Central nervous system drug delivery biology essay

Science, Biology

Disorders of the central nervous system are common worldwide; one of the most common causes of neurological disorders is alcohol abuse. This is one of the leading causes of deaths and efficient treatment of this and other central nervous system (CNS) disorders is indeed a public health concern. Efficient delivery of drug molecules for therapeutics is severely hampered by various barriers to biological membranes (Chen &Liu, 2012; Bengley, 2004). The blood brain barrier, a formidable barrier to drug delivery in CNS drug delivery presents a challenge in therapeutics (Bengley, 2004). Although beneficial in protecting the central nervous system, this barrier challenges effective drug delivery to the region by limiting access to the barest minimum for drugs utilizing the lipid mediated and carrier/receptor mediated transport; however, in most cases the barrier completely precludes access (Alam et al, 2010). Due to the invasiveness of most of the highly effective techniques that overcome this barrier, coupled with the danger of opening the tight junctions or blocking the efflux receptors, alternate routes of delivery that bypass this barrier with no damage to it are the hallmark of modern research into drain drug development and delivery (Alam et al, 2010). With increasing populations affected with at least one form of neurological disorders and the ineffectiveness of formulations on the market, the olfactory route effectively targets the central nervous system, overcoming hepatic metabolism, tissue distribution and clearance; problems associated with oral and parenteral delivery (Pardridge, 1997). The olfactory route has been known to provide an efficient, non-invasive and rapid route of delivering drugs to the CNS bypassing the blood brain barrier (Alam et al, 2010, Alhenn et al, 2012). The blood brain barrier although effective in

limiting xenobiotics from the CNS, an advantageous protective mechanism, precludes adequate therapy for central nervous disorders (Alam et al, 2010). Various delivery approaches have been investigated with the most effective ones either being expensive or invasive. Polymeric devices such as wafers, microchips and nanospheres have been developed and extensively researched as delivery devices and have improved the delivery of medicines and vaccines (Alhenn et al, 2012). Polymer based devices are especially advantageous for olfactory drug delivery as they are found to be biodegradable, thermo-responsive, PH-responsive and mucoadhesive; these take advantage of the ph, temperature and protective mucus of the olfactory system (Halliday et al, 2012). Polymers with these properties are the basis for this proposed research in developing a sol-to-gel based delivery system to deliver quetiapine to the central nervous system via the nose. Based on five polymers, this project identifies one thermo-responsive polymer (Pluronic F127) as the primary ' smart' polymer for the development of the device. Four other mucoadhesive polymers which compose of various percentages of chitosan (low), chitosan (medium), PEG 4000 and carboxymethyl cellulose are formulated. These properties enable the conversion of the polymeric device into a gel in-vivo (nasal cavity) and its ability to overcome the rapid cilliary clearance in the nose which increases contact time and hence drug concentration and penetration into the brain. Sorbitol, benzalkonium chloride and ascorbic acid are included in the formulation to function as a humectant, an antimicrobial preservative and an anti-oxidant. Quetiapine, the active drug component is also included prior to analyzing the formulation. A total of sixty four devices will be formulated

using the cold method, evaluated and characterised based on their gel-strength, gel forming and gel melting temperatures, texture analysis, viscosity, clarity, rheological, drug release, differential scanning calorimetry, drug-polymer interaction analysis and hydrogel water content. The formulations with the optimum properties will be proposed as the appropriate device for quetiapine delivery via the nose for CNS delivery.

Background:

General context:

Neurological disorders are rather common with more than eighty million of the United States population suffering from at least one form of neurological disorder; more than 98% of small molecule drugs do not cross the blood brain barrier (BBB) and almost all large molecule drugs do not cross the barrier at all (Pardridge, 1997). Common neurological disorders include Alzheimer's disease, Parkinson's disease, stroke, brain tumors, HIV, anxiety, schizophrenia, depression, epilepsy and drug abuse (Alam et al, 2010; Pardridge, 2005). The burden thereof is unimaginable as many more individuals develop these yearly with majority unable to be effectively treated (Pardridge, 2005). Antipsychotics, antiepilieptics and antidepressants are a few of such medications for treating certain CNS disorders. A significant number of patients on antiepileptic drugs do not receive sufficient benefit from their medications (Halliday et al, 2012). No therapy exists for neurological disorders such as Alzheimer's, Huntington's disease and Parkinson's disease (Pardridge, 2005). Despite the availability of candidate drugs, most central nervous (CNS)disorders remain untreated due to the

negligible transport across the blood brain barrier, the blood- cerebrospinal fluid and other barriers of the central nervous system (Chen &Liu, 2012; Bengley, 2004). Entry into the brain is regulated by two main fluids; the blood and cerebrospinal fluid (Chen & Liu, 2012). Many disorders of the CNS are untreatable because, novel drugs are discarded despite adequate pharmacological effect at their receptors due to relatively negligible transport across the blood brain barrier (Bengley, 2004). The blood brain barrier is made up of specialized semi-permeable endothelial cells that prevent xenobiotics from accessing the brain (Alam et al, 2010). These cells function to maintain homeostasis, vascularisation of normal tissues, activation of cells of the blood and fibrinolysis (Alarm et al, 2010). Bengley (2004) categorises the function of this barrier into two; maintains a separate region of the cerebrospinal fluid and the brain ISF and protects neuronal function within the brain (Bengley, 2004). Transport of systemic molecules across this barrier is through one of two processes known as lipid-mediated transport and carrier-mediated/receptor-mediated transport system; the former allows molecules with molecular weights lower than 500 Daltons to cross, carrier-mediated transport carries nutrients whilst receptor mediated transports peptides (Pardridge, 1997). Polar molecules like glucose are unable to diffuse into the brain as result of the existing tight junctions which prevent the paracellular pathway (Bengley, 2004). The modification of the cells in the central nervous system, exist to limit transport across the membrane; these include the existence of tight junctions, a reduction in macropinocytosis and decrease fenestrae (Bengley, 2004). Other features include the presence of transporters including the amino acid carrier LAT1,

efflux transporters such as the infamous P-glycoprotein and multidrug resistance related proteins MRPs (Chen & Yiu, 2012). The endothelium, pericyte, astrocyte and neurons make up the cerebral microvasculature; the endothelium controls brain permeability (Pardridge, 1997). The three layers that make up the blood brain barrier include the endothelial layer composing the tight junctions and forming the inner wall of the capillary vessels; the basement membrane follows and it is on this that the pericytes and astocyte feet processes lie (Alam et al, 2010). The tight junctions offer an extremely high level of electrical resistance in comparison to that found in other parts of the body; that is 1500-2000 cm 2 compared to 3. 33cm2, proving the high resistance of the blood brain barrier (Alam et al, 2010). The blood-cerebrospinal fluid barrier which is more commonly called the choroid plexus plays an essential role and is involved in drug transport (Alam et al, 2012). This barrier together with the blood brain barrier plays an essential role in controlling homeostasis within the brain (Alam et al, 2012). In the absence of the endothelial junction at certain sites of the brain, circumventricular organs which have lesser surface area relative to the blood brain barrier, tight junctions exist to limit diffusion of substances into the central nervous system (Alam et al, 2012). Transport across the blood brain barrier occurs by various mechanisms including facilitated diffusion which is responsible for the transport of amino acids, nucleosides and small peptides (Alam et al, 2012). Endocytosis with particular reference to bulk-phase endocytosis is limited due to the endothelial cells however; receptor endocytosis transports different hormones, enzymes, plasma membranes and growth factors (Alam et al, 2012). Various receptors exist for transport of particular substances

however these have a lower capacity and higher affinity compared to the absorptive-mediated transport which is triggered by electrostatic interaction between a positively charged molecule and the negatively charged surface of the plasma membrane (Alam et al, 2012). Carrier mediated transport also exists on the endothelium membrane of the brain capillaries in either direction of blood flow be it from the brain to the blood or vice versa (Alam et al, 2012). This pathway is exploitable in drug design where the drug is formulated to assume the molecular structure of an endogenous molecule (Alam et al, 2012). These transporters are known as influx transporters since they carry molecules into the brain however, on the other extreme end are the efflux transports which actively transport substances out of the brain after they have been successfully transported into the brain (Alam et al, 2012). The major barrier that they pose is to pharmacological agents; the ATP binding cassette transporter, P-glycoprotein is the principle efflux transporter (Alam et al, 2012). P-glycoprotein ‘ throws out’ a high number of lipophilic amphipathic drugs and was hypothesized to be the cause of the poor penetration of relatively larger molecular weight lipophilic drugs into the brain (Schinkel, 1997). Schinkel (1997) stated a confirmation of this hypothesis by mentioning the various invitro experiments with mice that lacked this transporter (known as knockout mice), or mice treated with molecules that blocked the function of these transporters. A relatively higher penetration of drug molecules was seen when the transporter was thus absent (Schinkel, 1997). Certain pathogenesis result in an increase or a decrease in p-glycoprotein; tissues collected from the brain cells of patients with Parkinson's show a decrease in p-glycoprotein whereas a relative

increase in the transporter was seen in patients with epilepsy (a phenomena hypothesized to be the cause of drug resistance in the latter)was described by Chen & Yui (2012). A recently identified transport route known as cell-mediated transcytosis is a well established mode of transport for pathogens like Cryptococcus neoformans and the HIV virus known as the ' Trojan horse' model (Chen & Yui, 2012). This route as mentioned by Chen & Lui (2012) relies on the monocytes and macrophages of the body's immune system to cross the blood brain barrier. Pathological conditions such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, infectious diseases, stroke, brain tumours, trauma, ischemic conditions and pain offers some advantages to the delivery of drugs in that, disruptions of the blood brain barrier integrity has been identified affecting specific transport systems present in the central nervous system (Chen & Lui, 2012). Oxidative stress, the presence of inflammatory mediators, lipid mediators, and vasogenic agents has also been shown to alter the permeability of the blood brain barrier (Chen & Yui, 2012). This has been envisioned to offer a window of opportunity to the delivery of drugs that are unable to be transported successfully (Chen & Yui, 2012). However, although this may be advantageous for drug delivery, there is an increased rate of neurodegeneration as in the case of Alzheimer's disease where restoration of the integrity of the barrier is of a greater essence than taking advantage of it for drug delivery (Chen & Yui, 2012). Pardridge (2005) stated that all large molecule drugs and about 98% of small molecule drugs do not cross the blood brain barrier which makes targeting of drugs to the brain a very difficult task. Only a few molecules possess the criteria for transport across;

these criteria include molecular weight less than 500 Daltons, unionized molecules, a log P value close to 2 and cumulative hydrogen bonding less than 10 (Chen &Yui, 2012). The reduction in molecular mass and the lipophilic alterations of the small molecule drug is essential to increase their penetration significantly (Pardridge, 2005). An effective solution to the blood brain barrier challenge is essential for correlation of laboratory success into the clinical therapy without which, central nervous therapeutics will remain ineffective (Pardridge, 2005).

Previous scientific literature:

To overcome the barrier to drug delivery across the brain endothelium, exploitation of the carrier mediated transport system and of medicinal chemistry to enable drug molecules transport across the blood brain barrier is one of the approaches that have been (Pardridge, 2005). A classical example is the reformulation of polar substances to mimic the structure of nutrients; gabapentin, melphalan and laevodopa have been designed using this concept and they have been successfully transported across the blood brain barrier (Alarm et al, 2012). The alteration of the structure via medicinal chemistry, modifications of the lead compound makes the drug molecule transportable in opposition to the lipophilicity of the drug; this requires an adequate knowledge of the characteristics needed for carrier mediated transport across the blood brain barrier (Pardridge, 2005). To date, the most effectively identified inhibitors are those of P-glycoprotein; an important transporter that is responsible for inhibiting the entry of antineoplastic drugs and which can cause multidrug resistance due to its over-expression

(Dantzing et al, 2002). P-glycoprotein inhibitors have been identified as potential facilitators of transport of drugs that are substrates to the transporter; one such success in this approach involves the drug Pluronic P85 which increased the transport of drugs which are substrates to the efflux transporter (Chen & Yui, 2012). This approach has been identified to be better suited for acute disease states where the inhibition of the transporter is needed to increase the concentration of the drug in the brain for a relatively short duration of time as seen in brain tumors (Chen& Yui, 2012). First generation inhibitors of the transporter include verapamil and cyclosporine A, second generation inhibitors include dexverapamil and valspodar, finally, third generation inhibitors include LY335979 and XR9576 (Dantzing et al, 2002). The important factor to consider in regard to the inhibitors is that the effect of inhibition needs to be long enough to be efficacious but short enough to avoid causing toxicity (Dantzing et al, 2002). Another approach that tends to bypass the barrier is known as trans-cranial delivery; these include three neurosurgical approaches namely intracerebral implantation, intracerebroventricular infusion and convection enhanced diffusion (Pardridge, 2005). The intracerebral and intracerebroventricular approach is limited since it relies on diffusion of the drug which decreases with a square of the diffusion distance (Pardridge, 2005). The seriousness of this is seen as diffusion across a 0. 5mm causes a 90% reduction in the drug concentration from an intracerebral implant (Pardridge, 2005). The pro-drug approach delivers chemically modified hydrophilic drugs to the brain upon reaching the BBB by reacting with an enzyme and being transported into the brain (Alam et al, 2010). The use of cationic proteins takes advantage of the

difficulty in proteins delivery by reformulation as cations and enhancing brain delivery by the electrostatic attraction with anions on the surface of the BBB (Alam et al, 2010). BBB disruption is another approach suggested as a means to open the tight junctions by utilizing ultrasonic waves or electromagnetic waves (Alam et al, 2010). The use of hypertonic solution like mannitol is capable of achieving this phenomenon and is utilized in the hospitals to treat brain tumor treatment (Alam et al, 2010). Infusion of mannitol leads to the disruption of the blood brain barrier and causes the shrinkage of the endothelial cells causing seizures in animals and humans (Pardridge, 2005). The disruption of the barrier by using such means leads to the influx of toxic molecules like albumin (Pardridge, 2005). Other solvents such as tween 80 and ethanol are known to have similar effects (Pardridge, 2005). The use of chimeric peptides, cyclodextrins and Antibody directed pro-drug approach (ADEPT) are some other approaches that have been suggested to enhance CNS drug delivery (Pardridge, 2005).

Recent literature and current developments

The cutting edge developments in CNS drug delivery aim to provide improvements in drug targeting to the region (Alam et al, 2010). Novel approaches involving the use of liposomes as a means of hiding the drug from opsonization; they conceal drugs with hydrophobic, amphoteric or hydrophilic characteristics within or on the surface of the micelle surface (Alam et al, 2010). Monoclonal antibodies and cationic proteins are useful as targeting vectors in modulating the distribution of the liposome-encapsulated molecules in the brain; through absorptive-mediated or

receptor-mediated transcytosis, they are able to gain access into the brain (Alam et al, 2010). Pegylated liposomes have provided a longer circulation of the liposomes and resulted in have been used as therapeutic cures for brain tumors (Alam et al, 2010). Other mechanisms exploited in recent years include use of monoclonal antibodies, molecular Trojan horses, transnasal delivery and use of monolithic devices, (Halliday et al, 2010; Alam et al, 2010). The rapid euphoric action of cocaine-sniffing by addicts has been linked to the rapid absorption, targeting action of nasal delivery and the direct route of delivery between the nose and the central nervous system (Illum, 2002). The olfactory route is non-invasive and involves nasal delivery via the olfactory bulb (Alhenn et al, 2012). Various drugs have been successfully delivered via the olfactory route including peptides like insulin (Bengley, 2004). Animal studies also confirmed a 27 time higher drug concentration of dopamine following intranasal administration after 4 hours whereas less than 1% of administered drugs in other routes reached the brain (Illum, 2002). A higher concentration of apomorphine and melatonin intranasally administered in man was reported by lllum (2002). This route not only bypasses the blood brain barrier, but bypasses also, hepatic metabolism, drug distribution to other tissues, early elimination and the delayed onset of action of CNS (Ugwoke et al, 2005). The high permeability of this region coupled with the extensive vascularity makes it ideal for rapid drug delivery of poorly absorbed drugs (Arora et al, 2002). The nasal cavity is about 12cm long and is divided by the superior, middle and inferior turbinate (Kublik & Vidgren, 1998). The epithelium covering the surface of the nostrils is made up cells like basal, columnar and goblet cells whilst

resting on the basement membrane (Kublik & Vidgren, 1998). The nasal epithelium has inflammatory cells, blood vessels and two sub-mucosal glands (Kublik & Vidgren, 1998). Transport via the nasal region has been suggested to be due to endocytosis/pinocytosis of the constituted drug molecule to the olfactory bulb or diffusion to the olfactory nerve (Alhenn et al, 2012) and then to the central nervous system. The nasal region has an average temperature of 32oC and an ideal pH of about 5. 5-6. 5 in adults but much higher in children (5. 0-7. 0) (Arora et al, 2002). The mucosal layer of the nasal region's thickness depends on various factors; however the thickness controls mucocilliary transport hence a viscous mucus layer inhibits the cilliary action of the nasal cilia and inhibits mucocilliary clearance (Kublik & Vidgren, 1998). The action of the cilia known as the mucocilliary action is the defence mechanism of the nasal region to clear mucus as well as xenobiotics on the surface, the effectiveness of this mechanism reduces the contact time of nasally administered devices, their efficiency and permeability (Arora et al, 2002). In effect, a reduction in this mechanism translates better contact with the nasal mucosal and hence delivery of the drug (Arora et al, 2002). Monomers, covalently joined to form polymers have various properties which determine the characteristics of the resulting polymer (Halliday et al, 2012). Polymers can either break down in the body (biodegradable) or not (non-biodegradable) in which case the break-down products need to be removed from the body either surgically or by the body itself (Halliday et al, 2012). Polymeric devices such as wafers, microchips and nanospheres have been developed and extensively researched as delivery devices (Alhenn et al, 2012).' Smart' polymers have been classified

based on their ability to undergo structural changes in response to physical, chemical or biological stimuli like temperature, pH, ionic strength and magnetic strength (Pillai & Panchagnula, 2001). Thermo-responsive polymers in the solution swell and release the drug entity from the gel in response to changes in temperature and is based on the temperature difference between the environment and the nasal mucosa (Pillai & Panchagnula, 2001). They are classified as negatively thermo-sensitive, positively thermo-sensitive and thermally reversible based mainly on their critical solution temperature characteristics (Swamy & Abbas, 2012). Mucoadhesive polymers overcome the rapid cilliary clearance in the nose thereby increasing contact time and hence drug concentration and penetration (Swamy & Abbas, 2012). Mucoadhesion of the gel allows the drug-polymer complex to stay in the nose for a long period of time, thereby increasing absorption and the resident time of the drug (Ugwoke et al, 2005). Mucoadhesion is influenced by factors such as molecular mass of the polymer, present functional groups, polymer concentration and environmental pH (Ugwoke et al, 2005). The use of bio-degradable polymers to deliver drug entities intranasally employing both thermoresponsiveness and mucoadhesion is of importance as it overcomes the major barriers to intranasal drug administration whilst maximizing drug targeting.

How will the problem be addressed?

The problems with CNS drug administration are addressed head on in this project due to the formulation and the device thereof. Intranasal administration not only maximizes the concentration of drug reaching the

brain but also, with the use of specific polymer properties, the project overcomes the natural barriers in the nasal mucosa. By the use of the intranasal route, the problems associated with the blood brain barrier are curtailed and drug targeting, the gold standard of drug delivery, is fully achieved. Thermoresponsive and mucoadhesive polymers used in the formulation of the device enable the swelling of the polymer to allow adhesion to the nasal mucosa as well as reduce the mucocilliary barrier to drug administration. The end result is the increase in contact time of the polymeric drug device, increasing penetration and concentration of quetiapine reaching the brain. At the end of project, the formulated device will provide knowledge of the polymer ratio combination for effective delivery, gelation temperature, viscosity, rheological and the drug release properties of the device with reference to the polymer combination thereof.

Intended design and methods of investigation

Rationale and strategy for choice of formulation:

The polymers chosen are ' smart/intelligent" polymers that undergo a phase change based on environmental conditions; they are non-toxic and biodegradable as neurological disorders may require daily instillation and as such safety is an essential (Bromberg&Ron, 1998). The formulation will be designed using one thermoresponsive and four mucoadhesive polymers; with the inclusion of other excipients as antioxidants, antimicrobial preservatives and humectants. Carbapol, a PH responsive polymer is not chosen as the primary ' smart' polymer, as it does not gel quickly enough to eliminate the initial rapid mucocilliary clearance (Zhou & Donovan, 1996)

and has the potential to alter the temperature-sensitivity of the formulation (Bromberg&Ron, 1998). Pluronic F 127, Methylcellulose, chitosan (low), chitosan (medium) and PEG 4000 are the polymers of choice. Pluronics/poloxamers as stated by Bromberg & Ron (1998) are approved FDA/EPA copolymers that are usually incorporated as thermoviscofying agents. They also have less mucocilliary clearance as indicated by Zhou & Donovan (1996) as well as, the ability to limit enzymatic action on the drug (Bromberg&Ron, 1998), excellent drug release profile and low toxicity profile (Westerink et al, 2002). Methylcellulose, had a much lesser mucocilliary clearance in both normal and damage mucosa as found in Zhou & Donovan's (1996) study. The need for cross linkers is eliminated as they are known to exert some form of toxicity and carcinogenicity (Bromberg&Ron, 1998). Chitosan, as a mucoadhesive polymer possesses excellent permeability enhancing properties, is slowly bio-degradable, biocompatible and has no eminent side effects; most importantly, is known to act synergistically with poloxomer 407 to optimise drug release and stability (Westerink et al, 2002). PEG 4000 is known to show an outstanding safety profile and has the ability to alter the gelation temperature; PEGs are also known to loosely and reversibly complex active compounds (e. g. drug) and possibly prevent degradation and promote stability (Mokarram & Alonso, 2006, Yuan et al, 2012). The polymers and excipients will be formulated as the sol-to-gel device using the cold method; all sixty four (64) preparations will be evaluated based on various characteristics and properties.

Materials and methods:

Materials:

Pluronic F127, Chitosan (low), Chitosan (medium), PEG 4000, carboxymethylcellulose, simulated nasal electrolyte solution , test tubes, beakers, water bath, refrigerator, magnetic stirrer, rod, sorbitol, benzalkonium chloride, ascorbic acid, plate and cone viscometer, rheometer, texture analyzer, FTIR spectrometer, uv spectrometer, USP apparatus and dialysis bag. All reagents are of analytical grade and purity.

Polymer concentrations:

Pluronic F 127; 17%w/w, 18%w/w, 19%w/w and 20%w/w (Pisal et al, 2004). Chitosan (low) and chitosan (medium): 1mg/1ml (Mokarram & Alonso, 2006; Swamy & Abbas, 2012) and 0. 3%w/v (Swamy & Abbas, 2012). Carboxymethycellulose: 3%w/v and 1. 5%w/v (Swamy & Abass, 2012, Kolsure & Rajkapoor, 2011)PEG 4000: 0. 6%w/v (Yuan et al, 2012) and 1% (Mokarram & Alonso, 2006).

Choice of other excipients

0. 5%w/v sorbitol is used as a humectant as it prevents dehydration of the nasal mucosa (Kolsure % Rajkapoor, 2011). 0. 02%w/v Benzalkonium chloride is used as a preservative to prevent microbial action (Kolsure % Rajkapoor, 2011). Ascorbic acid 0. 01-0. 1%w/v is also employed as an antioxidant (Medicines complete, 2012).

Method for gel preparation:

The cold method as described by Zaki et al (2007) is used to prepare the polymer compositions. The drug poloxomer combination is prepared to determine the optimal concentration (Y%w/w) to be utilized for the preparation, as certain drugs increase or reduce the gelling temperature. Quetiapine (water soluble), the mucoadhesive polymers are dissolved in water which has been equilibrated at 4oC-8oC (Ur-Rehman, et al, 2011) prior to adding to a weighed amount of pluronic F127 (17%w/w-20%w/w) and stirred with a magnetic stirrer. The aqueous solution is kept at 4oC (Pisal et al, 2004) for about 48 hours until a clear solution results (Ur-Rehman et al, 2011). Gels containing the excipients are slightly adapted to the cold method (Pisal et al, 2004). All water soluble materials are dissolved in water before adding the pluronic F127 to optimize the mixing (Pisal et al, 2004). Gel solutionPluronic 127Muco (A)Muco (B)Muco (C)Muco (D)AY%w/whighLowLowLowBY%w/wHighhighHighHighCY%w/wHighLowLowHighDY%w/wHighHighLowLowEY%w/wHighLowHighLowFY%w/wHighHighLowHighGY%w/wHighHighHighLowHY%w/wHighlowHighHighIY%w/wLowLowLowLowJY%w/wLowhighHighHighKY%w/wLowLowLowHighLY%w/wLowHighLowLowMY%w/wLowLowHighLowNY%w/wLowHighLowHighOY%w/wLowHighHighLowPY%w/wLowlowHighHighA total of sixty four (64) preparations will be prepared using the above table and permutated as below for each of the mucoadhesive polymer; the formulated systems are evaluated appropriately. Scheme for formulation

Evaluation

Formulations are evaluated based on characteristics such as clarity, texture analysis, sol-to-gel temperature, drug release analysis, viscosity and gel-strength. The optimal temperature concentration with appropriate gellation temperature (y%w/w) is obtained from the various concentrations of thermoresponsive polymers with the drug. A graph of temperature (oC) against pluronic F127 concentration will visualize the effect of quetiapine on different concentrations of the drug (Pisal et al, 2004) and as such, enable the optimum concentration to be chosen. The various formulations are inspected under black and white light to evaluate the clarity of the formulations (Kant et al, 2011). The plate and cone viscometer is used to test for the viscosity and rheological properties of the formulated devices so that patients will comply with instillation directions (Kant et al, 2011). The texture analysis characterizes the formulations based on properties like firmness, consistency and cohesiveness; the texture analyzer is used in this evaluation (Kant et al, 2011). The sol-to-get transition temperature and PH are evaluated to determine the gelling temperature (Swamy & Abass, 2012) and analyse the in-situ gelling (Kant et al, 2011) using the water bath and timer (Swamy & Abass, 2012). The ' visual tube inversion method' is employed as described by Ur-Rehman et al (2011). 1g of the sample is placed in a 13mm test tube (Ur-Rehman et al, 2011) and immersed into a water bath and heated at specific temperatures and rates (Swamy & Abass, 2012). Temperature is increased by 1oC and allowed to equilibrate through out the formulation for 5 minutes (Pisal et al, 2004). The sample is analysed for gellation at such a time that the meniscus fails to move upon 90oC tilting

(Swamy & Abass, 2012) ; the temperature of the bath is slowly cooled and the gel melting temperature is recorded to be when the meniscus moves upon 90oC tilting(Ur-Rehman et al, 2011). The critical gellation temperature is recorded as the mean of three sample recordings ± SD (Ur-Rehman et al, 2011). The rheometer is used to determine the gel-strength (Kant et al, 2011). An amount of gel in its sol form is prepared in a beaker and raised a rate whilst a probe is pushed through the gel (Swamy & Abass, 2012). Using the Fourier transform Infra Red (FTIR) spectroscopy, the nature of such forces of interaction between the drug and polymer using the KBr pellet method is determined (Kant et al, 2011; Swamy & Abass, 2012). The thermogravimetric analysis is used to quantitatively analyse the quantity of water in the hydrogel (Kant et al, 2011, Swamy & Abass, 2012). The reference cells of the calorimeter is filled with water and the pressure of both cells set to 15psi; the heating and cooling cycles between 2-65oC and scan rates of 90, 60 or 30oC/h is used to obtain the thermograms(Ur-Rehman et al, 2011). The onset temperature, area under the peak, peak temperature and endset temperature of the endothermic peak is obtained from analyzed data (Ur-Rehman et al, 2011). The invitro-drug release analysis is evaluated using the USP paddle method (Yuan et al, 2012). 1g of the gel formulations (Zaki et al, 2007) containing 50mg of quetiapine is filled into a semi-permeable dialysis bag (Yuan et al, 2012). The bag is sealed appropriately and clamped to avoid leakage of the gel (Yuan et al, 2012). The test is performed in an appropriate dissolution medium i. e. 500mls of simulated nasal electrolyte solution (SNES) (Zaki et al, 2007). Drug release studies is performed at 35 ± 0. 5oC and stirred at a speed of 50 rpm(Zaki et al, 2007);

5ml of the sample is withdrawn at appropriate times (5, 10 , 15 , 30 , 45 , 60 , 90 , 120 , 180 , 240 , 300 and 360mins each) and analysed using the uv-spectroscope at 273nm (Zaki et al, 2007). Prior to evaluation, the sample is centrifuged at 6700g for 2minutes to allow suspended gel in the sample to settle before analysis (Ur-Rehman et al, 2011).

Data analysis

The parameters of all variables will be calculated using the appropriate standard methods (Yuan et al, 2012). The values for the Cmax, Tmax, Kel (elimination rate constant as determined by the regression line by the log concentration versus time curve), Ka (absorption rate constant by the method of feathering), mean absorption time (1/Ka) are expressed as the mean value ± standard error of the mean (S. E. M.) of six determinations (Yuan et al, 2012). Release is analysed against the various release models (zero, first and higuichi models); the equation of the model that fits the drug release is used appropriately to calculate rate of release as a fickian/non-fickian release model (Yuan et al, 2012). The exponential equations are used to determine the amount of drug released (Zaki et al, 2007) as shown below; Equation 1 (Zaki et al, 2007).

Annotated Bibliography:

Alam . M. I., Beg . S., Samad, . A., Baboota, . S., Kohli, . K., Ali, . J., Ahuja, . A., Akbar, . M. (2010). Strategy for effective brain drug delivery. European Journal of Pharmaceutical Sciences 40 (2010) 385–403

The journal explains the selective delivery to overcome the difficulty of drug access by comparing direct and chemical based delivery whilst finally re-diverting to novel approaches; it extensively deals with liposomes as a potential intranasal delivery.

Allhenn,. D., Boushehri,. M. A. S. , Lamprecht, . A.(2012). Drug delivery

strategies for the treatment of malignant gliomas. International Journal of

Pharmaceutics 436: 299– 310

Reviewing the difficulty in obtaining an excellent prognosis for brain tumors as a result of poor delivery to the brain, this journal discusses trans-nasal and polymeric drug delivery as novel therapies for effective treatment.

Arora. P., Sharma, . S., Garg, . S., (2002). Permeability issues in nasal drug.

Delivery. DDT 7(18):

This review focuses on factors affecting permeability in the nasal cavity and provides information for optimizing delivery without compromising the physiology of the cavity.

Bengley,. D. (2004). Delivery of therapeutic agents to the central nervous

system: the problems and the possibilities. Pharmacology & Therapeutics

104 (2004) 29– 45

The author of this journal does not only evaluate the problem with CNS delivery but clearly discusses the potential possibilities to overcome them. He reviews both novel and previous strategies and stresses on the drug delivery aspects of these strategies.

Bromberg, . L. E., Ron, . E. S. (1998). Temperature-responsive gels and

thermogelling polymer matrices for protein and peptide delivery. Advanced

Drug Delivery Reviews 31 (1998) 197–221

This journal discusses various thermoresponsive gels, their applications in drug delivery as well as copolymer formulations that incorporate ' intelligent' polymers together with their loading and toxicology.

Chen, . Y., Liu, . L. (2012). Modern methods for delivery of drugs across the

blood–brain barrier. Advanced Drug Delivery Reviews 64 (2012) 640–665

While emphasizing the anatomy of the BBB, this journal focuses on the various modern delivery methods as a subset of the various receptors that inhibit drug transport. The authors review nanotechnological advances to the delivery problem and explain the ability of pathological changes to be advantageous.

Dantzing, A. H., De Alwis, . D. P., Burgess, . M. (2002). Considerations in the

design and development of transport inhibitors as adjuncts to drug delivery.

Advanced drug delivery reviews 55: 133-150.

The importance of the p-glycoprotein receptor and its impact on central nervous system disease management is the focus of this journal; the various P-gp inhibitors are considered as well as the impact of modulation on toxicity and efficacy.

Halliday, A. J., Moulton, . S. E., Wallace, G. G., Cook, . M. J.(2012). Novel

methods of antiepileptic drug delivery — Polymer-based implants Advanced

Drug Delivery Reviews 64 (2012) 953–964

This journal links the burden of epilepsy to the insufficient therapy from drugs marketed for the disease and focuses on development of polymeric based implants to delivery loaded drugs to effectively treat epilepsy.

lllum,. L. (2002). Nasal drug delivery: new developments and strategies DDT

7(23):.

This journal provides various " in-man proof of concept" to the nasal administration of conventional drugs and discusses this as a novel delivery method.

Kant,. A., Reddy,. S., Shankraiah, . M. M., Venkatesh, . J. S., Nagesh . C

(2011). Insitu gelling system-An overview. Pharmacologyonline 2: 28-44

This journal over-views the advantages of in-situ gels, the most popularly used polymers and their property in the formulation (as mucoadhesives, enhancers, and ' intelligent polymer') and various evaluation parameters for the optimal delivery system.

Kolsure,. K. P., Rajkapoor, . B. (2011). Thermoreversible zolmitriptan nasal gel for acute migraine attack. Journal of Current Pharmaceutical Research; 8 (1): 08-14

This journal compares Pluronic F127 and F68 for formulating sol-to-gel devices using the cold method for intra-nasal administration and treatment of migraines; the preformulation properties of the device is analysed by evaluating in vitro characteristics that optimize drug release.

Kublik , H., Vidgren , M. T. (1998). Nasal delivery systems and their effect on deposition and absorption. Advanced Drug Delivery Reviews 29: 157–177

This journal relates the deposition and absorption of nasally administered drugs to their bioavailability as a function of the mucocilliary clearance of the nasal cavity by using several in vivo and in vitro methods.

Mokarram, . R., Alonso,. M. J. (2006). Preparation and evaluation of chitosan nanoparticles carrying diphtheria toxoid as new carriers for nasal vaccine delivery in mice. Archives of Razi institute 61 (1): 13-25

The journal discusses the targeted ability of chitosan-PEG for nasal delivery of diphtheria toxoid and evaluates its improvement; the preparation, loading and characterization of the polymer components fueled the concluding remarks. The advantage of PEG inclusion is evaluated as a function of the in-vitro drug release.

Mygind,. N., Dahl, . R. (1998). Anatomy, physiology and function of the nasal

cavities in health and disease. Advanced Drug Delivery Reviews 29: 3–12

This journal links the anatomy and function of the nasal cavities with the effect of certain conditions on the absorption of drugs; it reviews hence the barriers and functional structures within the cavity that affect nasal drug administration.

Pardridge . W. M. (1997). Drug Delivery to the Brain. Journal of Cerebral

Blood Flow and Metabolism 17: 713-731

This review article discusses the detailed anatomy of the BBB, highlights previous advances in brain delivery and sums up by stating intelligently the need to merge delivery with development at an early stage.

Pardridge, W. M. (2005). The Blood-Brain Barrier: Bottleneck in Brain Drug

Development The American Society for Experimental NeuroTherapeutics, Inc.

2: 3–14.

This journal emphasizes the BBB delivery problem (' bottlenecks') and highlights the growth of CNS disorders. It also shows the clear possibility of improvement upon solving the delivery problem.

Pillai, . O., Panchagnula, R. (2001). Polymers in drug delivery Current Opinion

in Chemical Biology 5: 447–451

Focusing on the current advances in polymer science, this journal discusses the role of hydrogels that respond to external stimuli as well as the non-toxic degradation of biodegradable polymers; the idea of combining various polymers as a future advancement is also considered.

Pisal, . S. S., Paradkar, A. R., Mahadik, . R. K, Kadam, . S. S.(2004). Pluronic

gels for nasal delivery of Vitamin B12. Part I: Preformulation study.

International Journal of Pharmaceutics 270: 37–45

The preformulation study of pluronic based delivery of vitamin B12 is designed to improve delivery as well as compliance; the consideration of various parameters and functional excipients using the cold method.

Schinkel, . A. H. (1997). P-Glycoprotein, a gatekeeper in the blood–brain

barrier. Advanced Drug Delivery Reviews 36 (1999) 179–194

This journal investigates the ability of p-glycoprotein transporters to increase the amount of drug delivered to the CNS by using knockout mice models. They provide a means of optimizing pharmacotherapy for brain disorders as well as disorders elsewhere in the body.

Swamy, . N. G. N., Abbas,. Z. (2012). Mucoadhesive in situ gels as nasal drug

delivery systems: an overview. Asian Journal of Pharmaceutical Sciences, 7

(3): 168-180

Consideration of the various evaluation methods for in-situ polymeric gel formulations is given in this journal as well as their ability to provide a sustained and prolonged action of the drug incorporated.

Ugwoke, M. I., Agu , R. U., Verbeke , N., Kinget, R. (2005). Nasal

mucoadhesive drug delivery: Background, applications, trends and future

perspectives. Advanced Drug Delivery Reviews 57: 1640– 1665

This journal demonstrates the cutting edge intranasal delivery of poorly absorbed drugs as improved by utilizing mucoadhesive polymers which serve additionally as absorption enhancers while characterizing them to include their safety thereof.

Ur-Rehman,. T., Tavelin, . S., Gröbner (2011). Chitosan in situ gelation for

improved drug loading and retention in poloxamer 407 gels. International

Journal of Pharmaceutics 409: 19–29

The gellation characteristics of chitosan based delivery systems is evaluated as a targeting approach and studied using DSC and tube inversion. The dissolution analysis and the control over PH release by varying polymer composition are also considered in this journal as a solubilising technique/approach for optimizing the formulation.

Westerink, . M. A. J., Smithson . L. S., Srivastava,. N., Blonder,. J. Coeshott ,. C., Rosenthal, G. J. (2002). ProJuvantTM (Pluronic F127®/chitosan) enhances the immune response to intranasally administered tetanus toxoid. Vaccine 20: 711–723

As a chitosan and Pluronic F127 based polymeric device is developed for intranasal administration and discussed in this journal, the optimal loading showed a synergistic effect between the polymers and the drug incorporated on the immune system.

Yuan,. Y., Ying,. C., Li ,. Z., Hui-ping, . Z., Yi-Sha,. G., Bo,. Z., Xia, . H., Ling,. Z., Xiao-hui,. W., Li, . C. (2012) Thermosensitive and mucoadhesive in situ gel based on poloxamer as new carrier for rectal administration of nimesulide. International Journal of Pharmaceutics 430: 114– 119

This journal analyses the effect of a mucoadhesive polymer, the incorporated drug as well as PEG on the gellation temperature and the optimum release characteristics and gellation temperature thereof based on various percentages of the components.

Zhou, . M., Donovan, . M. D. (1996). Intranasal mucocilliary clearance of

putative bioadhesive polymers. International journal of pharmaceutics 135:

115-125.

Considering various mucoadhesive polymers, this journal analyzes the mucocilliary action of the nasal cavity and its ability to reduce drug absorption and compares this to a damaged nasal mucosa.