of drugs (Higgins, 1992). ABCB1 transporters (ABC transporter

subfamily) such as PGP are responsible for efflux of chemically modified and conjugated compounds by cytochrome P450 enzymes (Szakacs et al., 2006). Hanke et al. (2010) have studied the interactions of commonly used nonionic surfactants with the human efflux transporters ABCB1 (PGP) and ABCC2 (MRP2). These efflux transporters are majorly responsible for limited oral bioavailability of several drugs (Szakacs et al., 2006; Fricker and Miller, 2002). In this study, the interactions of structurally diverse nonionic surfactants such as, cremophor EL, cremophor RH 40, polysorbate 80, pluronic PE 10300, vitamin E TPGS 1000 and sucrose ester L-1695 with above mentioned efflux transporters have been studied. In addition to solubilizing property, several researchers have reported the use of nonionic surfactants as inhibitors of human efflux transporter ABCB1 that influences the disposition of many drugs (Batrakova et al., 2003; Tayrouz et al., 2003; Tellingen et al., 1999; Mountfield et al., 2000; Rege et al., 2002). Additionally, because of earlier identification of ABCB1 than ABCC2, the interactions between nonionic surfactants and the efflux transporter ABCB1 have been studied broadly compared to ABCC2, where limited study on interactions with surfactants have been performed (Juliano and Ling, 1976; Collnot et al., 2006; Batrakova et al., 2003; Dudeja et al., 1995; Woodcock et al., 1990; Paulusma et al., 1996). Interactions of pharmaceutical surfactants such as cremophor EL or polysorbate 80 with ABCB1 have been studied completely, but not with ABCC2. An inhibitory activity of cremophor EL, vitamin E TPGS 1000 and polysorbate 80 (at higher concentration) on both efflux transporters have been reported. It has been observed that Pluronic PE 10300 and sucrose ester L-1695 inhibit ABCB1 but not ABCC2. However, Cremophor RH 40 is able to inhibit ABCC2 but not ABCB1 (Hanke et al., 2010).

Conclusion

In addition to physicochemical aspects of polymers, their interaction with biological membranes and its components must also be strictly considered while selecting polymer for desired formulation. Polymers have shown both beneficial and harmful effects on drugs bioavailability, especially in case of drugs used in cancer treatment. Therefore, biological interaction of polymer/s influencing transportability profile of actives must be greatly considered to achieve maximum drug bioavailability.

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