Conventional drug delivery system biology essay

Science, Biology

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\n[/toc]\n \nCurrently, conventional drug delivery systems are used by major pharmaceutical products in the market to treat serious illness. There are various routes of drug delivery administration engaged in providing a therapeutic substance to a patient. The most common drug delivery method is known to be oral (by the mouth) administration which is known to be the very first and earliest drug delivery procedure utilized in the pharmacy industry. It is one of the quickest growing, most practical and cost-effective route for drug delivery systems. Most oral medicines available at pharmacies are presented as tablets, liquids or capsules which have a high degree of drug stability and provide the correct dosage. However, there are various factors that make this particular route problematic. For instance, the drug that is administered normally would distribute throughout the body interacting not only with the target cells but also with the normal healthy cells which often results in toxic effects. The distribution of the drugs to the entire body gives rise to significant undesired side effects such as low pH of gastric juices, the first pass effect of the liver, oral metabolism and gastrointestinal (GI) disorders (Alhan et. al., 2010). Normally, conventional drug delivery causes the initial concentration of the drug in the body to spike

up above the level of toxicity and then gradually becomes ineffective over time. Systemic administration of the drug often requires high concentration to maintain a therapeutic effect because of the dilution effect and the difficulty of drug placement in the target site. These problems together with the lack of patient education in drug administration (Ghate and Edelhauser, 2008) seek methods where concentration, duration, and bioavailability of drug medications could be controlled to reduce side effects due to systemic absorption, and improve patient compliance by reducing the frequency of administration. With recent advances in genomics, biotechnology and chemistry, extensive research has designed a revolution in new techniques for microparticulate drug delivery system. These new approaches should be capable of releasing the drug at therapeutically suitable levels over the intended time period and/ or targeting the drug to the specific tissues without resulting in any unintended systemic effects (Ciolino et al., 2009a). This microparticulate drug delivery system should also pose the merits of good quality particles, which include biocompatibility, comfort, cost-effectiveness and also good storage properties. The drug release kinetics of the microparticulate should also be preferably linear and zero-order, showing the deliverance of a consistent quality of drug per unit time (Ciolino et al., 2009a). Current researches have observed the emergence of polymers as carriers that respond to pH shift, temperature, electric or magnetic field for microparticulate drug delivery system*. Changes that are due to neutralization of charged groups is caused either by pH shift or the addition of an oppositely charged polymer, alters the potency of hydrogen bonding with a rise in temperature or ionic strength and results in collapsing of the

hydrogels and properties and structure of the polymer network*. This successful approach could be conducted by complexation of polymers to form polyelectrolytes complexes. These complexes avoid the use of chemical cross linking agents and hence minimize the possible toxicity and other unwanted effects of the substance. Various dosage forms have been utilized to produce stable aggregated macromolecules in polyelectrolyte complex to deliver drug at target sites, controlling the drug release rate and hence maintaining the therapeutic level over the intended time period.

Polyelectrolyte (PEL)

The term polyelectrolyte (PEL) implies that when a class of macromolecular compounds dissolved in a suitable polar solvent (water), a huge amount of elementary charges formed along the macromolecular chain of repeating units (1). Usually, a polyelectrolyte in its uncharged state would act like any other macromolecules however a slight dissociation in its ionic (side) group would cause a drastic change in its properties (2) such as chain conformation, diffusion coefficients, solution viscosity, polarizabilty and miscibility (3-6). Charged polymers can be grouped as anionic PELs and cationic PELs depending on the type of charges. Biological macromolecules such as RNA, DNA, proteins and several polysaccharides also carry charges. PEL can be divided into ‘ strong’ and ‘ weak’ depending on their dissociation behaviour (Figure 2). PEL can be divided into ‘ strong’ and ‘ weak’ depending on their dissociation behaviour (Figure 2). A ‘ strong’ PEL dissociates fully in solution independent of the pH value (Figure 2a)* whereas the ‘ weak’ PEL in solution is not completely charged at intermediate pH. In ‘ strong’ PEL, the polymer synthesis merely enforces specific distribution and the total charge

along the polymer chain, causing the charges unable to move along the polymer chains. As for ‘ weak’ PEL, the charges could be adjusted by experimental parameters (e. g. pH, counterion type and ionic strength of the solution) (Figure 1. 2b)* as the distribution of charges is usually fluctuating in time and location and only the average is given by thermodynamic parameters. Typically, random coils are formed in solution due to the presence of uncharged polymers. The molecular weight of the polymer and the quality of the solvent influences the size of the polymer coil in the solution. The polymer coil enlarges as the segment-self repulsion and polymer-solvent interaction takes place in a good solvent whereas in poor solvent, the segment-self interactions are stronger than the polymer-solvent interaction leading to precipitation. The inter and intramolecular interactions are nearly similar in theta solvent (θ solvent) and hence the polymer coil acts like ideal chains (psedudo-ideal behavior) assuming exactly their random walk coil dimensions. Electrostatic interaction also affects a charged PEL as the charges along the polymer coil are all of the same sign and accordingly repel each other, leading to a coil expansion. The pH value of the solution of ‘ weak’ PEL and the addition of salts would also affect the charge density^. Kuhn and Flory * have acknowledged the electrostatic excluded volume which involves the swelling of the PEL chain due to the electric repulsion and hence causing excluded volume. This concept basically illustrates the expansion of a fully charged PEL in solution and also the effects of low molecular weight electrolyte which causes an increase in the ionic strength and therefore shrinks the polymer coils. The hydrogels or polymeric systems are well tolerated with excellent biocompatibility,

biodistribution, and bioavailability and also are sensitive to changes in environmental circumstances*. However, the properties of polyelectrolytes are affected not only by the chemical composition or the stoichiometry of the polymer such as molecular weight, stereochemical fitting linear charge density, charge distribution of the polymeric chain, nature of the ionic groups and degree of ionization of each oppositely charged but also by secondary experimental conditions like the concentrations, mixing ratio, mixing order, duration of the interaction, temperature, ionic strength and pH of the reaction medium (3-6).

Polyelectrolyte Complexation (PEC)

One interesting feature of PELs is their complexation behavior [57-59], when it mixed with another PEL of opposite charge. It was previously found by Fuoss and Sadek (1949) that polyanions and polycations in aqueous solution (e. g. polymer-polymer, polymer-drug and polymer-drug-polymer) would interact through electrostatic interaction and Flory-Huggins mixing free energies of the elecotrolytes that result in the precipitation of polysalts (i. e., polyelectrolyte complexes-PECs) (Michaels and Miekka 1961) in a complexation process (Figure 3) closely linked to self-assembly or spontaneous association (Thünemann et al. 2004). It is also known as " scrambled egg structure" (Figure 1) to define the morphology of the complexation formed. The driving force behind this complex formation is due to the gain in entropy caused by the release of low-molecular-weight counterions (Figure 2). Even though electrostatic interactions constitute the foremost attractive forces in the process, other interactions such as hydrogen bonding, ion dipole forces, dipole-dipole forces and hydrophobic

interactions also aid the complexation process providing a great sterical fit on the polymer chemical structures and tacticity (Thünemann et al. 2004). Formation of complexes displays compact structures with a very high degree of ordering and crystal like properties. The type of PEC is categorized into three kinds which are soluble, colloidally stable and coacervate complexes depending on properties of the polyelectrolyte.

Colloidally stable PECs

PEC complex formation between strong polyelectrolytes results in aggregated polymer chains and also macroscopic flocculation within the solvent and the polymers. The aggregation might be able to be stopped at a colloidal phase and a polydisperse system of almost spherical particles attained by constructing an adequate diluted technique (C < 0. 1 g/ml)^. Strong polyelectrolytes are basically from a 1: 1 stoichiometry. Conversely, smoother, entropy driven charge neutralization is proposed instead of strictly restricted binding in full binding found for the polymer in deficiency. This indicates that two nearby charges behaves like a diffuse charged milieu than like two discrete charges (‘ binding sites’). The stoichiometry could also be dependent on polymer flexibility as rigid polymers with uneven charge distributions causing inability to reconform and hence leading to formation of non-stoichiometric PECs. This formation could also be due to polymer branching as the oppositely charged polyelectrolytes would be inaccessible to the charges of the inner part of the molecules. Divergences from 1: 1 stoichiometry would take place when polyelectrolytes develop a denser structure due to the existence of salts. This is supported by an earlier work done by utilizing salt concentration as a function to treat the complexation

stoichiometry (8). Considering the distribution of charges present in the complexes, the nature of PECs have been discussed for many years stating that if they are considered as macromolecules, co-polymers, or gels. Basically, the outer shells of the colloidal PEC contain several polyelectrolyte sheets that consist of incomplete compensated charges and hence providing a net charge complex whereas the inner parts which is a 1: 1 stoichiometry, comprises homogenous, charge-neuralised core and hence high entanglements are overcome. Further secondary aggregation would be minimized by the extra components in the outer shell that tends to stabilise the particles. However, the particles would destabilise and flocculate with the addition of salts or when the molar mixing ratio is nearly 1 *. Large amount of PEC formation in purified water is controlled by the kinetics process resulting in frozen structures that is distant from the thermodynamic equilibrium. In non-stoichiometric mixtures, a steady dispersion of PEC colloids happens when the concentration is below 1g/L. Several studies have indicated that the small size of PEC formation is preferred due to entropic reasons, bimodal size distribution and also as an effect of electrostatic repulsion whereas large cluster formations promotes to decrease the total surface area of the system. High compact structures are triggered from strong polyelectrolytes with appropriate charge densities (0. 3-0. 7g/mL). More swelling of the colloidal particles would initiate as charge densities mismatch. In a very much diluted system, the amount of polymer chains per particle involved in single complex are tremendously high and improves with increasing the concentration of the component solutions*. According to Dautzenberg and Rother *, the addition of salt changes the ionic strength of

formed PECs causing either an instant swelling or deswelling of PEC while coagulation which is dependent on the concentration of the colloidal particle is a much slower process. Two crucial effects of salts on PEC formation (&) are the drop in the aggregation level as the polymer would adjust to the low stiff and more coiled framework when the quantity of salt is minute while higher quantity of salts results in macroscopic flocculation as excess components in the outer shell tends to stabilise the particles. It have also been investigated that the interaction between polyelectrolytes also dependent with the valence (uni- or divalent) of the salt.

Water-soluble PECs

Water-soluble PECs formation occurs when permutations of polyions with various molecular weight and poor ionic groups present in a mixture of non-stoichiometric ratios under definite salt conditions. Kabanov and Zezin ^ have illustrated (Figure 3) that the complex formed would implement a conformation comprising hydrophilic single-stranded segments and hydrophobic double-stranded segments. The complex tends to reconform to a structure closer to its thermodynamic equilibrium when a minute amount of salt is present. However, when salt concentration increases, the shielding of the polyelectrolyte charges would cause in shrinking of PECs. A more rise in salt concentration results to completely complexed, precipitating species; the precipitates finally redissolve and both constituents continues as free polyelectrolytes in the solution. According to Kiriy et al., the conformation of PECs contains long polycations and short polyanions. The PECs deposited on a mica surface were examined by AFM imaging indicates that when excess short polyion is present, the PEC becomes as micelle-like structure,

conversely, when excess long polyion is present, it tends to wrap around the hydrophobic segments of the PEC structure.

Coacervates

A coacervate is formed when the mutual binding of two oppositely charged polyelectrolytes is of reasonable strength as a consequence of low charge density. The coacervate is a liquid-like, mobile, and reversible structure that is usually formed in two phases, one polymer rich and one very dilute. A study done by Spruijt et al. [17], indicating that increasing salt concentration results in a decrease in the occurrence of interfacial tension between these two phases. Vanerek and van de Ven have investigated on the formation of coacervate complexed from cationic polyacrylamide (CPAM) and sulphonated Kraft lignin. It has been suggested that the coacervate formation is influenced by the molecular weight of CPAM where a shorter chain would take up a coiled structure effortlessly and hence precipitates. Basically, the soluble, colloidal and coacervates complexes occurs concurrently. Complex coacervation has been utilized as drug carriers in microparticulate drug delivery system.