

FORMULATION AND EVALUATION OF ERGOTAMINE TARTRATE LYOPHILIZED NASAL INSERT

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ABSTRACT

Lyophilized nasal inserts represent an alternative route for the administration of drugs. The aim of this study is to prepare a firm single dose unit of nasal insert containing ergotamine tartrate which allows easy administration in the nasal cavity and prevent first pass metabolism leading to increased bioavailability. The insert was prepared by applying freeze drying technique using 2% w/w of different polymers. The prepared inserts were evaluated for appearance, bioadhesion potential, water uptake, in vitro drug release and imaged by scanning electron microscopy. The results showed that the prepared nasal inserts have a smooth surface and a spongy-like appearance. No interaction occurred between the drug and different polymers as revealed in DSC and FT-IR. Higher viscosity of the polymer causes a greater degree of water uptake and high bioadhesion potential; this in turn reduces the drug release, as the diffusional path length of drug becomes longer. The study revealed an inverse relationship between water uptake, bioadhesion potential and in vitro drug release. The order of drug release from different inserts is HPMC E5 > PVP K90 > Sodium alginate > Carrageenan > NaCMC > Xanthan Gum > Chitosan.

Keywords: Ergotamine Tartrate, Insert, Chitosan, Carrageenan, Xanthan Gum, Sodium alginate

INTRODUCTION

Nasal insert is one of the novel solid dosage forms; it consists of a sponge like hydrophilic polymer matrix in which the drug is embedded. The insert has several advantages over other dosage forms since it is a single unit dosing with a high potential for systemic administration. Also, the insert avoids the harsh conditions of the gastrointestinal tract and the hepatic first pass effect and can pass blood brain barrier. Upon contact with the highly vascularized nasal mucosa, the polymer sponge takes water up and rapidly forms a gel from which the pharmaceutically active ingredient is liberated in a controlled fashion. The use of bioadhesive polymers ensures prolonged nasal residence time for extended release application [1].

Ergotamine Tartrate has a very low bioavailability after oral administration due to extensive first-pass metabolism. Compared with intravenous bioavailability, oral bioavailability is about less than 1% [2] while rectal bioavailability is 1-3% and intramuscular bioavailability is 47%. Ergotamine is metabolized in the liver by largely undefined pathways; 90% of the metabolites are excreted in the bile and the elimination half-life is about 2 hours [3]. The drug is used in the treatment of acute attacks of migraine, cluster and other vascular headaches [4]. Due to structural similarity with neurotransmitters such as serotonin, dopamine and epinephrine, ergotamine can thus bind to several receptors acting as an agonist. The anti-migraine effect is due to the reconstruction of the intracranial extra cerebral blood vessels through the 5-HT_{1B} receptor and by inhibiting trigeminal neurotransmission by 5-HT_{1D} receptors thus relieving headache [3].

In this study, nasal inserts based on bioadhesive polymers, as hydroxypropyl methyl cellulose (HPMC E5), polyvinyl pyrrolidone (PVP K90), sodium carboxymethylcellulose (NaCMC), chitosan, carrageenan, xanthan gum and sodium alginate were developed and characterized.

MATERIALS

Ergotamine Tartrate (Amoun Pharm. Company, Cairo, Egypt), Hydroxypropyl methyl cellulose E5 ([HPMC E5) and Xanthan Gum (Sigma Aldrich Chemical Co., Germany), Polyvinyl pyrrolidone K90 (PVP K90) (Fluka AG, Buchs SG, Switzerland), Sodium Carboxymethylcellulose (NaCMC) (ADWIC, Egypt), Chitosan, Carrageenan and Sodium alginate (Fluka, BioChemika, Switzerland) and Cellulose membrane (molecular weight cut-off 10,000) (Sigma-Aldrich, Denmark). Other chemicals used were of analytical grade and were purchased from local market.

METHODS

Compatibility study of Ergotamine Tartrate and Polymers

Compatibility between the drug and polymers is an essential factor in determining the effectiveness of polymeric delivery system. The possible drug-polymer interaction was studied via differential scanning calorimetry (DSC), and Fourier transform infrared (FT-IR) spectroscopy performed for Ergotamine Tartrate, pure polymer and physical mixture between them.

DSC Study

Samples were analyzed using DSC model TA-60 ESI, Shimadzu, Kyoto, Japan. Definite weights were placed in aluminum pan and heated from room temperature to 400 °C at a rate of 10 °C/min with indium in the reference pan in an atmosphere of nitrogen.

FT-IR Study

Infrared Spectra of drug were done using FT-IR spectrophotometry (Genesis II, Mattson, England). A disc shape samples were prepared using potassium bromide technique.

Preparation of Ergotamine Tartrate Nasal Inserts

Different Polymers, at concentration 2 % w/w namely, HPMC E5, NaCMC, Sodium Alginate, Carrageenan, Xanthan and PVP K90, were dispersed in distilled water by the aid of mechanical stirring at 60-65 °C to obtain clear solutions. The drug was then added under continuous stirring for 15 min until a uniform preparation of gel was obtained and left overnight to remove any entrapped air bubbles. 0.5 ml of each polymer gel were then placed into blister moulds and frozen at -25 °C for 1h. The samples were then freeze dried in the Freeze drier (Gamma 2-20, Martin Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Germany). After freeze drying, the inserts were stored in desiccators until use [5].

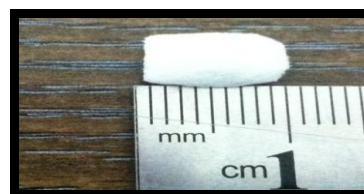


Fig. 1: Shape of the Nasal insert

In case of Chitosan, the polymer was dispersed in 1% glacial acetic acid solution under magnetic stirring, and then the drug was added with continuous stirring to ensure uniform distribution [6]. The inserts were then prepared as mentioned above, Dimensions of each insert was 9X3 mm and it contains 2 mg of the drug as shown in Figure 1.

Evaluation of Ergotamine Tartrate Gels

Visual Inspection of Gels

The prepared gels formulae were examined visually for color, clarity and homogeneity.

Evaluation of Rheological Properties of Prepared Gels

Before casting gel into insert moulds, the viscosity of each gel used was measured. The viscosity was determined using a cone and plate viscometer (Brookfield Co., Model HBDV-I+ CP, Middleboro, MA, USA). The flow behavior of the different gel bases was studied according to the following equation:

$$\text{Log} S = N \log D - \log \eta$$

Where D is the shear rate in s^{-1} ; S is the shear stress in dyne/cm^2 ; η is the viscosity in cp; and N is Farrow's constant [7].

Visual Appearance of Inserts

All inserts were visually examined for flexibility, surface smoothness, and appearance.

Drug Content of Inserts

Each insert was dissolved in 50 ml Sorensen's phosphate buffer, (PH 7.5) the absorbance of the solution was then measured spectrophotometrically at 305 nm. The test was done on 10 individual inserts [8].

Scanning Electron Microscopy of inserts

Inserts were cut with a razor blade to expose the inner structure, fixed on a sample holder with double-sided tape and coated under an argon atmosphere with gold to a thickness of 6.5 nm (SCD 040, Bal-Tec GmbH, Witten, Germany). The samples were then observed with a scanning electron microscope using secondary electron imaging at 10 kV in order to observe the surface and the cross section morphology of the inserts [9].

Bioadhesion Potential of Inserts

Adhesion studies were performed by adding 1.5 % hot agar solution in Sorensen's phosphate buffer, (PH 7.5), then the mixture was casted on a glass plate and left to gel at 4-8 °C for 3h. Each insert, was placed on top of the gel in a vertical position, and due to gravity it moved downward. The displacement in cm was measured as a function of time. The adhesion potential was inversely related to the displacement of the insert [10].

Water Uptake Study

Inserts were placed on a filter paper, the lower side of the filter was immersed in a Petri dish containing Sorensen's phosphate buffer, (PH 7.5), filled to a height of 0.5 cm in order to keep the filter paper soaked during the experiment. The Petri dish was closed with

parafilm to prevent evaporation of water during the experiment. The weight of each insert was determined with an analytical balance at predetermined time at 0.5, 1, 2, 3, 4, 5, 6 hrs. The water uptake of the inserts was then calculated using the following equation [8].

$$W(\%) = \frac{W2 - W1}{W1} * 100$$

Where, W1: weight of dry insert

W2: weight of wet insert

In-vitro Drug Release Study

In vitro release studies of Ergotamine tartrate from insert were performed by placing the insert inside a tube. A cellulose membrane was tied on one end of the tube, and then it was vertically immersed in a beaker with 30 ml of Sorensen's phosphate buffer of pH 7.4. The contents of the beaker were stirred using a magnetic stirrer at 50 rpm and kept at 37 ± 0.5 °C. At predetermined time intervals, 1 ml samples were withdrawn and replaced with fresh buffer. The withdrawn samples were analyzed for Ergotamine tartrate by measuring the absorbance at 305 nm and the percentage of drug release was calculated [11].

RESULTS AND DISCUSSION

DSC Study

DSC thermograms of drug are shown in Figure 2, the pure drug shows characteristic endothermic peak at 191°C immediately followed by a decomposition exothermic at 198°C. All the DSC curves demonstrated the characteristic peak of the drug indicating the absence of any interaction between drug and the used polymers [12].

FT-IR Study

To further confirm the absence of possible interactions between drug and the investigated polymers (HPMC E5, PVP K90, NaCMC, Chitosan, Carrageenan, Xanthan Gum and Sodium alginate), FT-IR absorption spectra were recorded. The infrared spectrum of pure Ergotamine Tartrate showed the principle bands at 3331.43 cm^{-1} broad band corresponding to OH and NH groups in addition to absorption bands at 1643.05 cm^{-1} and 1724.05 cm^{-1} attributed to carbonyl groups. Physical mixtures of drug and studied polymers showed all characteristic bands of the drug, without changes, which indicate that there no interaction occurred between the drug and all used polymers, this agrees with the results obtained in DSC results.

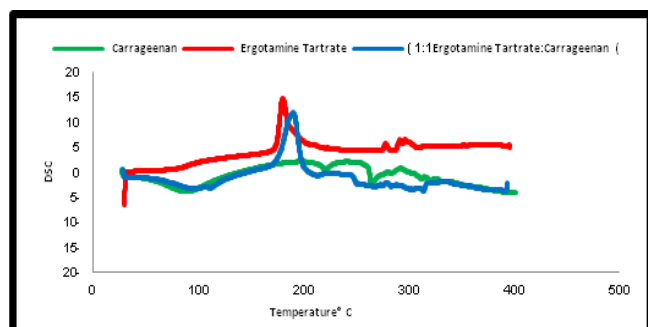
Physical Evaluation of Ergotamine Tartrate gels

Visual inspection of gels

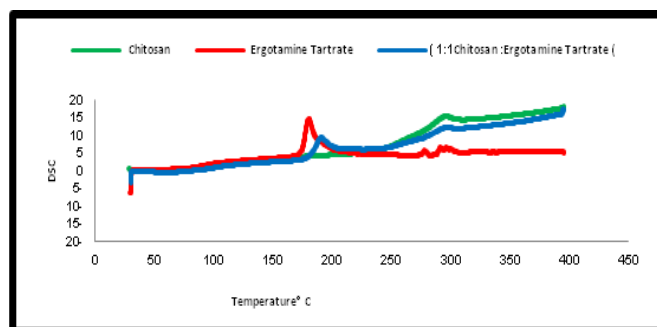
The visual inspection of the gel showed that all gels were homogenous, free from capping lamination or chipping and yellowish white in color (similar to original color of the drug).

Rheological properties

The rheological behavior of each polymer used was investigated in table 1. All the formulae exhibited shear thinning behavior since n larger than 1[7]. The viscosity of the polymers followed the order: Chitosan > Xanthan Gum > NaCMC > Carrageenan > sodium alginate > PVP K90 > HPMC E5.



a)



b)

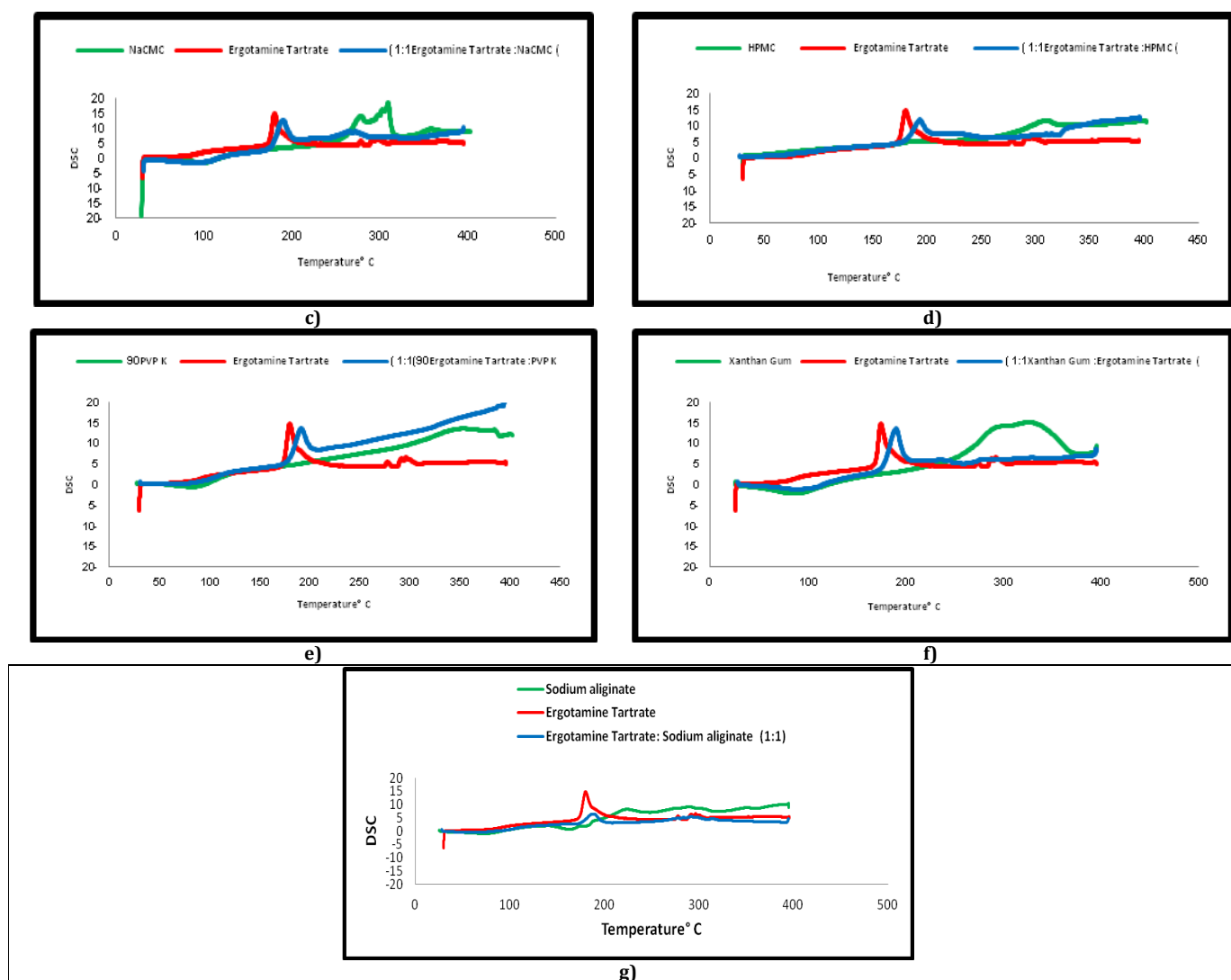


Fig. 2: a) DSC thermogram of Ergotamine Tartrate, Carrageenan and Ergotamine Tartrate - Carrageenan [1:1 w/w] physical mixture, b) DSC thermogram of Ergotamine Tartrate, Chitosan and Ergotamine Tartrate - Chitosan [1:1 w/w] physical mixture, c) DSC thermogram of Ergotamine Tartrate, NaCMC and Ergotamine Tartrate - NaCMC [1:1 w/w] physical mixture, d) DSC thermogram of Ergotamine Tartrate, HPMC E5 and Ergotamine Tartrate - HPMC E5 [1:1 w/w] physical mixture, e) DSC thermogram of Ergotamine Tartrate, PVP K 90 and Ergotamine Tartrate - PVP K 90 [1:1 w/w] physical mixture, f) DSC thermogram of Ergotamine Tartrate, Xanthan Gum and Ergotamine Tartrate - Xanthan Gum [1:1 w/w] physical mixture, g) DSC thermogram of Ergotamine Tartrate, Sodium alginate and Ergotamine Tartrate - Sodium alginate [1:1 w/w] physical mixture.

Table 1: Rheological Properties of Different Ergotamine Tartarate Gels.

Formulation	Farrow's constant [n]	Rheological behavior	Viscosity [max.] [c.p]
HPMC E5	3.2153	Shear thinning	10840
PVP K90	3.9667	Shear thinning	17790
Sodium alginate	3.9386	Shear thinning	20280
Carrageenan	3.957	Shear thinning	23550
NaCMC	3.6385	Shear thinning	31370
Xanthum	3.6556	Shear thinning	71245
Chitosan	4.1614	Shear thinning	99460

Evaluation of Ergotamine Tartrate Inserts

All nasal inserts were found to have spongy appearance, very good flexibility and smooth surface, which are advantageous in placing the insert in the nose with minimum discomfort.

Drug content of the Inserts

The drug content in the prepared inserts was in the range from 95.2% to 102.4%. This indicates that the adopted method of

preparation gave reproducible results and that the drug was uniformly distributed in the polymeric matrix [8].

Scanning Electron Microscopy (SEM) of the inserts

Figure 3 shows the SEM images of Ergotamine tartartate inserts containing 2%w/w of Carrageenan, NaCMC, HPMC E5, PVP K90, Na-alginate, Xanthan gum and chitosan polymers.

The images show that the porosity was homogenously distributed and increased with increasing polymer hydrophilicity. Two different

pore morphologies are present; one exhibiting round porosity, small and circular cavities, and other presenting longitudinal pores, large and elongated cavities [13].

The insert containing Carrageenan, NaCMC, Xanthan gum and chitosan exhibited less porosity than inserts containing HPMC

E5, PVP K90, Na-alginate polymers. Increasing porosity of the inserts surface, promoted the increase of drug diffusion and the opening of the channels. This was reflected in the release studies, wherein the release increased with the increase in level of pore former [14].

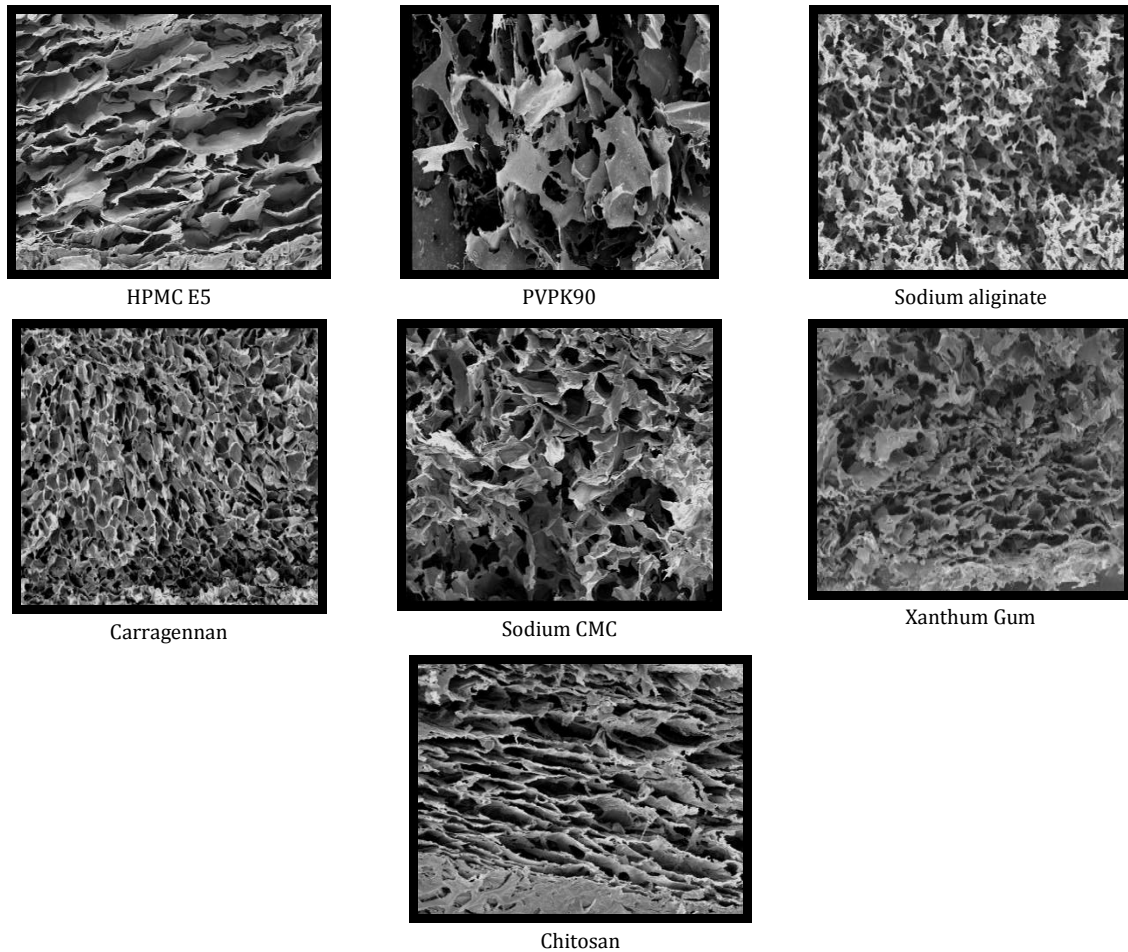


Fig. 3: scanning electron microscopic pictures of insert cross sections [polymer 2%w/w, V=1.5ml]

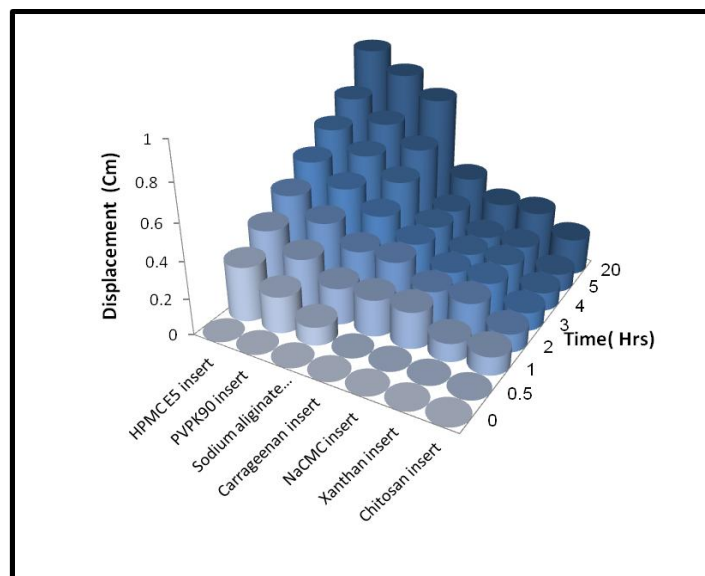


Fig. 4: Adhesive profile of inserts prepared using different polymers

Bioadhesion potential of inserts

After the insert is administered into the nasal cavity, it adhere to the nasal mucosa then it transform into gel due to uptake of water which is a prerequisite for bioadhesion. The vertical displacement of inserts on an agar was used as a measure of bioadhesion potential.

Almost instantaneous displacement and therefore a low bioadhesion potential was obtained with HPMC E5, PVP K90 and Na-alginate inserts, due to their low molecular weight and therefore low solution viscosity compared to other used polymers figure 4. These inserts hydrated rapidly, dissolved, and flowed down on the agar gel [11].

No or very little displacement was observed with carrageenan, NaCMC, xanthan gum and chitosan inserts. These polymers are known to have good bioadhesion, because of their high molecular weight therefore high viscosity, which would result in longer residence times and slow movement on the agar [10].

Water uptake of the inserts

The water uptake of inserts depends on the type of polymer used. This is an essential step for initiating the bioadhesive character

starting shortly after the beginning of water uptake [15]. Additionally, the rate and extent of water uptake affect the drug release from the insert [8].

In this study, it has been demonstrated that an inverse relationship exists between water uptake and percentage of drug release. The increase in degree of water uptake is based mainly on the viscosity, i.e. the higher the viscosity, the higher water uptake. Much water is required to wet the viscous polymer and to form a thick gel layer which reduces the drug release, as the diffusional path length of drug becomes longer. Conversely reduction in the polymer viscosity, reduces water uptake and the thickness of gel layer, this enables faster drug release [16]. Polymers with low solution viscosity disappeared after 2 hrs (for PVP K90 and HPMC E5 inserts) and 3 hrs (for Na-alginate inserts). The dissolution of the inserts contributed to the poor bioadhesion potential [17].

As in Figure 5, chitosan showed the highest water uptake ability among all the polymers. High viscosity of chitosan provided the formation of a gel network structure, thus favoring a greater entry of water [11]. HPMC E5 inserts, on the other hand, took up much less water [1].

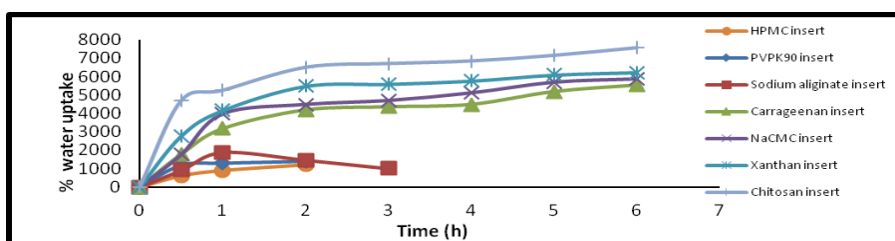


Fig. 5: Percentage water uptake behavior of Ergotamine Tartarte inserts prepared from different polymers.

In-vitro release of Ergotamine Tartrate from different inserts formulations:

Figure 6 shows the release of drug from different prepared inserts. According to percentage drug release, higher drug release was obtained from HPMC E5, PVP K90 and Na alginate inserts which is due to their low viscosity. Slower drug release was obtained from carrageenan, NaCMC, xanthan gum and chitosan inserts due to their high viscosity.

The obtained results showed an inverse relationship between the viscosity and the percentage of drug released. As viscosity increase of

the insert, the drug release decrease. These finding are similar with the results obtained by [18], who concluded that, the release of the drug is dependent on viscosity [19]. According to drug release, inserts can be arranged in descending order as follows: HPMC E5 > PVP K90 > Na alginate > Carrageenan > NaCMC > Xanthan Gum > Chitosan.

It is clear from table 2 that the release of the drug from the prepared insert formulae follows diffusion mechanism and some of them showed an anomalous non fickian release others showed fickian diffusion according to Korsemeyer-peppas equation.

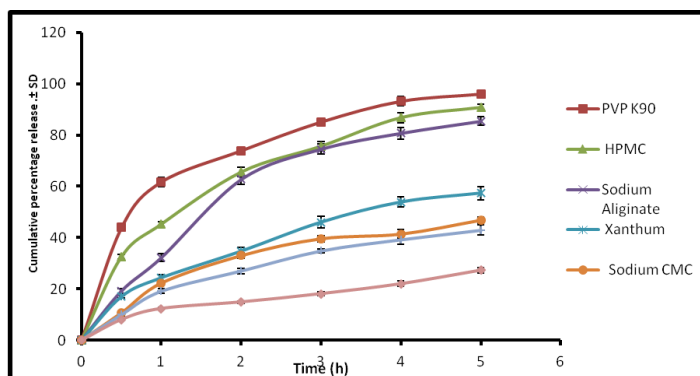


Fig. 6: Cumulative percentage release profile of Ergotamine tartrate inserts prepared using from different polymers

Table 2: Drug release kinetic of different formulation nasal inserts

Formulation	r 2			Best fit	Korsemeyer – Peppas release		
	Zero Order	First Order	Higuchi's release		Slope [n]	R2	Transport mechanism
NaCMC	0.8937	0.7601	0.961692	Diffusion	0.6115	0.948	Anomalous
HPMC E5	0.9407	0.8721	0.98786	Diffusion	0.5046	0.9989	Anomalous
Na alginate	0.8872	0.7941	0.956372	Diffusion	0.8538	0.9948	Anomalous
Carrageenan	0.9458	0.8284	0.989993	Diffusion	0.6189	0.9785	Anomalous
Xanthan Gum	0.9713	0.9107	0.993835	Diffusion	0.5447	0.9967	Anomalous
PVP K90	0.9115	0.8438	0.971978	Diffusion	0.3755	0.9695	Fickian diffusion
Chitosan	0.9824	0.9399	0.963444	Diffusion	0.4855	0.9739	Fickian diffusion

CONCLUSION

Lyophilized nasal inserts represent an alternative route for administration of bioadhesive solid dosage form for the systemic delivery of drugs. The spongy matrix structure of the nasal inserts is an important factor to ensure rapid hydration and gelatination of the inserts. The results showed that the viscosity has the main effect on water uptake, bioadhesion potential, and in vitro drug release.

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