
Niosomal Sumatriptan Succinate for Nasal Administration

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Niosomes of sumatriptan succinate were prepared using lipid hydration method. The prepared niosomes were evaluated for entrapment efficiency, size analysis and *in vitro* release studies. Further, the niosomes were evaluated for nasal absorption using an *ex vivo* animal model. The entrapment efficiency was found to be $57.9 \pm 0.96\%$. The niosomes released 58.71% of sumatriptan succinate over a period of 6 h and 78.1% of the drug was absorbed from the nasal mucosa *ex vivo*.

Niosomes (non-ionic surfactant based vesicles) are formed from the self assembly of non-ionic amphiphiles in aqueous media resulting in closed bilayer structures. These structures are analogous to phospholipid vesicles (liposomes) and are able to encapsulate solutes, are osmotically active and stable¹. The low cost, greater stability and resultant ease of storage of non-ionic surfactants² has led to the exploitation of these compounds as alternatives to phospholipids. The self assembly of non-ionic surfactants into vesicles was first reported in the seventies by researchers in the cosmetic industry³ but have since being studied as drug targeting agents.

Sumatriptan succinate is a potent and selective 5-hydroxy tryptamine receptor agonist⁴. Chemically it is 3-(2-(dimethylamino)ethyl) N-methyl-1H-indole-5-methylsulphonamide butane-1,4-dionate (1:1). It is indicated in the treatment of acute migraine attacks with or without aura. A single dose of 100 mg produces complete relief from headache in 50-73% of attacks within 2 h of treatment. However, oral bioavailability is poor with only 14 % of the dose reaching systemic circulation. This is likely due to extensive presystemic clearance on first pass.

Nasal route, due to its easy access, can be a probable alternate route to deliver drugs that have poor oral bioavailability or for those that cause gastric irritation.

Nasal route of administration would also circumvent the presystemic metabolism thus increasing the bioavailability of the drugs. In addition, due to the presence of microvilli and high vasculature, the absorption can be expected to be faster compared to oral route. Drugs are administered intranasally using many delivery systems such as sprays⁵, insufflations⁶, nebulizers⁷, gels⁸, microspheres⁹ and liposomes¹⁰. A number of surfactants have been reported to enhance the absorption of drugs through the nasal mucosa to a level significant to achieve their systemic effects¹¹. Niosomes, being vesicles formed by self assembly of non-ionic surfactants, can be expected to enhance the permeation of the active drug moiety through the nasal mucosa. So in the present study, sumatriptan succinate, a 5-HT agonist was encapsulated in non-ionic surfactant vesicles (niosomes) and evaluated for the absorption of it through the nasal mucosa using an *ex vivo* animal model described by Hussain *et al*¹².

Sumatriptan succinate was a generous gift sample from M/s. Natco Pharmaceuticals Ltd., Hyderabad. Span 60, cholesterol, dicetyl phosphate and sephadex G-50 were purchased from Sigma Chemical Company, St. Louis, USA. All other chemicals were of analytical grade and were used as procured.

Niosomes were prepared by adopting the procedure of Azmin *et al*³. Span 60 (47.5 mg), cholesterol (47.5 mg) and dicetyl phosphate (5 mg) were dissolved in 10 ml of diethyl ether in a round bottom flask. The solvent

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was evaporated under reduced pressure at a temperature of about 60° using rotary evaporator, to obtain a thin uniform layer of solid mixture deposited on the wall of the round bottom flask. This film was hydrated by adding 10 ml of phosphate buffer saline (pH 7.4) containing 25 mg of sumatriptan succinate in divided quantities and intermittently mixing on a vortex mixer at about 50° until a good dispersion of the mixture was obtained. Sonic dispersion was carried out using a probe sonicator (Escco, Model EUC 300) for 30 s at 1 min interval for a total sonication of 3 min. After sonication, the suspension was maintained at room temperature for 2 h to allow niosomes to form and seal.

The size of the vesicles was determined by light microscopy using calibrated eye piece micrometer. Entrapment efficiency of the vesicular carriers was determined by column chromatography using Sephadex G-50. Niosomes which eluted out first could be identified as slightly dense, white opalescent suspension. Collection was continued till no turbidity was seen. Elution was continued again, the untrapped sumatriptan succinate was collected to determine the entrapment difference. Elution was taken complete when no difference in absorption could be detected between the eluent and normal saline. The absorbance of free sumatriptan succinate was measured after suitable dilution at 227 nm using a double beam UV spectrophotometer (UV 240 Graphicord, Shimadzu, Tokyo).

Niosomes containing known amount of drug were subjected to *in vitro* release studies in 100 ml of phosphate buffer saline of pH 7.4 (PBS) using Sigma dialysis sac. Aliquots of 10 ml samples were withdrawn at regular intervals and replaced with the same amount of fresh PBS. The samples were analysed spectrophotometrically at 227 nm.

Nasal perfusion method described by Hussain *et al.*¹², was used to study the absorption of sumatriptan succinate across nasal mucosa. Wistar Albino rats weighing 180 to 200 g were used for experiments. The animals were anaesthetized using pentobarbitone sodium (50 mg/kg i.p.). An incision was made in the neck of the rat and the trachea was cannulated with a polyethylene tube to prevent the rat from breathing through the nose. Another polyethylene tube, which served to introduce the perfusion solution into the nasal cavity, was inserted through the oesophagus to the posterior part of the nasal cavity. The nasopalatine area was closed with an adhesive agent to

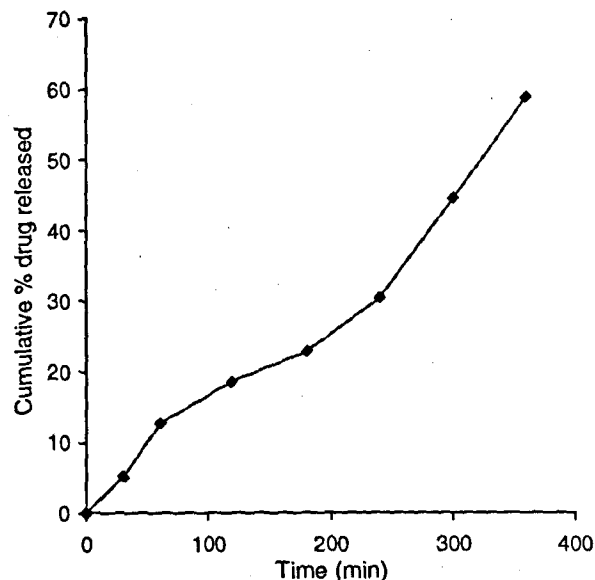


Figure 1: *In vitro* release studies of sumatriptan succinate from niosomes across sigma dialysis membrane in PBS pH 7.2

prevent drainage of the drug solution from nasal cavity into the mouth. The nasal cavity was rinsed with 10 ml of normal saline, by injecting it through the oesophageal cannulation tubing. Perfusate solution (50 ml) containing known amount of niosomes or plain drug was placed in a beaker and was stirred continuously by means of a magnetic stirrer. The drug solution was then circulated through the nasal cavity of the anaesthetized rat by means of a volumetric infusion pump (Doltron PIM 303). The perfusing solution passed through the oesophageal cannulations, to the nasal cavity and dripped from the nostrils, where it was collected by means of a funnel and delivered back to the beaker again. The perfusion rate was maintained at 6 ml/min. At regular intervals of time, 5 ml perfusate was withdrawn and analysed for drug content after replacing the perfusate with fresh phosphate buffer saline of pH 7.4.

Sumatriptan succinate could be successfully encapsulated into niosomes by lipid layer hydration method. The vesicles produced by this method were a heterogeneous population of multilamellar vesicles having spherical geometry with occasional oval ones¹. The niosomes prepared were in the size range of 3.3 to 13.2 nm, the mean diameter being 5.81 nm. The smaller size of niosomes could be due to better hydration of the film formed and presence of surfactants. The entrapment efficiency was found to be 57.9 ± 0.96 %.

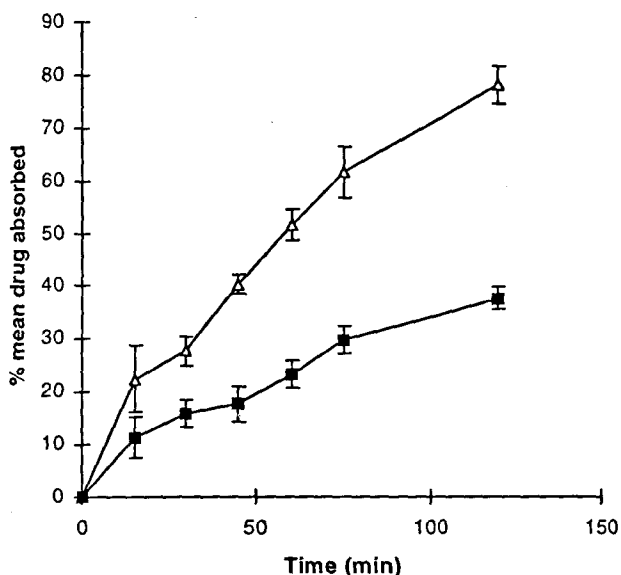


Figure 2: *Ex vivo* nasal perfusion of sumatriptan succinate from niosomes (Δ) and plain drug (\blacksquare) across rat nasal mucosa

A plot of % cumulative drug released versus time is shown in Fig. 1. Niosomes released 58.7% of sumatriptan succinate over a period of 6 h. The results of *ex vivo* nasal perfusion of sumatriptan succinate from niosomes in comparison with that of plain drug solution are depicted in Fig. 2. Only 15.83 %, 23.40 % and 37.71 % of the drug was absorbed from the plain solution whereas, 27.7%, 51% and 78.1 % of the drug was absorbed from the niosomes at the end of 30 min, 1 h and 2 h respectively. These results indicate that sumatriptan succinate encap-

sulated in the niosomes is better absorbed when compared to the plain drug across nasal mucosa and would be expected to produce a better pharmacologic activity, which needs to be further evaluated by *in vivo* studies.

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