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Review Paper

Applications of Donnan Membrane Equilibrium Phenomenon in Pharmaceutical Formulations

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ABSTRACT

Donnan equilibrium generation significantly affects the transfer of active moities across the membrane both synthetic as well as natural. With the help of certain effective congeners we can enhance the penetration of drugs which follow this phenomenon. Also we can synthesize certain membranes having specific fixed charge groups which can exhibit an effect on distribution of co-ions and counter-ions across the membrane. Also there are certain methods which can prove to be useful in synthesizing such membranes. The generated Donnan equilibrium potential also need to be measured if it's intended to use as a parameter in formulation. For measuring this potential an equipment named tender-APXPS can be used by research scientists. For such thing a detailed literature review as well as keen understanding of compounds being used is required. Applying Donnan equilibrium phenomenon, requires a back-up of physical and analytical chemistry with formulation knowledge. Also the compatibility of the congener with the drug need to be considered. This article reviews about different methods which can be applied to use this Potential generated at the interface.

INTRODUCTION

There are certain drugs which face difficulties in their penetration process. Despite having good solubilities, the drugs are inefficient in crossing the barrier and enter the site of action. Such issues are common in formulations of class II and class IV drugs of BCS classification. To overcome such issues Scientists try different techniques to enhance the transfer of drugs across the interface. Some of them include the use of polymers into the formulation and also altering the mechanism of release of drugs from the dosage form. This helps to a considerable extent and increases the transfer of drugs across the membrane. Selection of polymers also play a vital role in enhancing the permeation of drugs. Also the charges of the polymer and drug molecule should match to have

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the desired effect of enhanced penetration. This can be achieved by using some interfacial effects which are generated at the moment of transfer of drug molecules to the site of action.(2)The use of ionizable polymers help increase the absorption of certain drugs. This occurs due to generation of Donnan Potential at the membrane/surface interface. For example, if a membrane is taken and sodium chloride solution is kept on one side and negatively charged colloids with it's counter-ions is kept on another side the smaller ions i.e. sodium and chloride ions can easily cross the membrane but the colloidal anionic particles can't. This leads to formation of unequal distribution of charges across the membrane further leading in generation of potential at interface particularly termed as Donnan Potential. Also, the polymers and the groups present on the membrane play an important role in diffusion of desired ions i.e. drug molecules. Ion Exchange Membranes (IEM) are vital in electrodialysis (ED), reverse electrodialysis (RED), reverse osmosis (RO), pressure retarded osmosis (PRO), etc. They are often synthesized from cross-linked hydrocarbons based polymers which have ionizable functional groups on their backbone. Generally, these functional groups are covalently bonded. This covalent crosslinking prevents the dissolution of IEM and also controls the polymer swelling in the aqueous electrolyte solution. If the polymer is negatively charged, it exhibits selective permeability for the cations and hence they can be called as cation exchange membranes (CEMs). Similarly, polymers having selective permeability for anions can be termed as anion exchange membranes (AEMs). The charge on the polymer can be determined by determining ion exchange capacity (IEC). IEC is the milliequivalents of fixed charge on the polymer chains per gram of dry polymer. The more accurate way to express the charge density of the polymer is by determining the concentration of fixed charged groups on the membrane. It's given as, mols of fixed charge group per unit volume of water sorbed by the IEM, $C_A^{m,w}$. Most influence on transport and sorption in IEMs is due to these charge groups.(3)According to the solution-diffusion model, in dense IEMs, ion transport is influenced by ion sorption. Fixed charge groups cannot leave the membrane when equilibration of an IEM with an electrolyte solution is done as they are covalently bound to the membrane. In this situation, a Donnan equilibrium develops between the membrane and continuous external solution. Counter-ion (ions of opposite charge as to that of fixed charge groups on the membrane) concentration in the membrane can be 2-3 folds higher than continuous external solution at low external solution concentration. To achieve electroneutrality, adequate molar amount of counter-ions sorb into the IEM to balance the fixed charge groups on the IEM. On the other hand, co-ion concentration in the IEM seems to be lower than in low external solution concentration. Such situation leads to unequal distribution of ions at the membrane solution interface and gives rise to a potential, probably called the Donnan Potential. This potential inhibit co-ion sorption in the IEM and counter-ion desorption from the IEM. This phenomenon is termed as Donnan Exclusion. Due to generation of Donnan Potential the co-ion sorption decreases. Actually, decreased co-ion sorption is desired in practical applications as it help increase membrane selectivity for transport to occur by electric field gradient. The extent of co-ion exclusion is dependent on strength of Donnan Potential. Thermodynamic approach can be used for deriving Donnan Potential E_{Don} equation. Strong Donnan potentials arise when there is large difference in counter-ion activities of membrane and solution respectively. From equation by observing counter-ion activities it can be said that fixed charge groups on the membrane influence the generated Donnan potential at fixed external salt concentration. In most experimental cases,

majorly the counter-ions in the membrane have activity to balance the fixed charge groups of membrane. Increment in fixed charge group concentration of membrane also raises the concentration of gegen ions (i.e. counter-ions) in the membrane, this results in higher value of Donnan potential even though all other factors remaining constant (i.e. outside solution concentration). By observing the equation, it can be said that co-ion exclusion is dependent on Donnan potential. Scientists have noticed, low co-ion concentration at high values of Donnan potential. (3)Ideally, when the fixed charged group concentration in the membrane increases it should deplete the co-ion concentration in the membrane. This happens due to stronger Donnan Exclusion. These fixed charge group concentrations can be altered. It can be increased by adding more ionogenic groups into the membrane matrix. This also increases the IEC (ion exchange capacity). This additionally increases the amount of water entering into the membrane. This leads to enhanced hydrophilicity due to inclusion of extra charged groups in the membrane. This usually happens with IEMs prepared from linear polymers. However, at times it can also be seen that increasing the IEC can also increase water entry and ultimately decrease the fixed charge group concentration. The unit for fixed charge group concentration is mol of ion per L of sorbed water. This ultimately depletes the Donnan exclusion of co-ions. So, it is very difficult for researchers to find accuracy in fixed charge group concentration and to predict the ion sorption phenomenon. Further studies are required for optimizing the concentration of ionogenic groups present on the membrane. Systematic studies are required to elaborate the relation between fixed charge group concentration and ion sorption in charged membranes. By formulating newer strategies in this section, Donnan exclusion can be more profoundly explored and how suppression of co-ion sorption takes place can be known.

Although, there is no such literature available as synthesizing IEMs is really a difficult task. Also, to predict the water content and fixed charge group concentration is a bit tedious task. Previously, IEMs were prepared by using two or three step procedures and that becomes difficult to independently format membrane properties such as water content and fixed charge group concentration. Nowadays, with the development of technology, IEMs can be synthesized easily by using one step.

METHODOLOGIES :-

There are few such methodologies that can be used to calculate the Donnan Potential and allied Donnan exclusion and ion sorption phenomena. But there is no single method which can altogether predict each and every thing related to Donnan potential. There needs to be more detailed research to be done to explore this arena. Scientists are trying their level best to aggregate most of the things. With upcoming technology this will become more easy and accuracy can be increased by implementing newer strategies into this research. One such method is by evaluating the enhancement in permeation of drug with it's negatively charged anionic congener by the help of generated Donnan potential. In ancient literature, Higuchi et al. hypothesized the use of polyelectrolyte sodium carboxy methyl cellulose for increasing the absorption of drugs such as Sodium Salicylate and Potassium Benzyl Penicillin. Also, Farang et al. elucidated enhanced permeation of salicylates in the presence of different carboxy methyl celluloses. Rege et al. reviewed the effect of commonly used non functional ingredients on permeability of some less permeable drugs. In this study, researchers want to study the increased absorption of drug molecules in the presence of ionizable polymers.

And this can be efficiently explained by Donnan membrane phenomenon. In this study, Polacrilin potassium was used as ion exchange resin as a tablet disintegrant. This resin had a weakly acidic cationic resin. Chemistry wise it is a partial potassium salt of a copolymer of methacrylic acid with divenyl benzene. It can be expected that the flux of an anionic drug permeation can be enhanced by the presence of an anionic non-diffusible polymer such as Polacrilin potassium. The main purpose of this work was to describe the effect of this polymer added as disintegrant in tablets on the permeation of Diclofenac potassium which is anionic in nature. In this research work, the permeation study was done *in vitro* and fraction of drug absorbed i.e. bioavailability studies was done *in vivo*. In this study, scientists have evaluated this phenomenon through in-vitro permeation by the help of Franz Diffusion Cell apparatus. In this assembly, Dialysis membrane was used as a separating medium. Diclofenac potassium was selected as the active drug on which permeation studies were to be performed. A 1:1 ratio of Diclofenac potassium and Doshion P544DS (i.e. Polacrilin Potassium) was taken and placed in donor compartment of Diffusion cell apparatus. The receiver compartment of Diffusion cell was filled with pH 6.8 Phosphate buffer. For investigation of this phenomenon occurrence, the standard assembly was also built up. In this assembly plain Diclofenac solution was evaluated using the same experimental set-up. In the end results of both the assemblies were compared. The receiver compartment was having capacity of 22 mL. After every 30 minutes the sample was withdrawn from the port of the Diffusion cell. After withdrawl of sample equal volume of buffer solution was replaced through the sampling port to maintain the sink condition. The extracted samples were further analyzed through UV-Visible spectroscopy. The wavelength was taken as 273 nm. Scientists chose this Dialysis membrane depending on it's molecular weight cut-off. Diclofenac potassium has molecular weight of 334.25 g/mol. To stop the polymer (i.e. Polacrilin potassium) and to allow only Diclofenac potassium to pass through, Dialysis membrane of smallest molecular weight cut-off was preferred. Also, Scientists calculated the Permeability Coefficient of Diclofenac potassium. It is simply the ability of the drug to cross through the membrane.(2) The next method involves the study of IEMs (i.e. Ion Exchange Membranes) and evaluate the effect of the fixed chemical groups present on the membranes. For this purpose, scientists have used a series of cross-linked CEMs (i.e. Cation Exchange Membranes) and AEMs (i.e. Anion Exchange Membranes) which were synthesized in the research laboratories. The membranes contain different fixed group charge concentration and water content in them varied independently. The variation in the fixed charge groups was made by controlling the amount of charged monomer species in the polymer mixture. Also, concentration at equilibrium of co-ions and counter-ions in the membranes priorly equilibrated with hydrophilic NaCl solutions were calculated as a function of external NaCl solution concentration by using a desorption method. The data gathered in this study, was interpreted using a thermodynamic model which was designed based on Manning's Counter-ion theory. The negatively charged monomer used in this experiment the negatively charged monomer used was 2-acrylamido-2-methylpropane sulfonic acid (AMPS), positively charged monomer was [2-(methacryloxyloxy)ethyl] trimethylammonium chloride (MAOTMAC) and the crosslinker was glycerol dimethacrylate (GDMA). The solvents used were ultrapure deionized (DI) water and 1-propanol. The initiator used was 2,2'-azobis(2-methylpropionamide)dihydrochloride. Though in this study, scientists designed the membranes still they more or less corresponded to the commercial

IEMs. In earlier days, IEMs were synthesized using a long step procedure which was very difficult, but now with the development of technology, usage of one step procedure eliminates this difficulty. But there is a kind of risk associated with this technique that the monomers and the crosslinkers should be compatible with each other. And if they are not they can undergo PIPS (Polymer Induced Phase Separation). The membranes to be synthesized were named according to their individual IECs (i.e. Ion Exchange Capacity). Cation exchange were named as CAXXX and Anion Exchange were named as AAXXX. Then following specific procedures, scientists synthesized the membranes, calculated the membrane water content, ion sorption, co-ion and counter-ion concentrations. (3)Another approach deals with direct measurement of Donnan Potential generated at the membrane/solution interphase. This has a profound influence on transport and selectivity of solutes across semi-permeable membranes. Although Donnan potential is having long history, still direct measurement of Donnan potential and experimental verification of Donnan's framework has been tedious due to lack of appropriate interfacial experimental techniques. This didn't provided the development of novel membranes having more selective nature for certain specific ions. So, scientists of this study decided to develop an experimental methodology for direct measurement of Donnan potential in a commercial ion exchange membrane equilibrated with mono and divalent external salt solutions (i.e. NaCl and $MgCl_2$). The measurements of this experiment were based on Binding Energy shift in membrane related core levels detected by tender Ambient Pressure X-ray Photoelectron Spectroscopy (tender-APXPS). (4)

DISCUSSION AND CONCLUSION :

In the first approach, Scientists found an increase in permeation rate of the drug by using it's negatively charged congener. The ratio 1:1 which was used by the scientists showed an enhancement of Diclofenac potassium across the dialysis membrane. This was confirmed by using Franz Diffusion cell apparatus. To check the enhancement in permeation rate, it was compared with the standard formulation which was containing the respective negatively charged polymer. (2)In the next mentioned approach Scientists investigated how fixed charge group concentration influences ion sorption behavior in cation exchange membranes (CEMs) and anion exchange membranes (AEMs) while keeping membrane water content nearly constant. The results showed that membrane water content slightly decreased with increasing external NaCl concentration because of osmotic deswelling, but remained similar among all synthesized membranes. The results showed that,Counter-ion concentration increased with increasing membrane fixed charge group concentration because more counter-ions were required to maintain electroneutrality within the membrane. Co-ion sorption decreased as fixed charge group concentration increased, confirming that stronger fixed charge density enhances Donnan exclusion and suppresses undesired ion entry into the membrane. The reduction in co-ion sorption was more pronounced in CEMs than AEMs, even though both membrane types had similar increases in fixed charge concentration. A thermodynamic model based on Donnan equilibrium and Manning's counter-ion condensation theory was applied to interpret the experimental data. The model accurately predicted ion sorption in AEMs without adjustable parameters, indicating relatively homogeneous membrane structures.

However, the model poorly predicted CEM behavior unless the Manning parameter (x) was treated as an adjustable value. This suggested that

CEMs had structural inhomogeneity or phase separation, leading to uneven distribution of fixed charge groups. The discussion emphasized that not only the amount of fixed charge groups, but also their spatial distribution inside the membrane, strongly affects ion exclusion and membrane selectivity. High charge density can increase counter-ion condensation, which weakens the effective Donnan potential and reduces co-ion exclusion efficiency. Overall, the study concluded that optimizing both fixed charge concentration and charge distribution architecture is essential for designing high-performance ion exchange membranes for applications such as desalination, electrodialysis, and controlled ion transport systems.(3)In the next study Scientists successfully demonstrated the first direct measurement of the Donnan potential at the membrane/solution interface using tender ambient pressure X-ray photoelectron spectroscopy (tender-APXPS). The researchers used a commercial cation exchange membrane (CR-61) equilibrated with NaCl and $MgCl_2$ solutions of varying concentrations. The results showed that,binding energy shifts in membrane-related S 1s and O 1s peaks directly corresponded to changes in the Donnan potential. Lower external salt concentrations produced higher Donnan potentials due to stronger ion partitioning between membrane and solution phases. The Donnan potential decreased as the external salt concentration increased, approaching zero when the external ion concentration became similar to the membrane fixed charge concentration. The study also evaluated the effect of counter-ion valence. Membranes equilibrated with $MgCl_2$ showed lower Donnan potentials than those equilibrated with NaCl at the same concentration because divalent Mg^{2+} ions reduce co-ion exclusion more effectively than monovalent Na^+ ions. Experimental data closely matched predictions from the Manning/Donnan thermodynamic model, confirming the validity of existing ion-partitioning theories. However, small deviations were observed at low $MgCl_2$ concentrations, likely due to limitations in the theoretical assumptions regarding electrostatic interactions in polymers. The scientists concluded that their method provides a powerful new approach for directly studying ion transport and membrane selectivity, which could improve the design of membranes for applications such as drug delivery, water purification, energy storage, and biological systems.(4)

FUTURE PROSPECTIVES :

In future, the technique of using Donnan potential in Drug Delivery Systems can take a huge bloom, if Scientists collaborate with Physicists and Chemists. By integration of all such researchers, solution on poor permeability of certain drugs can be found out. Also the dose can be managed according to the disease and site of action. Following are some prospectives which can be incorporated.

1. Advanced Transdermal Drug Delivery Systems

Donnan membrane equilibrium can be further explored to improve permeation of poorly permeable drugs through the skin by controlling ion distribution and electrochemical gradients in topical and transdermal formulations.

2. Smart Controlled Drug Release Systems

Future pharmaceutical formulations may use Donnan equilibrium to design responsive hydrogels and polymeric matrices capable of releasing drugs in a controlled and site-specific manner depending on pH or ionic strength.

3. Improved Ophthalmic and Nasal Drug Delivery

Application of Donnan principles may enhance drug retention and permeation across ocular and nasal membranes, leading to improved bioavailability and prolonged therapeutic action.

4. Targeted Delivery Using Ionic Polymers
Novel ionic polymers and polyelectrolyte complexes based on Donnan equilibrium may be developed for targeted delivery of anti-inflammatory, anticancer, and peptide drugs.
5. Enhanced Bioavailability of Poorly Soluble Drugs
Donnan equilibrium can help optimize ion exchange systems and charged excipients to improve solubility, dissolution, and absorption of poorly water-soluble drugs.
6. Development of Stimuli-Responsive Hydrogels
Future research may focus on Donnan-driven swelling behavior in hydrogels for applications in wound healing, tissue engineering, and sustained drug delivery.
7. Nanocarrier and Liposomal Drug Delivery
Incorporation of Donnan equilibrium concepts into nanoparticles, liposomes, and nanoemulsions may improve drug loading efficiency, stability, and controlled release characteristics.
8. Personalized Pharmaceutical Formulations
Donnan equilibrium-based systems may enable personalized medicine by tailoring ionic composition and membrane interactions according to patient-specific physiological conditions.
9. Applications in Protein and Peptide Delivery
Since biological macromolecules are often charged, Donnan equilibrium could play an important role in improving stability and permeation of proteins, peptides, and vaccines.
10. Integration with Biomedical Devices
Future biomedical implants and drug-eluting devices may utilize Donnan membrane equilibrium for sustained and programmable drug release directly at the target site.
11. Mucoadhesive Drug Delivery Enhancement
Charged polymers utilizing Donnan equilibrium may improve adhesion and permeation across mucosal membranes, enhancing oral, buccal, and vaginal drug delivery systems.
12. Combination with Modern Permeation Enhancement Techniques
Donnan equilibrium may be combined with microneedles, iontophoresis, sonophoresis, and nanotechnology to achieve synergistic enhancement in drug permeation and therapeutic efficacy.
13. Biopharmaceutical and Gene Delivery Applications
Future studies may investigate Donnan-based ionic interactions in gene delivery systems, RNA therapeutics, and biologics for improved transport across biological barriers.
14. Development of Safer and More Efficient Excipients
Research into novel ionic excipients and charged biopolymers may create safer pharmaceutical formulations with improved stability and reduced toxicity.
15. Applications in Artificial Membranes and Organ Models
Donnan equilibrium concepts may support development of artificial skin, dialysis membranes, and organ-on-chip systems for pharmaceutical testing and drug screening.

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