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REVIEW ARTICLE

Thermoreversible insitu gel for nasal drug delivery

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ABSTRACT

The conventional formulation route of administration is having the problem of drainage of instilled formulation, poor patient compliance as in the case of vaginal and rectal delivery system. The blurred vision and irritation to mucosa is observed in the case of ocular and nasal delivery also a big problem. Thus these problems force the researchers to find out another way to administration for such drugs. Several researchers are working to attain the therapeutic drug concentration at the intended site of action for sufficient period of time to elicit the pharmacological action. The most acceptable way for the administration of such drug has attained by formulating mucoadhesive and thermo reversible gel formulation for several drugs .The present work is focused to collect the reported researches for such drugs with special focus on Sertraline hydrochloride.

Key words: Therapeutic drug, Mucoadhesive, Thermoreversible, Sertraline HCL

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INTRODUCTION

Sertraline HCL is a potent selective serotonin (5-hydroxy tryptamine,5-HT) reuptake inhibitor which is administered orally in the treatment of major depression. Being a SSRI the most common adverse effects are gastrointestinal disturbances such as nausea, dry mouth, constipation, diarrhea, decreased appetite, flatulence, vomiting, or pharynx disorder and dyspepsia. It undergoes extensive first pass metabolism with a daily dose of 25-100mg (Rajendran, 2016; Parikh, 2005). The oral bioavailability of Sertraline is about 45% because of extensive first pass metabolism in liver and gut wall. The nasal drug delivery system have been researched for use in systemic drug delivery system because of high permeability of the nasal mucosa as well as avidness of first pass metabolism, and other side effect. Thermoreversible mucoadhesive insitu gel and thermo reversible gel system of drug administration for several drugs including Sertraline HCL has been reported by several researchers on different animal models(Bhimavarapu *et al.,* 2013; Prajapati and Goyal, 2013),the present work is focused on the available literature review of certain antidepressant drugs with special focus on Sertraline HCL. The formulation and evaluation of in-situ mucoadhesive nasal gel of venlafaxine hydrochloride has been reported to show the prolonged residence of drug formulation in the nasal cavity. In this study the researchers planned to formulate insitu nasal gel of venlafaxine hydrochloride for systemic delivery. Here they used xanthamgum as natural mucoadhesive polymer to formulate nasal insitu gel of venlafaxine hydrochloride.

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For the sustain release to reduce mucociliary clearance. The carbopol 940 gel was used as the key ingredient for the conversion of formulation. The 32 full factorial design was used to study effect of varying concentration of independent variables carbopo l940(xi) and xanthamgum (x2) on viscosity and mucoadhesive strength and dependent variables invitro drug release. From the result 32 full factorial study they concluded that the amount of xanthamgum and carbapol 940 significantly affect the dependent variables such as percentage cumulative drug, release, mucoadhesive strength, viscosity. They reported by using this way of delivery of drug optimum point can be reached in the shortest time with minimum effects (Manohar *et al.,* 2015). Specifically in case of sertraline hydrochloride the oral bioavailability enhancement study has been given by nanoprecipitation and solvent diffusion techniques for stable nanosuspension. The nanosuspension has been prepared to separately by different methods like preparation of nanosuspension by nanoprecipitation. In this method researchers from the nanosuspension of sertraline hydrochloride by the nanoprecipitation method with various ratios of polymers and surfactants. Precipitation of nanosuspension by solvent diffusion method was used by researchers as an another method .The invitro dissolution study was performed as per the USP paddle method in 0.1N HCL. The crystalline structure of drug were also studied, the molecular interaction, morphology, and particle size of nanosuspension were also mitigated. In their result they reported that the nanoprecipitation method with drug and PVP K25 (1;1) showed its potential in the enhancement of the drug release rate (99% in 45 min.). The synergistic effects of reduction of drug crystalline and particle size were reported to be increase in the dissolution rate of SRT HCL by providing a

stable nanosuspension. The again found that in the in vivo study the maximum plasma concentration and area under the curve values of selected nanosuspension in rabbits were greater than that of the commercial tablets (tablet potiga 50 mg) (Pawar *et al.,* 2016). Another drug for which the formulation and evaluation of nasal insitu gel has been reported is losartan potassium. The formulation formed was performed with the aim to improve its nasal bioavailability,here the researchers incorporated losartan potassium into the blends of thermo reversible polymer carbopol 934P in the form of in situ gel by cold technique to reduce the mucociliary clearance with the thought that it will increase the contract of formulation with nasal mucosa to which was meant to improve the absorption of which in turn gave good absorption nasal mucos(Gondkar *et al.,* 2015). The development and in vitro evaluation of mucoadhesive buccal patches of sertraline HCL has been reported. The mucoadhesive buccal patches of antidepressant patches of sertraline HCL was prepared by solvent casting using eudragit and HPMC E15 LV. The patches were prepared by taking weighed quantity of polymer and by gradually adding it to continuous stirring to one third of the required volume of distilled water (60 ^{o}C). Finally they made the final volume by adding cold water and added the glycerin as plasticizer in the polymeric solution. Then they prepared gel and left it overnight at room temperature to obtain bubble free film. Then after pouring the gel in the plastic rings and allowed it to stick. The characterization of the prepared gel was done by gelation temperature, PH, Drug content, Gel strength, Permeation studies, Stability studies etc. In the results researches reported that as the concentration of carbopol increase there was decrease in gelation temperature. The PH of all the formulation was reported between the nasal PH ranges (4.5-6.5) with is in tolerable range in contact with nasal tissue. The drug contacts of formulation between 98.28-101.08 % were reported. They found that as the level of carbopol increase mucoadhesive strength also increases.

They found that the increase in viscosity gel increased with temperature and it was also that all liquids were in liquid state at room temperature. The release of drug was reported to be up to 99.65% in 80(480) min during this .They also found that the biopolymer and their used composition for their insitu gel preparation gently affect the drug release. The floor of petric dish and to dry at 40OC in ovan after this they cut the prepared patches into 1×1cm2 and packed in suitable wax paper for further evaluation. After this the researchers evaluated the prepared patches for their weight variation, thickness, folding endurance, surface PH, swelling index ,moisture uptake studies, moisture absorbance studies for drug excipient compatibility testing. In their results they found that the optimized patches showed the drug release and indicated non-ficikian release kinetics and diffusion as chain relaxation mechanism. From the whole study researches concluded that all the prepared patches are effective and showed excellent sustained drug release (Bhimavarapu *et al.,* 2013). Thian-Yuan Zhang *et al* reported preparation of sertraline loaded chitosan nanoparticles and the pharmacokinetics studies to prevent the secretion of the drug in the milk of breastfeeding mother to infants. In this they aimed to alter the biodistribution of sertraline by loading the drug into chitosan nano of articles. In their result they demonstrated an effective way to load the water soluble sertraline into nanoparticles, and keep the size around 200 nm. In their in vivo results demonstrated the difference of sertraline concentration in plasma after the intravenous injection through marginal ear vein in rabbits. Their results indicated that the nanoparticles encapsulation may change the biodistribution of sertraline and after a window for breastfeeding (Zhang *et al.,* 2016). The formulation development of sertraline hydrochloride micro emulsion for intranasal delivery has been reported. The research was performed with the objective to improve the solubility of sertraline hydrochloride by formulating microencapsulation containing STH to accomplish rapid onset of action and to bypass the first pass metabolism. Researchers developed micro emulsions system with capmul MCM as oil phase, labrosol as surfactant and transcutolP as co-surfactant for intranasal delivery of STH. The microencapsulation (SME) of STH was prepared by titration method after characterization of phase behavior and solubilization capacity of the developed micro emulsion system. Researchers evaluated the prepared micro emulsion for globule size drug contents, nasal ciliotoxicity, percentage transmittance, PH and viscosity. They performed their invitro studies for nasal absorption on goat nasal mucosa. In their result the reported that drug showed high solubility of 117 mg/ml in a micro emulation containing 22.2% camul MCM, 44.5% (w/w) surfactant/ co-surfactant(labrasol transcutolP at 2:1) and 33.3% water. In their invitro studies the nasal absorption was found to be 66.07± 6.78% from SMF2. From their study they concluded that intranasal micro emulsion of STH may be beneficial for the treatment of depression (Kumar, *et al.,* 2009).

Similarly the evaluation of Thermoreversible mucoadhesive insitu gel for intranasal delivery of naratriptan HCL has been reported. The drug is used for migraine headaches but its use is limited due to its poor bioavailability. To solve the problem the researchers tried to give an alternate system of drug delver hence selected the above mentioned work. For their work they formulated the gel using poloxamer 407 as Thermoreversible polymer and carbopol p 934 as mucoadhesive polymer then they formulated gel and characterized for gelation temperature, gel strength, mucoadhesive strength, viscosity, invitro drug release and ex-vivo permeation study using sheep nasal mucosa. In their research they found that the release rate is directly proportional to the ccentration of carbopol 934 where as poloxamer 407 was reported to reduce the rate of drug release. From histopathological study of sheep nasal mucosa they reported no signs of damage to columnar epithelial cells from this they concluded nontoxic nature of the formulated gel. More over the stability studies performed by them as per ICH guidelines, they reported the stability of the gel (Shelke, *et al.,* 2015). Again in one more similar research reported by different researchers on sumatriptan.

The Thermoreversible mucoadhesive gel for nasal delivery of the drug. The researchers used Thermoreversible polymer Pluronic F127 and mucoadhesive polymer Carbopol 934P. They modulated the fermutions to have gelation temperature below 34OC to ensure gelation at physiological temperature after intranasal administration. Researchers were keeping on the determination of gelation temperature by physical appearance as well as by rheological measurement for this. They decreased the gelation temperature of formulation by addition of carbopol. In their result they found the significant increase in effective permeation coefficient by using sheep nasal mucosa. By this they found that effective permeation coefficient could by significantly used by using in-situ gelling formulation with carbopol concentration 0.3% or greater and histopathological examination detected any damage during in-vitro permeation studies.

They concluded that thePF127 gel formulation of Sumatriptan with in-situ gelling and mucoadhesive properties with increased permeation rate which promising for prolong nasal residence time and nasal absorption(Majithiya, *et al.,* 2006). Swatantra K.S Kushwaha (2011) reported advances in nasal trans- mucosal drug delivery. In their study they added the mechanism of nasal absorption. They represent two types of mechanism.

a. First mechanism
b.Second mechanism

They also mentioned the different factors affecting the characteristics of nasal drug delivery, formulation factors, physiological factors, challenges and opportunities for nasal delivery system and current approaches for nasal permeation enhancement (Kushwaha *et al.,* 2011) . Chein., *et al.* (1989). He gave nasal systemic drug delivery and also Gopinath et al.(1978)added target site of intranasally sprayed substances and their transport across the nasal mucosa both the studies also mentioned the advantages and disadvantages of nasal absorption(Chain *et al.,* 1989). Upendra C.Galgatte., *et al.* (2013).has given development of in situ gel for nasal delivery: design, optimization, in vitro and in vivo evaluation.In their study they proved that in situ gel is suitable for administration of sumatriptan succinate through nasal route. The ease of administration coupled with less frequent administration enhances patient compliance(Galgatte *et al.,* 2014) . Singhvi I. *et al.* (2000). Developed UV spectrophotometric and HPLC method for estimation of sertraline HCL in pharmaceutical preparation. The UV spectrophotometric method is based upon determination at 441.5 nm using chloroform as a solvent. Estimation was carried out for HPLC method on an inertsil c18 column (250 mm×4.6 mm I.D) with a 80:20 (v/v) mixture of Methanol: Acetate buffer as mobile phase. The flow rate 1ml/ min and the analytes are monitored at 220 nm) (Gorle *et al.,* 2017).

Spencer EP., *et al.* (1996). Developed RP-HPLC method for simultaneous estimation of sertraline and nor sertraline in pharmaceutical preparation. These two pharmaceuticals was carried out on an Spherisorb c18 column (150 mm ×4.6 mm I.D) with a 19:1 (v/v) mixture of Methanol:Water as mobile phase. The flow rate 1ml/ min and analytes are monitored at 215 nm. Ashish Gorle., *et al.* (2017).has reported a possible way to improve the therapeutic effectiveness of levetiracetam via nose to brain.In their result they form an excellent mucoadhesive strength of formulation which did not showed any remarkable damage to nasal mucosa and retained good stability over the period of 90 days . And they added that the formulation are safe with respect to nasal administration and could be utilized effectively in management of epileptic disorder(Gorle *et al.,* 2017). Patel R. *et al.* (2009). Developed RP-HPLC method for simultaneous estimation of Alprazolam and Sertraline in pharmaceutical preparation. These two pharmaceuticals was carried out on an ODS Nucleosil C18 **(**150 mm ×4.6 mm I.D) with a 50:50 (v/v) mixture of Acetonitrile:Phosphate buffer as mobile phase.The flow rate 1 ml/min and the analytes are monitored at 230 nm .

REFERENCES

Bhimavarapu,R.D., et al.,2013. Development and in vitro evalution of mucoadhesive buccal patches of sertraline HCL. *American Journal of Advanced Drug Delivery*,1(3): 313-322 www.ajadd.co.uk.

Chain, Y.W., *et al.,* 1989.Nasal systemic drug delivery. Dekker., 1-77.

Galgatte, U.C., Kumbhar, A.B., Chaudhari, P.D. 2014. Development of in situ gel for nasal delivery: design, optimization, in vitro and in vivo evaluation. *Drug Deliv.,* 21(1) : www.tandfonline.com/loi/idrd20.

Gondkar,S.B., Kakad, J.K. and Saudagar, R.B. 2015.Formulation and Evaluation of Nasal In-Situ of Losartan Potassium. *International Journal of Universal Pharmacy and Bio Sciences.,* 4(4): 34-57 www.ijupbs.com.

Gorle, A., Rathod, N., More,A. 2017. A possible way to improve the therapeutic effectiveness of levetiracetam via nose to brain. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*., 8(2): 2258-22690.

Kumar, A. *et al,*. 2009. Formulation development of sertraline hydrochloride microemulsion for intranasal delivery. *International Journal of Chem Tech Research.,* 1(4): 941-947.

Kushwaha, S.K.S., Keshari, R.K., Rai, and A.K. 2011. Advances in nasal trans- mucosal drug delivery. *Journal of Applied Pharmaceutical Science.,* 1(07): 21-28 www. japsonline.com.

Majithiya, R.J. *et al.,* 2006. Thermoreversible-mucoadhesive Gel for Nasal Delivery of Sumatriptan. *AAPS PharmSciTech.,* 7(3): 1-7 www.aapspharmscitech.org.

Manohar, S.D., Pakhale, B.A., Saudagar. R.B., 2015. Formulation and evaluation of in -situ mucoadhesive nasal gel of venlafaxine hydrochloride. *International Journal Of Institutional Pharmacy And Life Science.,* 5(4): 185-198 www.ijipls.com.

Parikh, D.K. 2005. Feasibility of transdermal delivery of fluoxetine. *AAPS Pharm Sci Tech.,* 6: E144-1149.

Pawar, A.R., Choudhari, P.D., Nidhane, A.B., 2016. Oral Bioavailability Enhancement of Sertraline Hydrochloride by Nanoprecipitation and Solvent Diffusion Techniques for Stable Nanosuspension. *Asian Journal of Pharmaceutics.,* 10(3).

Prajapati, N.B. and Goyal, A. 2013. Thermoreversible mucoad hesive insitu gel:A review. *International journal of Innovative Drug Discovery.,* 3(2):67-84 www.ijidd.com.

Rajendran, V. 2016. Effect of noisome in the transdermal delivery of antidepressant sertraline hydrochloride. *Journal of Scientific and Innovative Research*., 5(4): 138-148 www.sirjournal.com.

Shelke,S., *et al.,* 2015. Formulation and evaluation of Thermoreversible mucoadhesive in-situ gel for intranasal delivery of naratriptan hydrochloride. *Journal of Drug Delivery Science and Technology.,* 238-244 www. elsevier.com/ locate/jddst.

Zhang, T.Y., *et al.,* 2016. Preparation of sertraline-loaded chitosan nanoparticles and the pharmacokinetics studies.African *Journal of Pharmacy and Pharmacology*, 10(3): 26-33 DOI:10.5897/AJPP2013.3772.

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