From Shrimp Shells to Brain Cells: Chitosan Nanoparticle Intranasal Delivery of Antimigraine Medication Sumatriptan Succinate

Chantelle Castelino & Kristen Arnold

Integrated Science Program, Class of 2022, McMaster University

SUMMARY

Migraines are the most common neurological disorder, affecting approximately 2.7 million Canadians in 2010/2011. While there is currently no cure, treatment options are available. Sumatriptan, an antimigraine medication, is available on the market as an oral tablet, subcutaneous injectable or nasal spray. With all three routes of administration, the drug's short plasma half-life of only two hours oftentimes necessitates recurrent doses. Subcutaneous administration has the highest bioavailability, but injections can cause bruising and bleeding which may discourage patients from this form of treatment. Through this literature review, the utilization of chitosan nanoparticles (CSNPs) as a delivery system for the intranasal delivery of sumatriptan succinate is discussed. Literature on sumatriptan, CSNPs and the limited literature combining the two was researched. To obtain a holistic understanding of the current mechanisms of treatment utilizing sumatriptan and how CSNPs will improve migraine treatment, primary and secondary literature was reviewed. The literature revealed that CSNPs allow for sustained drug release as a result of their mucoadhesive properties, over a period of approximately 24 hours, which will likely reduce the need for recurrent doses. Future clinical trials are necessary to investigate how CSNP delivery of sumatriptan succinate might enhance the quality of treatment for migraine sufferers. This research provides the potential for an effective, non-invasive treatment for migraines that could prove favourable to many, including those who currently struggle with effective treatment.

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INTRODUCTION

Pathophysiology of Migraines

Migraines are a common neurological disorder that cause severe, throbbing headaches, often presenting with nausea, loss of appetite, and increased sensory sensitivity to sound, light, and odours (Bolay, 2012). The trigemino-vascular system plays a key role in the pathophysiology of migraines and is comprised of peripheral and central structures of the trigeminal nerve as well as meningeal and cerebral blood vessels (Sokolov, Lyubashina and Panteleev, 2011). A migraine occurs when the trigeminal neurons and ganglion are stimulated, likely by cortical spreading depression (CSD). CSD is a self-propagating wave of neuronal depolarization that extends over the cerebral cortex and increases the cerebral blood flow (Pietrobon and Striessnig, 2003; Cui, Kataoka and Watanabe, 2014). The trigeminal fibers that innervate the meningeal and cerebral blood vessels stem from the trigeminal ganglion. Neuropeptides such as the calcitonin gene-related peptide (CGRP) and substance P (SP) are located within the trigeminal ganglion and are released when it is stimulated (Goadsby, 2012). Since the trigeminal afferent neurons innervate the meningeal blood vessels, the release of neuropeptides results in their vasodilation (Pietrobon and Striessnig, 2003). This causes the neurogenic inflammation of the meninges and dura mater, as well as other structural changes including plasma extravasation, mast cell degranulation, and platelet aggregation (Goadsby, 2012). As seen in Figure 1, the vasodilation produced by the release of CGRP further stimulates the meningeal afferents, resulting in more pain (Pietrobon and Striessnig, 2003). Moreover, a phenomenon known as sensitization contributes to increased pain during a migraine attack.

Chemical stimuli activate the trigeminal afferents and increase their sensitivity to physical stimuli such as coughing or sneezing. Chemical stimuli including protons, potassium ions, or inflammatory agents (serotonin, histamine, bradykinin, and prostaglandin E2) were used previously in a study to stimulate the rat dura mater (Strassman, Raymond and Burstein, 1996). When sensitization occurs, stimuli such as light and sound that are usually inoffensive cause a phenomenon known as allodynia (Pietrobon and Striessnig, 2003; Goadsby, 2012).

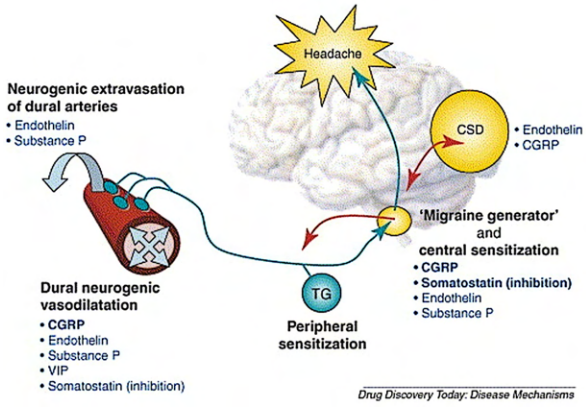

Figure 1 : Diagram illustrating the role of neuropeptides in the pathophysiology of migraines. Migraines are initiated with cortical spreading depression (CSD) which stimulates trigeminal ganglion. This triggers the release of neuropeptides including calcitonin gene-related peptide (CGRP) and substance P. This leads to the vasodilation of the meningeal blood vessels and the inflammation of the meninges and dura mater. The release of neuropeptides also results in sensitization, further stimulating the trigeminal nerves (Figure obtained from Just et al., 2006).

Evidence has shown an increase in the synthesis of serotonin and higher serotonin plasma levels during migraine attacks, indicating it plays a role in the pathophysiology of migraines. The axons of some serotonergic neurons project onto different structures of the trigemino-vascular system (Sokolov, Lyubashina and Panteleev, 2011). Two of the primary 5-hydroxytryptamine (serotonin) receptors are the 5-HT1B and the 5-HT1D receptors. When 5-HT1B receptors on the vascular wall are activated,

vasoconstriction occurs either indirectlyand directly, and stimulating these receptors may help induce exocytosis of CGRP and SP from trigeminal afferents (Sokolov, Lyubashina and Panteleev, 2011). On the other hand, 5-HT1D receptors are found presynaptically on the endings of the sensory trigeminal afferent fibers and are four times more common as 5-HT1B receptors. Their activation also leads to the inhibition of CGRP and SP through exocytosis modulation via synthesis inhibition, ultimately reducing the inflammation of the dura mater. Due to the critical role of these receptors in the pathophysiology of migraines, the study of 5-HT1B/1D receptor agonists has provided great insight into treatment options (Sokolov, Lyubashina and Panteleev, 2011).

Sumatriptan Background

Sumatriptan is one of the primary drugs currently used for the treatment of chronic migraines. It can be administered orally, rectally, subcutaneously and intranasally as the salt form, sumatriptan succinate (Derry, Derry and Moore, 2012). Although it is capable of traversing the blood brain barrier as a hydrophilic drug, it undergoes the first-pass effect when administered orally, where the concentration of the drug is significantly reduced. This causes an oral bioavailability of 15%, much lower as compared to subcutaneous administration, and in turn results in the need for higher doses (Hansraj, Singh and Kumar, 2015). The decreased bioavailability is largely due to pre-systemic metabolism occurring in the gut wall and liver. This is determined by a higher quantity of metabolite in the body following excretion. Approximately 62% of the administered dose is excreted following subcutaneous delivery, whereas only 37% is excreted following oral delivery. This can be explained by the incomplete absorption of sumatriptan following oral administration. The pharmacokinetics of sumatriptan vary based on the route of administration, as subcutaneous administration has a bioavailability of 96% (Lacey, Hussey and Fowler, 1995). In both cases the rate of absorption of sumatriptan into the system is rapid, although quicker for subcutaneous administration, explaining why the onset of pain relief is faster with subcutaneous treatment than oral treatment (Lacey, Hussey and Fowler, 1995).

The half-life for plasma elimination of sumatriptan is two hours for oral, subcutaneous, and current intranasal delivery, due to the body's rapid metabolism of the drug (Fowler et al., 1991). Many studies have investigated the need for additional dosing two hours following the first dose due to reoccurring symptoms (Dechant and Clissold, 1992; The Subcutaneous Sumatriptan International Study Group, 1991; Humphrey et al., 1991; Ferrari et al., 1994). Specifically, in a study conducted by the Oral Sumatriptan International Multiple-Dose Study Group (1991), 59% of the sumatriptan treatment group patients required the administration of a second dose due to persisting symptoms (Humphrey et al., 1991). The need for recurrent doses makes oral administration a suboptimal treatment option, further encouraging the investigation of intranasal treatment.

Mechanism of Action

Sumatriptan is an agonist of the 5-HT receptor and acts by vasoconstriction of the meningeal blood vessels. Although there are both pre- and postjunctional receptors involved in the pathophysiology of migraines, it is believed that sumatriptan works primarily through prejunctional mechanisms (Moskowitz and Cutrer, 1993). Sumatriptan is able to bind to the 5-HT receptor due to its similar chemical structure to serotonin, as seen in Figure 2. By binding to the prejunctional 5-HT1 receptors, it inhibits the release of certain neuropeptides, ultimately reducing the activation of the trigeminal nerve (Hansraj, Singh and Kumar, 2015; Dechant and Clissold, 1992). It binds with the highest affinity to 5-HT1D receptors, but also binds to 5-HT1B receptors with a lower affinity (Moskowitz and Cutrer, 1993). Moreover, it also functions by reducing neurogenic inflammation of the meninges and dura mater by inhibiting the release of

neuropeptides including CGRP, SP, and neurokinin A (Ferrari and Saxena, 1992).

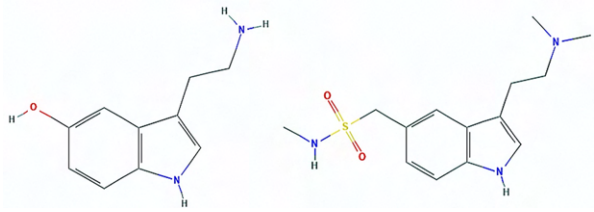

Figure 2: Chemical structures of serotonin (5-hydroxytriptamine) (left) and sumatriptan (right) (PubChem, 2020b; a)

DRUG AND DELIVERY SYSTEM RATIONALE

Migraines are the most common disabling neurological disorder, affecting an estimated 2.7 million Canadians in 2010/2011 (Weatherall, 2015; Ramage-Morin and Gilmour, 2014). Moreover, migraines fall within the top 10 causes of work disability in the world (Natoli et al., 2010). This disorder usually exists comorbidly with depression and its debilitating effects have a negative impact on various aspects of daily life, including education, sleep, and driving (Ramage-Morin and Gilmour, 2014). Despite the recognition of various targets to mitigate migraine attacks, there is currently no cure to the disorder (Purdy, 2010). Sumatriptan, a compound belonging to a class of drugs known as triptans, is an antimigraine medication that acts as a serotonin receptor agonist (DrugBank, 2020). Oral administration of sumatriptan results in low bioavailability, while subcutaneous administration has been reported to cause unpleasant local and general sensations following injection (Bussone and Rapoport, 2010, p.36). As such, there is a need to further investigate the potential for intranasal drug delivery of sumatriptan as a means of treating migraines.

Within the realm of drug delivery, nanoparticles (NP) have recently gained popularity, largely due to their ability to target specific sites and minimize the adverse effects of drugs (Gulati, Nagaich and Saraf, 2013). NPs can be defined as "submicron colloidal drug carrier systems which are composed of natural or artificial polymers ranging in size between 10 and 100 nm" (Gulati, Nagaich and Saraf, 2013). This field of technology is particularly promising for the delivery of drugs which experience reduced bioavailability through oral administration, or those which have trouble passing many of the body's barriers, including the blood-brain barrier (BBB) (Teleanu et al., 2018). NPs are primarily used to carry drugs that have low selectivity, high toxicity, and poor stability (Wang et al., 2011). This technology has the potential to conquer many of the limitations associated with the treatment of the most common neurological disorders: migraines. This literature review will focus on the use of CSNPs in the intranasal delivery of sumatriptan succinate, an antimigraine medication, to minimize the need for recurrent doses through sustained drug release. Sumatriptan succinate was primarily chosen because of its wide variety of delivery systems, which allowed for the comparison of our proposed system with current available systems. The choice of NP was largely due to three factors: low-cost availability, low toxicity, and various desirable physical and chemical properties.

DRUG DELIVERY SYSTEM BACKGROUND

History and Development of Chitosan Nanoparticles

CSNPs are a relatively new technology, gaining attention within the past few decades. In 2005, Wu et al. successfully constructed chitosan-TTP stable cationic NP complexes loaded with ammonium glycyrrhizinate. Then, in vitro and in vivo studies investigated the interaction of CSNPs with ocular surface epithelial cells (Salamanca et al., 2006). In 2013, a study demonstrated efficacious intranasal delivery of sumatriptan succinate via CSNPs in vitro using goat nasal mucosa and showed a drug release of 76.6 ± 1.3% within 28 hours (Gulati, Nagaich and Saraf, 2013). CSNPs have since been widely exploited for drug delivery, having

applications realized for antitumor drug delivery—particularly for the cytotoxic drug doxorubicin as delivery via NPs reduce its adverse side effects (Zhao et al., 2018). CSNPs have also demonstrated success in the delivery of proteins and peptides to avoid degradation by gastric enzymes (Zhao et al., 2018). The historical developments made through the research of CSNPs and more recent developments in its combination with sumatriptan have led to the current proposal of advancing the treatment of migraines through a CSNP delivery system.

Preparation of Chitosan

Chitosan (Figure 3a) is a modified biopolymer obtained by N-deacetylation of chitin (Figure 3b), a natural polymer that is abundantly found in various biological materials, but primarily crustacean shells (Divya and Jisha, 2018). Within the pharmaceutical industry, chitosan has great potential as a drug carrier; it's remarkable mucoadhesivity, or the adhesion between a material and a mucosal surface, makes it particularly applicable in facilitating the transport of therapeutic agents across mucosal membranes (Xu and Du, 2003). An additional property of chitosan that makes it desirable for drug delivery is that it dissolves in organic acids (Gupta, Jassal, and Chand, 2016). This property is necessary for the CSNP dissolution in the nasal cavity. Its solubility in organic acids is negatively correlated with molecular weight; as molecular weight increases, solubility decreases. The degree of deacetylation affects molecular weight, which in turn affects solubility (Gupta, Jassal, and Chand, 2016). This feature allows for the desired solubility to be obtained through adjustment of molecular weight via deacetylation. Drug loading into the NP can occur either during particle preparation, which maximizes drug encapsulation, or after particle formation (Yang and Hon, 2010). The process of chitin modification follows four steps: deproteinization, demineralization, decolouration and deacetylation (Dutta, Dutta and Tripathi, 2004). Deproteinization of chitin is achieved by extraction using sodium hydroxide and demineralization is achieved in a similar manner through extraction with hydrochloric acid solution (Dewi, Mudjijono and Angwar, 2014). Decolouration is achieved through chitin bleaching using an acetone/ethanol mixture to remove pigments, and finally, the modified chitin is deacetylated through concentrated sodium hydroxide treatment (Dewi, Mudjijono and Angwar, 2014).

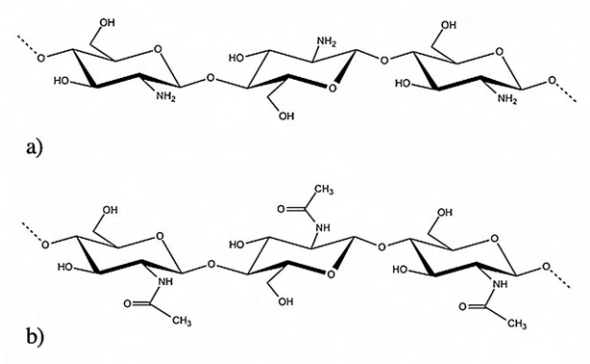

Figure 3: The chemical structures of chitosan (a) and chitin (b) (Rinaudo and Perez, 2019).

Synthesis of Chitosan Nanoparticles

CSNPs can be synthesized through various processes, where one common method of synthesis is ionotropic gelation (Gulati, Nagaich and Saraf, 2013). This technique involves dissolving chitosan in acetic acid and using a cross-linking agent such as sodium tripolyphosphate (TTP) (Gupta, Jassal, and Chand, 2016). Sodium TPP is a popular cross-linking agent due to its non-toxicity and electrostatic interactions with cationic chitosan (Yang and Hon, 2010). Through ionic interactions between oppositely charged groups, the positive amino groups on the chitosan interact with negatively charged groups of sodium TPP, as seen in Figure 4 (Gulati, Nagaich and Saraf, 2013). Evident in Figure 3a, chitosan has many hydroxyl (-OH) and amine (-NH2) functional groups, which react with the cross-linking agent to create the NPs (Rizeq et al., 2019). Charge matching is required to allow the TPP anions to cross-link through electrostatic forces and through this process, the reactants self-assemble into NPs with an overall positive charge (Rizeq et al., 2019). This characteristic is of particular importance when assessing the

mucoadhesivity of CSNPs; however, various factors of the preparation process affect the resulting CSNPs. It was found that increasing the cross-linking agent leads to an increased absorption capacity of the CSNPs (Gupta, Jassal, and Chand, 2016). This finding demonstrates the potential modifications that can be implemented in the synthesis process of CSNP formation to alter properties, such as absorption capacity, of the NPs.

subcutaneous, and current intranasal delivery is the low plasma half-life of approximately two hours, oftentimes resulting in the need for recurring doses or the risk of headache recurrence (Fowler et al., 1991). CSNPs have the ability to extend the duration for which sumatriptan succinate can remain in the body following administration, making the drug ideal for this form of biotechnology.

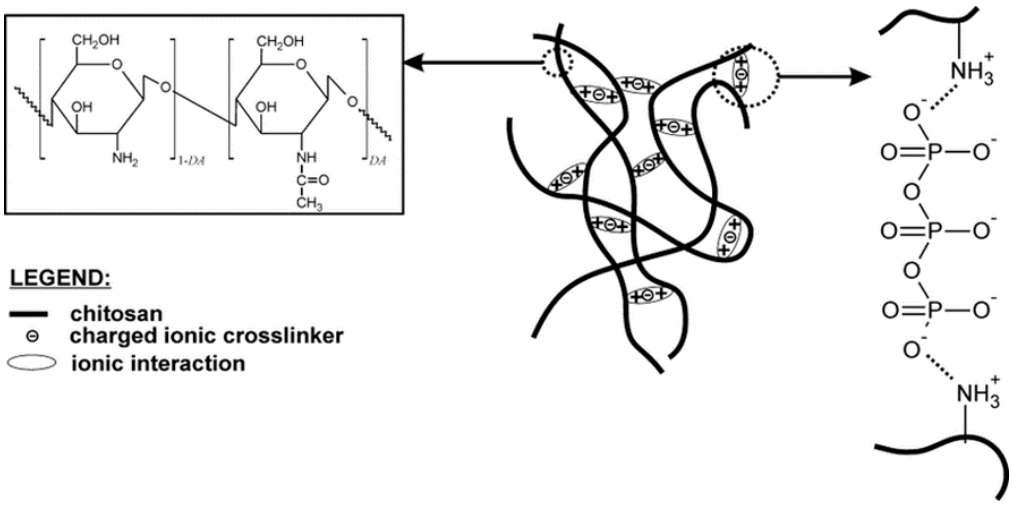

Figure 4: Diagram illustrating the formation of CSNPs. Ionic interactions occur between positively amino groups on chitosan and negatively charged TPP, the ionic crosslinker (Gierszewska and Ostrowska-Czubenko, 2016).

PROPOSAL

Sumatriptan Applicability to Chitosan Nanoparticles

There are various properties of sumatriptan succinate and CSNPs that make their combination an ideal form of drug delivery, one reason being that sumatriptan succinate is freely soluble in water, allowing for large amounts of the drug to be entrapped during the CSNP formulation process (Gulati, Nagaich and Saraf, 2013). This technology also has the potential to avoid many of the adverse effects currently experienced. The limited bioavailability of sumatriptan when administered orally leads to higher doses relative to subcutaneous administration to compensate for the loss of drug by the first-pass effect. Despite this, subcutaneous administration has increased adverse effects compared to oral administration, such as transient stinging and bruising and in some cases, bleeding at the site of injection (Brar and Saadabadi, 2020). However, the main downfall to oral,

While sumatriptan is FDA approved for intranasal delivery, the current intranasal delivery system—a nasal spray—does not utilize any drug carriers. Instead, it is simply the aerosol form of the drug (Casettari and Illum, 2014). One of the primary objectives of utilizing CSNPs for this drug's intranasal delivery is to implement its sustained release and, as a result, avoid the need for recurrent drug dosing following the initial dose. The nasal sumatriptan product currently available on the market has a very similar pharmacokinetic profile to oral sumatriptan which have a respective bioavailability of only 15.8% and 17% (Illum, 2003; RxList, 2020). The introduction of CSNPs will act as a nasal absorption enhancer, thereby predicted to increase the drug's current intranasal bioavailability.

Sumatriptan succinate dissolves freely in water, allowing for easy encapsulation during the formulation process. The current form of intranasal delivery of

sumatriptan (IMITREX Nasal Spray) comes in single doses of 5, 10, or 20 mg, administered through one nostril (RxList, 2020). Repeated doses can be administered after two hours, and 40 mg of drug should not be exceeded within 24 hours. Clinical trials will be required to determine the efficacy of the drug when delivered through the CSNPs, and whether the effect of the sustained drug release does in fact minimize the need for recurrent doses. The current IMITREX Nasal Spray is generally well tolerated at all doses and shows little adverse effects (RxList, 2020); however, intranasal drug delivery can be uncomfortable for some individuals and can, in few cases, cause nasal cavity discomfort (2.4% in placebo, 3.8% in IMITREX 20 mg) or throat discomfort (0.9% in placebo, 2.4% in IMITREX 20 mg) (RxList, 2020). Clinical trials will also evaluate whether use of CSNP in sumatriptan delivery will minimize these symptoms, as the entire dose is not being released simultaneously but rather over a time period of approximately 24 hours. CSNPs also exhibit low toxicity, however clinical trials will further investigate the toxicity of intranasal delivery (Nagpal, Singh and Mishra, 2010). The proposed CSNP sumatriptan system will utilize the Optinose Exhalation Delivery System, which incorporates exhaled breathing into the drug delivery system (Optinose US, Inc., 2019). The patient will simultaneously exhale and press a button on the device to inject the spray containing the sumatriptan succinate loaded-CSNP into the nasal cavity, illustrated in Figure 5. This novel delivery system is ideal as it transports the drug deep into the nasal cavity and reduces drug loss into the throat.

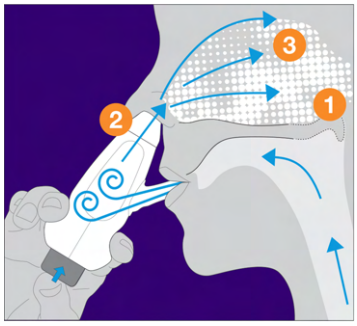

Figure 5: Illustration of the sumatriptan succinate-loaded CSNP delivery system. The user exhales into the device, minimizing drug escape into the throat and placing the drug deep into the nasal cavity (Optinose US, Inc., 2019).

Advantages of Chitosan Nanoparticles

Chitosan is commonly used as a drug carrier in the pharmaceutical industry due to its strong mucoadhesivity, and because it facilitates the transport of large molecules through mucous membranes (Xu and Du, 2003). The adhesivity of chitosan results from its amino and carboxyl groups which can form hydrogen bonds with the glycoproteins present in mucous membranes located in the nasal cavity. Moreover, the proteins of the mucous membranes are negatively charged, which allows a prolonged attraction of the membrane to the positively charged chitosan molecule (Figure 6). This allows for longer drug retention and a slower, continuous drug release (Wang et al., 2011). The mucosa covering the nasal cavities is only two to four millimeters thick, and the nasal epithelium located just beyond the mucosa is highly permeable, with only two layers of cells separating the nasal lumen from the blood vessel network (Chaturvedi, Kumar and Pathak, 2011).

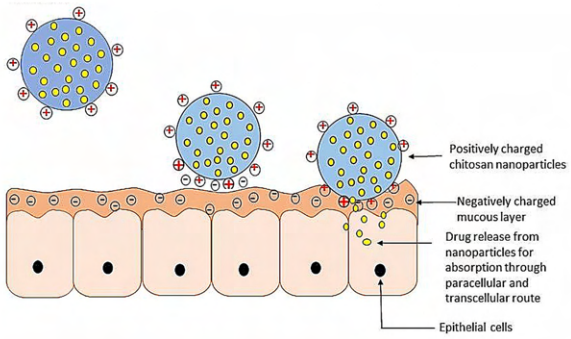

Figure 6: Interaction of a loaded chitosan NP with the mucous later and their opposing charges (Mohammed et al., 2017). The charged chitosan nanoparticles approach the mucous layer as the oppositely charged particles attract one another, leading to eventual drug release and adsorption.

The numerous benefits of CSNPs seem to outweigh the known deficits of the delivery system in discussion; however, there is limited research into the deficits of this technology. It has been found that CSNPs are more cytotoxic than chitin polymers, suggesting that the low toxicity of chitin cannot be used to justify the use of CSNPs. Degree of deacetylation also affects the cytotoxicity of the polymer, which must also be considered when implementing this technology. Further research is required to gain a better understanding of the risks associated with this technology (Jesus et al., 2020). Overall, the ability for CSNPs to release sumatriptan in a sustained, continuous manner will overcome the current difficulties that patients face with intranasal drug delivery; namely, the need for recurrent doses.

Sustained Drug Release

Drug release from CSNPs depends on the route of administration. In nasal drug delivery, the delivery system must be able to cross the nasal membrane; in CSNP delivery, this is overcome by the development of a mucoadhesive system (Mohammed et al., 2017). The nasal mucosa is a primary candidate for CSNP delivery as it is highly permeable and allows for great access to the absorption site of the drug (Fernández-Urrusuno et al., 1999). CSNPs are able to widen the tight junctions located between epithelial cells in the nasal cavity, releasing the drug through bioadhesion with the epithelial layer without causing significant damage to the nasal mucosa (Zhang et al., 2008). Through its interaction with the nasal mucosa, chitosan can retain its formulation for longer time periods within the nasal cavity, contributing to slow drug release (Casettari and Illum, 2014). The release of the drug that is encapsulated in CSNPs is largely pH dependent. In dilute acidic conditions, chitosan dissolves at a pH lower than 6.1 to 6.3 (Collado-González, González Espinosa and Goycoolea, 2019). The average pH of the anterior nasal cavity is 6.40 and the average pH of the posterior nasal cavity is 6.27, however nasal cavity pH is largely dependent on the individual and varies considerably (Washington et al., 2000). The delivery system under development will be administered in solution of around 6.3 pH so as to not dissolve the CSNPs prior to delivery. An in vitro study on sumatriptan succinate release from CSNPs in a phosphate buffer saline goat nasal mucosa at pH 5.5 found an initial burst release of 4.4% and sustained release of 76.7% for 28 hours thereafter (Gulati, Nagaich and Saraf, 2013). The nasal cavity pH can be decreased using buffers of around 0.13M, which could be implemented if an average nasal cavity pH of 6.3 is too high to achieve the desired CSNP sustained release rate, which will be investigated further in a clinical trial setting (Washington et al., 2000).

FUTURE DIRECTIONS

The future of CSNPs as a biomedical application, particularly for treatment of neurological disorders, is extremely promising. These NPs have recently been shown to improve oral delivery of sumatriptan succinate by assisting in the drugs passage beyond the BBB (Hansraj, Singh and Kumar, 2015). Their specific application within the realm of intranasal drug delivery has been investigated at a novel level. For example, CSNPs have shown efficacy in intranasal delivery of olanzapine, a drug used in the management of disorders such as depression and schizophrenia (Aderibigbe and Naki, 2019). Using pigs as an animal model system, CSNPs have also found use in the intranasal delivery of influenza vaccine, opening up the door for novel delivery methods of this vaccine in humans (Dhakal et al., 2018). Interestingly, the application of NPs to various fields has been growing rapidly and extends far beyond the realm of biomedicine.

As a whole, nanotechnology has a wide range of applications, with many being within the realm of cancer therapy and diagnosis. Recently, studies have investigated the use of NPs for early detection of cancers through their ability to attract cancer biomarkers (Zhang et al., 2019). Applications of CSNPs beyond the pharmaceutical industry utilize CSNPs adsorption, or its ability to hold molecules as a thin film surrounding the NP. Through further research into the efficacy of CSNPs in intranasal delivery of

sumatriptan succinate, its potential as a deliverer of antimigraine and other neurological disorder medications will be further investigated to advance our understanding of nanotechnology.

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