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BIOADHESIVE BRAIN TARGETED NASAL DELIVERY OF AN ANT ISCHEMIC DRUG

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ABSTRACT

Transnasal delivery is a non-invasive method of bypassing the BBB to deliver the drug substances and peptides to the CNS. Hence, in this work Vinpocetine SLNs was prepared by the high shear homogenization and ultrasonication method. Ten different bioadhesive nasal gels of Vinpocetine SLNs were prepared. Particle size analysis before and after SLNs dispersion and after 30 days storage in the refrigerator, Rheological Measurements, ex-vivo bioadhesive strength, histopathological studies and ex vivo permeation studies were performed to evaluate the prepared Vinpocetine SLNs bioadhesive nasal gels. Moreover, Vinpocetine SLNs tissue distribution and an in vivo pharmacokinetic study were carried. Bond strength ranged from 53.86 N/m*2* to 2002.104 N/m2.The drug targeting index (DTI%) was 380.46% and the nose to brain direct transport percentage (DTP%) was 73.71% suggesting a high targeting efficiency of the prepared Vinpocetine SLNs bioadhesive nasal gel formula G10.

Key Words: Vinpocetine, Tissue distribution, Bioadhesion, Nasal gel, Mucoadhesive**.**

INTRODUCTION

The euphoria derived from the sniffing of cocaine in conscious subjects occurs rapidly (within 3–5 min). It has been suggested that the reason for such rapid effects is, apart from a rapid nasal absorption, the presence of a direct pathway from the nasal cavity to the CNS and the capacity of the drug to concentrate selectively in specific regions in the brain. Various studies in animal models have confirmed that, at early time points after nasal administration, the concentration of cocaine in the brain was higher after nasal administration than after intravenous injection, thereby showing the existence of the pathway from nose to brain.*[1, 2]*

It was reported that nasal mucosa is composed of respiratory mucosa and olfactory mucosa. Under the former there are plenty of vascular, through which preparations can be absorbed into systemic circulation, and from the latter preparations can be directly delivered to CNS, bypassing the BBB.*[1]*

The use of solid lipid nanoparticles (SLNs) may offer an improvement to nose-to-brain drug delivery since they are able to protect the encapsulated drug from biological and/or chemical degradation, and extracellular transport by efflux proteins such as P-gp. Particle size is an important property that is associated with the mucosal transport, and particles smaller than 100 nm, in general, have higher transport. *[3, 4]* Furthermore, it has been previously reported that a small diameter potentially allows nanoparticles to be transported transcellularly through olfactory neurons to the brain via various endocytic pathways of sustentacular or neuronal cells in the olfactory membrane.*[5-7]*

An effective formulation strategy for nasal administration is the use of bioadhesive delivery systems. The aim is to promote adhesion of the formulation to the nasal mucosa, allowing an extended period of contact for drug absorption to occur. Nasal administration of bioadhesive polymer gels can be technically challenging and may require a specialized device, and there will also be a limit to the viscosity of gel that can be formulated for convenient nasal administration.

Vinpocetine is used in ischemic stroke. It lowers blood viscosity in patients with cerebrovascular disease, as a result of its vasodilating properties Vinpocetine, when taken on an empty stomach, has an absorption rate of 6.7 percent. The elimination half-life of the oral form is one to two hours and the majority of vinpocetine is eliminated from the body within eight hours.

The aim of this work is to formulate Vinpocetine SLNs bioadhesive nasal gel as a targeted drug delivery system able to provide a sustained, effective delivery of Vinpocetine in the brain so

as to decrease the dose, dosing frequency and increase patient compliance.

Materials and Methods

Vinpocetine (Batch No.: 099011-000) was kindly supplied by ACAPI (Badr City, Egypt). Glyceryl Monostearate (GMS), Tween 80, Pluronic F68 were purchased from Sigma-Aldrich (St. Louis, Missouri, USA). Carbopol 934p, (Goodrich Chemical Company, Ohio, USA). Hydroxypropylmethylcellulose, HPMC (Aqualon, U.K.). Methyl Cellulose (MC), Polyethylene Oxide (PEO), Carboxymethyl Cellulose (CMC) and Triethanolamine, TEM (E. Merck, Germany). Acetonitrile, Methanol, and Water were of HPLC reagent grade; Romil, London, UK. Glacial acetic acid, Perchloric acid (70%) and Triethylamine were of analytical reagent grade (J.T. Baker, Phillipsburg, NJ). All other reagents were of analytical grade.

Preparation of Vinpocetine SLNs Bioadhesive Nasal Gels.

The preparation of Vinpocetine SLNs was carried out by the high shear homogenization and the ultrasonication method *[8-11]*. 5% glyceryl monostearate (GMS) was used as the lipid component while the surfactant mixture was formed of tween 80: pluroinc F68 (1:1). Five different bioadhesive gel forming polymers namely Carbapol, MC, HPMC, CMC and PEO were used in two different concentrations as shown in table (I). 10% glycerol was added as humectant. *[12]*

Particle Size Analysis

Particle size analysis was performed by Photon Correlation Spectroscopy (PCS) using Zetasizer Nano ZS, Malvern Instruments (Malvern, UK). Particle size analysis and polydispersity index (PDI) were performed for the prepared SLNs before and after dispersion in the hydrogels. Further particle size analysis of formulae for formulae hadan average particle size diameter (Z-average) below 150NMm was performed after 30 days of storage in refrigerator*[13]*

Rheological Measurements of the Prepared Vinpocetine SLNs bioadhesive nasal gels.

The freshly prepared Vinpocetine SLNs bioadhesive nasal gels were subjected to tests for their rheological characteristics at 25°C using Brookfield Viscometer D.V.-I. Using spindle 41 (radius = 2.4cm, angle = 0.8 degrees).

Evaluation of the Ex-Vivo Bioadhesive Strength of the Prepared Vinpocetine SLNs Bioadhesive Nasal Gels.

The modified balance method *[14-18]* was used. The membrane used for mucoadhesive testing was fresh nasal sheep membrane*[19-22]* where it was cut into two pieces (2.25cm*2* in

surface area) and glued to the stainless steel plate and to the fixed glass plate using cyanoacrylate adhesive. *[23]* The force of adhesion (N) as well as the bond strength (N/m*2*) *[18]* were determined in replicates (n=3) and the mean values determined using equations 1 and 2 as follow:

$$\text{Force of Adhesion (N)} = \frac{\text{Mucoadhesive strength (g)}}{1000} \text{x} 9.8 \text{ .....Eq1}$$

$$\text{Bond strength (N/m}^2\text{)} = \frac{\text{Force of Adhesion (N)}}{\text{Surface area (m}^2\text{)}} \text{.....Eq2}$$

Statistical analysis was done using the SPSS software program (V.17) and post Hoc LSD test (least square difference) with 95% confidence level for the force of adhesion (N) and z-average. Differences were considered significant when $P \leq 0.05$. Statistical tests were done to show the effect of the entrapped Vinpocetine SLNs formula, gel forming polymer type and gel forming polymer concentration on the force of adhesion (N) or the z-average.

Histopathological studies

Histopathological studies were carried out using autopsy samples taken from fresh nasal sheep mucosa in different groups. *[24]* Five groups were examined where group I was treated with phosphate buffer saline pH 6.4 (as negative control), group II was treated with Vinpocetine dispersion in phosphate buffer saline pH 6.4, group III was treated with Vinpocetine SLNs formula F32, group IV treated with Vinpocetine SLNs bioadhesive nasal gels formula G10 and group V was treated isopropyl alcohol (nasal mucociliary toxicity agent used as a positive control), respectively*[24]*. Samples were fixed in 10% formol saline for twenty four hour then washed, dehydrated, deparaffinized and stained by hematoxylin and eosin stain as well as Masson trichrom for the collagen then examined through the electric light microscope.*[25]*

Ex vivo permeation studies:

It was carried out by following the procedure described by Steffen Lang et al. *[26]* Sheep nasal mucosa was excised and used at no more than 30 min after the excision. Samples were taken and inserted into the assimilated Franz diffusion chambers, the apical side of the tissue typically facing the donor compartment. The hydrogel equivalent to 150 mg was placed on the upper side of the nasal mucosa. The donor and the receiver compartment containing phosphate buffer pH 6.8 as the diffusion medium to maintain sink conditions and the temperature was maintained at 32℃. After 3 hours a sample from the receptor compartment was taken and examined using scanning electron microscope. Scanning electron microscope Model Quanta

250 FEG (Field Emission Gun) attached with EDX Unit (Energy Dispersive X-ray Analyses), with accelerating voltage 30 K.V., magnification14x up to 1000000 and resolution for Gun.1n). It was used to determine the shape of the permeated Vinpocetine SLNs and to demonstrate any possible distortion in the shape of the penetrated Vinpocetine SLNs achieved either due to preparation step or after nasal mucosal permeation.

Vinpocetine SLNs Tissue distribution

Forty Two rats were divided randomly into 14groups. Each group was composed of three rats. Eight groups received an IV injection of Vinpocetine SLNs at a dose level (0.44mg Vinpocetine/kg animal body mass)*[27]* in the tail vein with a slow IV bolus dose by a no. 7 needle, another six groups for the control received Vinpocetine Solution (in 10% ether), at the same dose level. Rats were sacrificed at different time intervals, the brain, heart, liver, spleen, lungs and kidneys were taken, squeezed and washed. A 20% by weight tissue homogenate of each organ was prepared Total Vinpocetine concentration in each organ was determined by HPLC analysis.

Pharmacokinetic analysis and brain targeting efficiency of Vinpocetine from the prepared Vinpocetine SLNs bioadhesive nasal gels.

Male Wistar Albino rats (aged 4–5 months) weighing between 200 and 250 g were selected for the study. Vinpocetine SLNs bioadhesive nasal gel formula G10 was prepared. For each rat either 100 µl gel was administered in its right nostril or an equivalent Vinpocetine dose administrated by IV bolus injection in the tail vein. Subsequently, Rat brains were dissected, washed and homogenized. Vinpocetine concentration in each rat was determined by HPLC analysis.

Pharmacokinetic parameters *[28]*,Drug targeting index (DTI) *[29, 30]* and Nose to brain direct transport percentage (DTP%) were calculated where:

$$DTI\% = \frac{(AUC_{Brain}/AUC_{Blood})_{i.n.}}{(AUC_{Brain}/AUC_{Blood})_{i.v.}} x100 \quad \text{.....Eq3}$$

$$DTP\% = \left[\frac{B_{i.n.} - B_x}{B_{i.n.}}\right] x\ 100 \quad \text{.....Eq4}$$

Where $B_x = (B_{i.v.}/P_{i.v.}) \times P_{i.n.}$,
B_x is the brain AUC fraction contributed by systemic circulation through the BBB following intranasal administration,
$B_{i.v.}$ is the $(AUC)_0^{48}$ (brain) following intravenous administration,
$P_{i.v.}$ is the $AUC)_0^{48}$ (blood) following intravenous administration,
$B_{i.n.}$ is the $AUC)_0^{48}$ (brain) following intranasal administration,
$P_{i.n.}$ is the $AUC)_0^{48}$ (blood) following intranasal administration and AUC is the area under the curve.

Full factorial statistical analysis was done using SPSS software program (V.17) and post Hoc LSD test (least square difference) with 95% confidence level for the area under the curve $(AUC)_0^{\infty}$, and mean residence time (MRT) and

differences were considered significant when P ≤ 0.05.

One way ANOVA statistical analysis was done using SPSS software program (V.17) and post Hoc LSD test (least square difference) with 95% confidence level for the area under the curve $(AUC)_0^{\infty}$, and mean residence time (MRT) and differences were considered significant when P ≤ 0.05.

Chromatographic conditions

The concentrations of Vinpocetine in rat plasma were determined by HPLC *[31]*. The HPLC system was composed of a model HP Agilent 1100 series with G1311A Quaternary Pump, G1315A Diode Array Detector and G1313A Autosampler. The analytical column was Hypersil C18 (100 × 4.6 mm, 5 µm) (Thermo, UK). The injection volume was 20 µl auto adjusted by the Autosampler; the mobile phase was methanol:water (80:20 (v/v)), containing 0.1% w/w triethylamine and adjusted to pH 7 using glacial acetic acid.*[32]*; the flow rate was 1.5 ml/min; the UV detector wavelength was 273 nm; the column temperature was 35 *o*C.

Results and discussion

The chosen Vinpocetine SLNs formula was selected after long study as it was the most promising Vinpocetine SLNs that can be effectively targeted to the brain. Where average particle size diameter (z- average) were 123 nm ± 10.58 , PDI = 0.141, entrapment efficiency percent of 89.09% ±1.49, zeta potential of -11.33 mv ±0.97, cumulative released percent after 96 hours (Q96) of 72.12 %±4.52 with zero order sustained release kinetics.

In order to exhibit gel-forming properties, the carboxylic acid groups (in the used Carbopol 934p) have to be neutralized. However, if sodium hydroxide was used it could reduce the zeta potential of the particles *[33]*, resulting in destabilization of SLNs dispersions leading to the particle growth and subsequent formation of semisolid gels. This phenomenon is well known for lipid nanoemulsions. *[34]* So Triethanolamine (TEA) was used as the alkali of choice.

Particle size Analysis

A slight increase in the measured mean particle size and the polydispersity index as shown in as shown in table (I) and figure (1), but the nanoparticulate structure could be maintained. Similar results were previously obtained. *[12]* This can be explained by the maintenance of integrity of the strong hydrogel network, rather than the existence of nanoparticle aggregations *[35, 36]* which can further be attributed to the presence of the gelling agent those obstacles a good dispersion of nanoparticles.

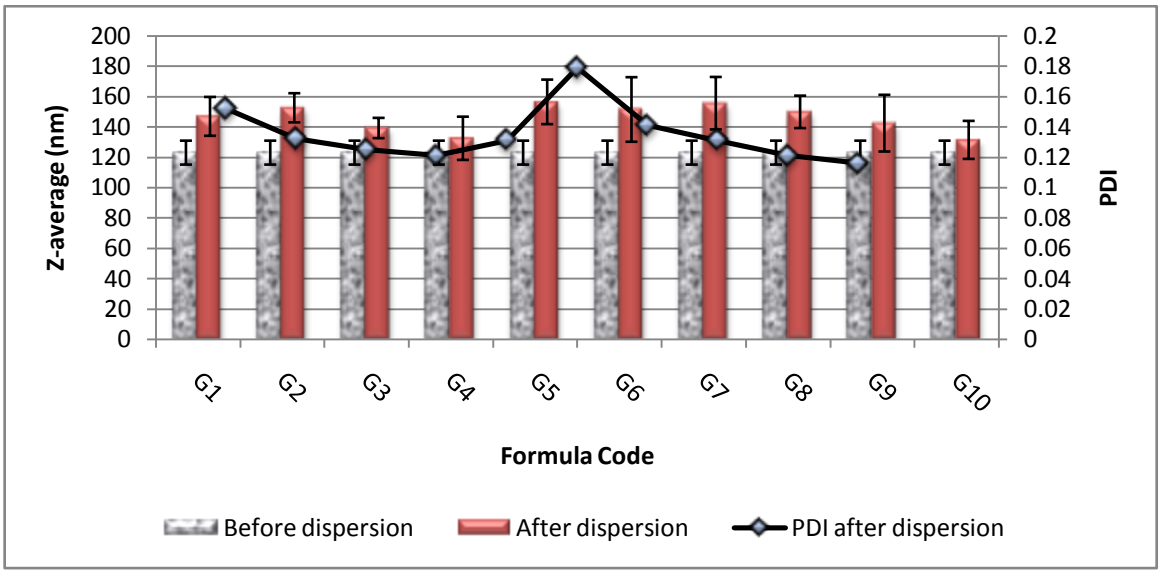

Figure 1: Mean particle size (Z-average) and PDI of Vinpocetine SLNs bioadhesive nasal gel formulae.

Table I: Different Vinpocetine SLNs bioadhesive nasal gel formulae and their particle size diameter (Z-average) and their force of adhesion.

Formula code	Composition	Z-average± S.D.		PDI	Force of adhesion N ± S.D.		Bond strength (N/m2) ± S.D.	
G1	5% MC	146.9	±15.6	0.152	0.012	±0.009	53.864	±42.063
G2	7.5% MC	152.56	±25.72	0.132	0.038	±0.002	167.108	±10.935
G3	4% HPMC	139.23	±9.8	0.125	0.119	±0.012	530.216	±55.378
G4	5% HPMC	132.45	±15.12	0.121	0.147	±0.011	654.640	±48.201
G5	5% CMC	156.45	±27.152	0.131	0.306	±0.020	1359.514	±89.430
G6	7.5% CMC	151.45	±14.24	0.179	0.336	±0.010	1495.117	±43.869
G7	5% PEO	155.6	±16.84	0.141	0.214	±0.015	952.270	±67.174
G8	7.5% PEO	149.87	±9.84	0.131	0.250	±0.015	1111.538	±67.598
G9	1% Carbopol	142.43	±9.36	0.121	0.381	±0.025	1692.424	±112.406
G10	2% Carbopol	131.4	±12.448	0.116	0.449	±0.016	1995.280	±71.006

Rheological Evaluation

All gel bases are shear thinning because of the inverse relationship between shear rate and either shear stress or viscosity.

Evaluation of Mucoadhesive Properties of the Prepared Vinpocetine SLNs bioadhesive Nasal Gels.

These high forces of adhesion for the prepared Vinpocetine SLNs bioadhesive nasal gels are due to the use of boadhesive polymers which have numerous hydrophilic groups, such as hydroxyl, carboxyl, amide, and sulfate. These groups attach to mucus or the cell membrane by various interactions such as hydrogen bonding and hydrophobic or electrostatic interactions.

These hydrophilic groups also cause polymers to swell in water and, thus, expose the maximum number of adhesive sites. *[37]*

The used polymers are expected to adhere to the nasal mucosal surface by the diffusion theory where the polymeric chains from the bioadhesive interpenetrate into glycoprotein mucin chains and reach a sufficient depth within the opposite matrix to allow formation of a semipermanent bond. The process can be visualized from the point of initial contact. The existence of concentration gradients will drive the polymer chains of the bioadhesive into the mucus network and the glycoprotein mucin chains into the bioadhesive matrix until an equilibrium penetration depth is achieved.The exact depth needed for good bioadhesive bonds is unclear, but is estimated to be in the range of 0.2–0.5 μm. *[38]*

Statistical ranking of various polymers used in this study would be Carbopol 934p> CMC< PEO< HPMC< Methyl cellulose. The increased bioadhesive properties of Carbopol resins may be due to their chemical nature as they are high-molecular-weight polymers formed of derivatives of polyacrylic acid that readily swell in water; the swelling exposes a large adhesive surface for maximum contact with the mucin (the glycoprotein predominant in the mucous layer) and, thus, provides excellent mucoadhesiveness as shown in table (I) and figure (2).

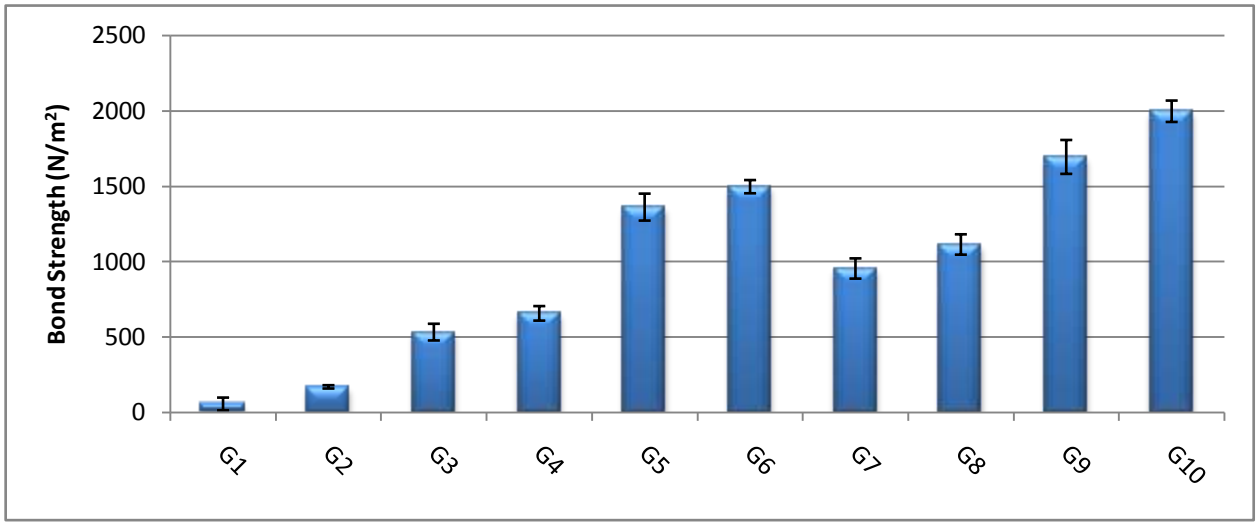

Figure 2: Average bond strength of the prepared Vinpocetine SLNs bioadhesive nasal gels.

Histopathological study

Histopathological investigation for groups I-IV, (Figures 3-7) in comparison to that of group V (treated with isopropyl alcohol as positive control) (figure 160 and 161) showed that there was no histopathological alteration observed in

the mucosal layer with the glandular structure and muscularis indicating that neither the drug being investigated (group II) nor the prepared Vinpocetine SLNs (group III) nor the prepared Vinpocetine SLNs bioadhesive nasal gel formula G10 (group IV) had any harmful effect on the nasal mucosa preserving the normal cell structure of the nasal sheep mucosa similar to the negative control used which was phosphate buffer saline pH 6.4 (group I negative control). On the other hand histopathological investigation for group V treated with isopropyl alcohol (nasal mucociliary toxicity agent used as a positive control) (figures 8 and 9) show lysis and destruction of the nasal mucosal cells.

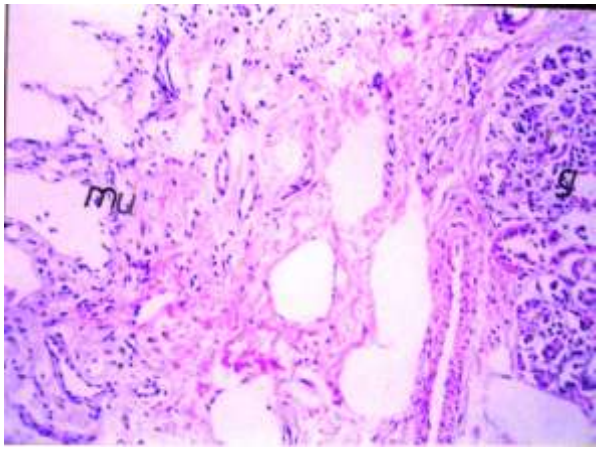

Figure 3:Mucosal layer of sheep nasal cavity for group I showing normal histopathological structure of the lining mucosal epithelium (mu) and glandular structure (g).

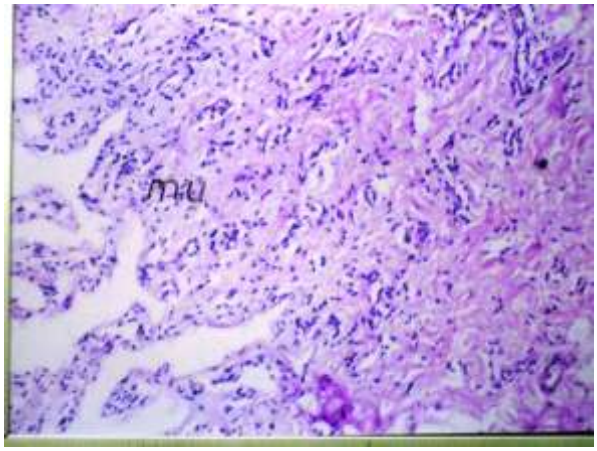

Figure 4:Mucosal layer of sheep nasal cavity for group II showing the intact normal histopathological structure of the lining mucosal epithelium (mu).

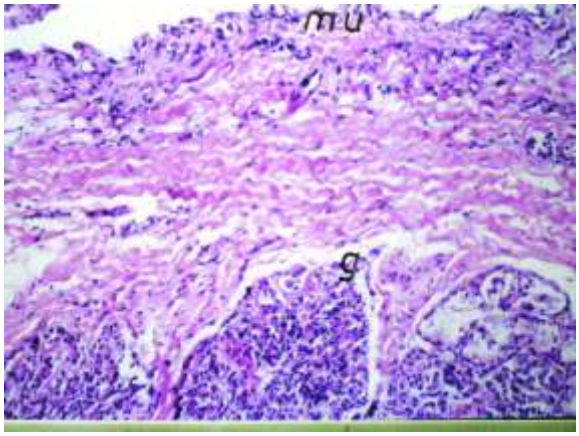

Figure 5:Mucosal layer of sheep nasal cavity for group III showing the intact normal histopathological structure of the mucosa (mu) and glandular structure (g).

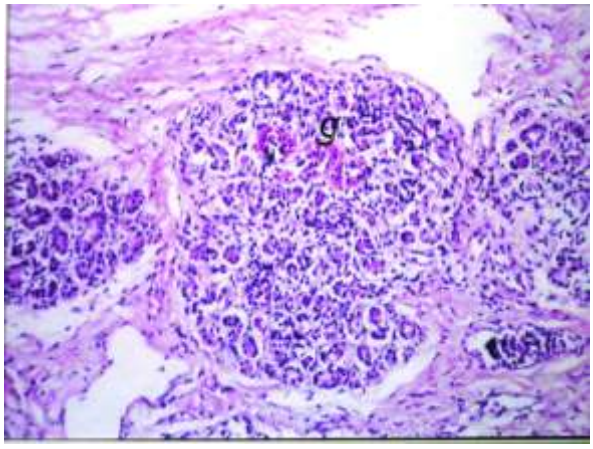

Figure 6:Mucosal layer of sheep nasal cavity for group III showing the normal histopathological structure of the glandular structure (g).

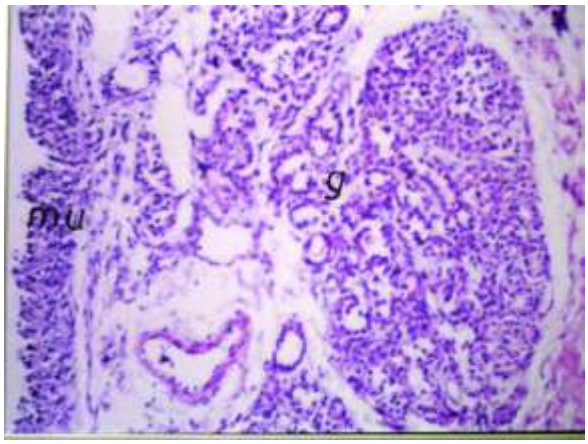

Figure 7:Mucosal layer of sheep nasal cavity for group IV showing the intact normal histopathological structure of the mucosa (mu) and glandular structure (g).

Ex vivio permeation studies

The scanning electron microscopic pictures for the exvivo permeate after using Vinpocetine SLNs bioadhesive nasal gel formula G10 through the freshly excised sheep nasal mucosa is shown in figures (10 and 11).

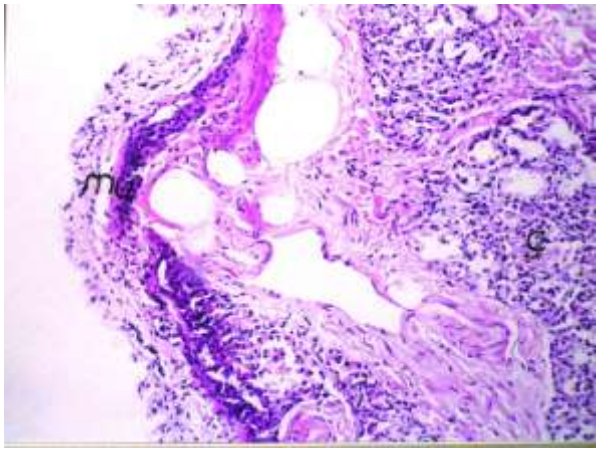

Figure 8:Mucosal layer of sheep nasal cavity for group V showing destruction of the mucosal layer (mu).

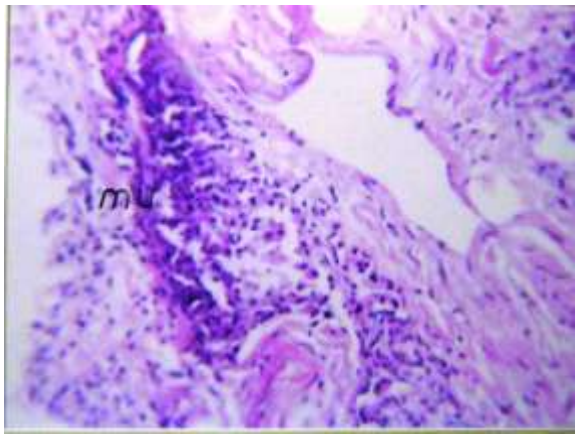

Figure 9:Mucosal layer of sheep nasal cavity for group V showing the magnification of the figure (160) to identify the destructed mucosa (mu).

It is clear that the prepared Vinpocetine SLNs were able to penetrate the nasal mucosa within short time interval. The permeated Vinpocetine SLNs were spherical in shape and without any distortion in their shape which may be induced during either dispersion of the Vinpocetine SLNs is the gel base or during Vinpocetine SLNs penetration through the sheep nasal mucosa.

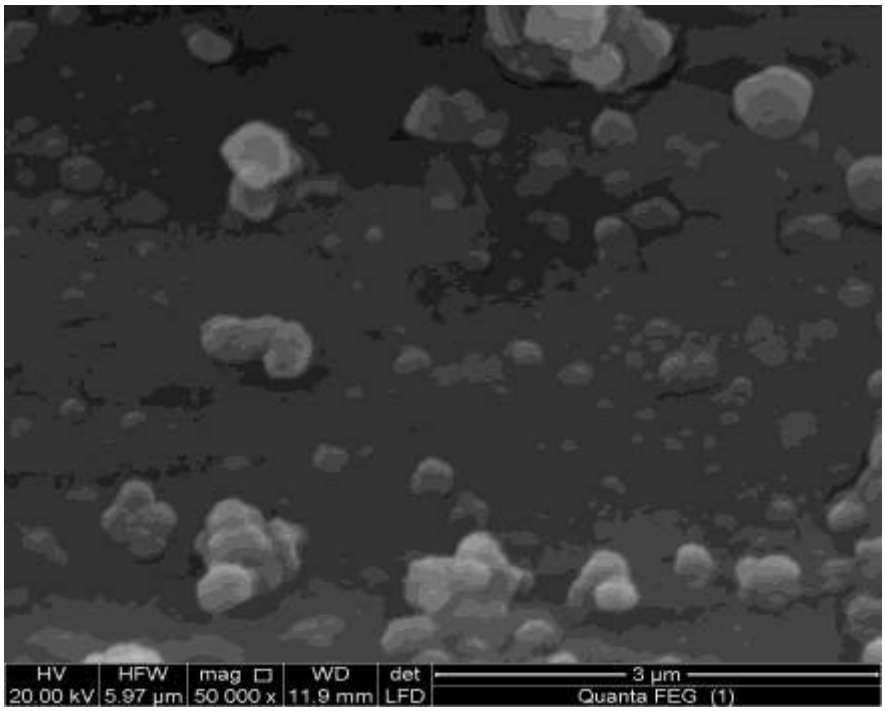

Figure 10:SEM picture for the permeated Vinpocetine SLNs from the nasal sheep membrane using Vinpocetine SLNs bioadhesive nasal gel formula G10.

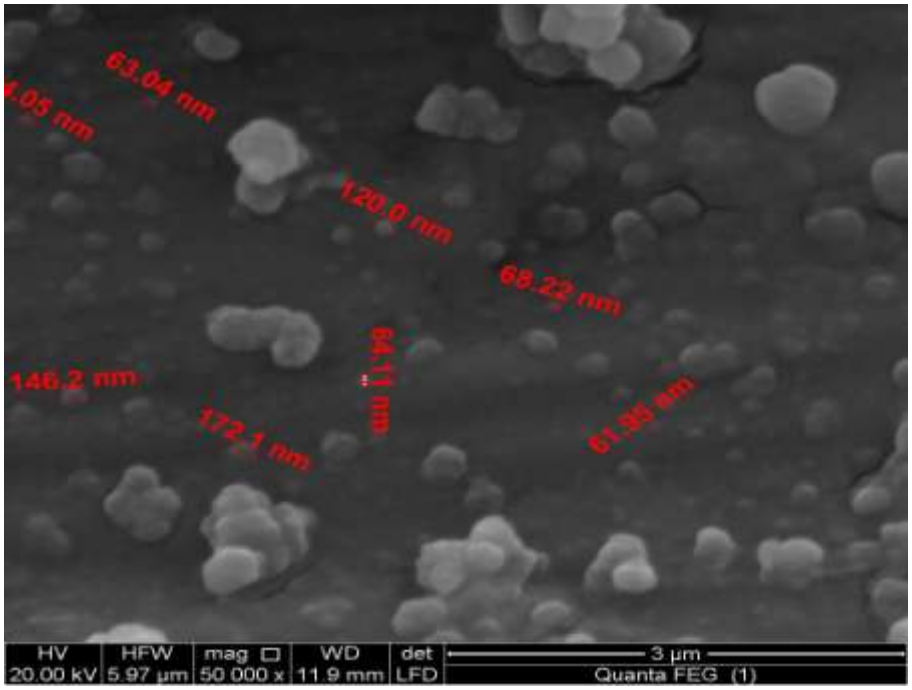

Figure 11:SEM picture showing the average diameter of the permeated Vinpocetine SLNs from the nasal sheep membrane using Vinpocetine SLNs bioadhesive nasal gel formula G10.

Vinpocetine SLNs tissue distribution

The results of Vinpocetine SLNs tissue distribution are shown in figures (12 and 13) and in table(II) after IV bolus injection of Vinpocetine solution. The drug levels were high in the lung, spleen, liver and kidney, moderate in brain, and low in heart. These results are in accordance with Yao et al,*[39]* who studied Vinpocetine pharmacokinetics and disposition in rats and got the same findings.

The Vinpocetine concentrations or in other words Vinpocetine availability in the brain and the spleen were increased after using the prepared Vinpocetine SLNs formula F32 while it was decreased in the liver, kidneys, heart and lungs. The increase observed in the brain concentration of Vinpocetine after using the prepared vinpocetine SLNs was significant while that observed in case of the spleen was not significant. The decrease observed in the Vinpocetine concentrations in the liver, kidneys, heart and lungs were significant. This indicates the increased targeting effeciency of the prepared Vinpocetine SLNs to the brain and the effective masking from the RES suggesting possible sustained effective targeting within the body.

These results are in accordance with Studying the pharmacokinetics of two anticancer agents, namely camptothecin and doxorubicin, drug accumulation in the brain was observed after both oral and i.v. administration when loaded into SLN. *[40, 41]*

The high brain concentration of Vinpocetine may be due to the adsorption of Poloxamer188 on the surface of Vinpocetine SLNs *[42]*. Because of the hydrophilicity and steric hindrance of Poloxamer188, opsonins are less adsorbed on the nanoparticle surface, which results in lower englobement of MNP to nanoparticle and longer resistance time in blood. The study of lipid microspheres transport containing clinprost and Tween 80-coated nanoparticles across blood–brain barrier showed the similar mechanism. Statistical ranking of different organs according to the AUC0-α as followed: Spleen≈ Liver>kidneys >Brain> Heart> Kidneys.

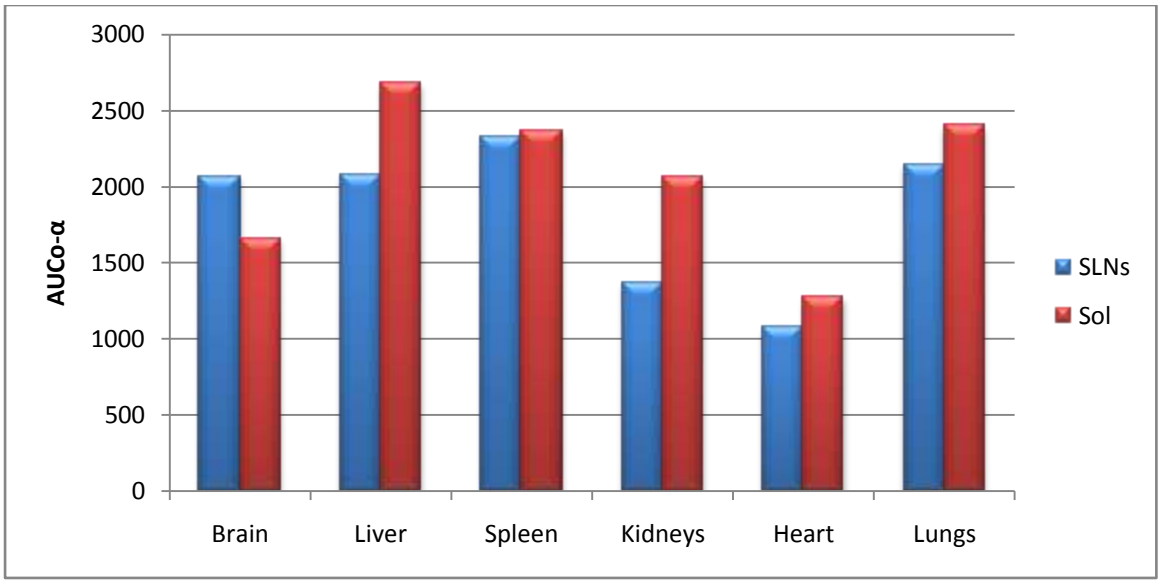

Figure 12: Tissue distribution of Vinpocetine and Vinpocetine SLNs.

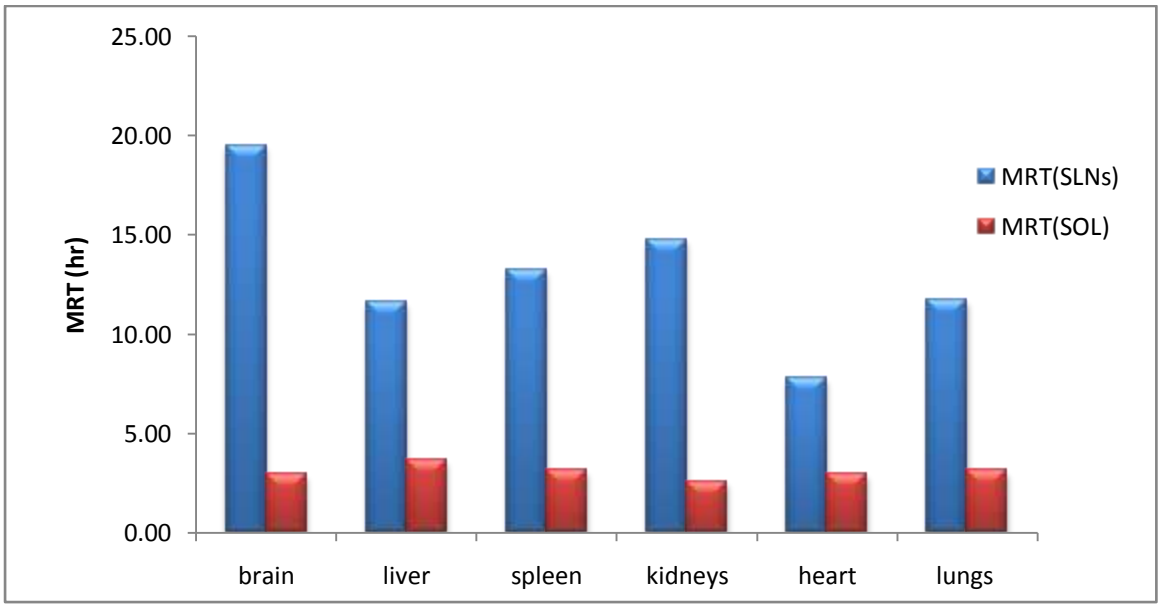

Figure 13: MRT after IV bolus of Vinpocetine solution and Vinpocetine SLNs.

Table II:Pharmacokinetic parameters and tissue distribution of Vinpocetine SLNs and Vinpocetine Solution in rats.

Time (hr)	Brain		Liver		Spleen		Kidneys		Heart		Lungs	
	SLNs	SOL	SLNs	SOL	SLNs	SOL	SLNs	SOL	SLNs	SOL	SLNs	SOL
K (hr-*1*)	0.05	0.417	0.068	0.34	0.062	0.376	0.064	0.395	0.068	0.4	0.087	0.361
AUC_{0-24}(ng/g.hr)	2070.40	1607.40	2076.15	2472.79	2331.09	2247.53	1370.26	2008.91	1075.66	1229.40	2147.21	2310.41
$AUC_{0-\alpha}$(ng/g.hr)	2954.77	1663.52	2407.99	2681.55	2833.84	2364.58	1729.50	2060.15	1210.61	1276.90	2511.07	2405.88
$AUMC_{0-24}$ (ng/g.hr)	18788.53	4228.93	15115.85	7394.25	17306.95	6091.75	11294.00	4776.32	6876.30	3264.92	16474.58	6415.19
$AUMC_{0-\alpha}$(ng/g.hr)	577700.79	4868.61	27960.10	9887.11	37427.10	7456.41	25528.96	5367.25	9411.48	3812.40	29389.51	7538.98
MRT (hr)	19.53	2.93	11.61	3.69	13.21	3.15	14.76	2.61	7.77	2.99	11.70	3.13

Pharmacokinetic analysis and brain Targetting efficiency of Vinpocetine form the prepared Vinpocetine SLNs bioadhesive nasal gels

Pharmacokinetic parameters of Vinpocetine were determined using non-compartmental analysis. Table (III) and figure (4) show Vinpocentine pharmacokinetic parameters after intravenous administration of the calculated animal dose. The calculated values of $AUC_{0-\alpha}$ of Vinpocetine calculated in the brain after the IV bolus and the IN Vinpocetine SLNs bioadhesive nasal gel formula G20 which are 1727.24 ng/g.hr and 4568.14 ng/g.hr respectively. The high Vinpocetine brain $AUC_{0-\alpha}$ in comparison to that after IV bolus injection is indicative of direct nose to brain transport bypassing the blood–brain barrier, *[43, 44]* hence prove the superiority of nose to brain delivery of Vinpocetine SLNs.

Reports in the literature *[1, 45, 46]* reveal that the drug uptake into the brain from the nasal mucosa mainly occurs via two different pathways. One is the systemic pathway by which some of the drug is absorbed into the systemic circulation and subsequently reaches the brain by crossing the BBB. The other is the olfactory pathway by which the drug partly travels from the nasal cavity to CSF and/or brain tissue. It can be concluded, that the amount of drug in the brain tissue after nasal administration is attributed to these two pathways. The DTP% and DTI% represent the percentage of drug directly transported to the brain via the olfactory pathway.

Table III:Pharmacokinetic parameters after Vinpocetine SLNs bioadhesive nasal gel formula G10 and IV bolus Vinpocetine solution.

Time (hr)	AUC (ng/g.hr)			
	IN Brain	IN Plasma	IV Brain	IV Plasma
0.5	19.10	84.57	119.46	930.58
1	51.58	194.06	239.63	755.83
2	211.56	461.88	399.30	1185.84
3	292.08	458.62	270.51	754.00
6	807.01	1082.13	465.13	1398.10
9	610.33	683.68	165.58	714.53
12	439.01	414.45		271.32
24	1288.48	956.92		
36	758.90			
K (hr-1)	0.495	0.526	0.346	0.387
T ½ (hr)	1.40	1.33	2.00	1.79
$(AUC)_0^t$(ng/g.hr)	4478.05	4336.29	1659.60	6010.21
$(AUC)_0^\infty$(ng/g.hr)	4568.14	4430.53	1727.24	6373.56
$(AUMC)_0^t$(ng/g)	56384.48	30669.94	4336.077	17451.82
$(AUMC)_0^\infty$(ng/g)	59659.64	32997.64	4965.738	18740.46
MRT(hr)	13.06	7.45	2.87	2.51
Cmax(ng/g)	293.23	485.79	480.68	1563.32
Tmax (hr)	2	2	1	0.5
DTI%	380.46%			
DTP%	73.71%			

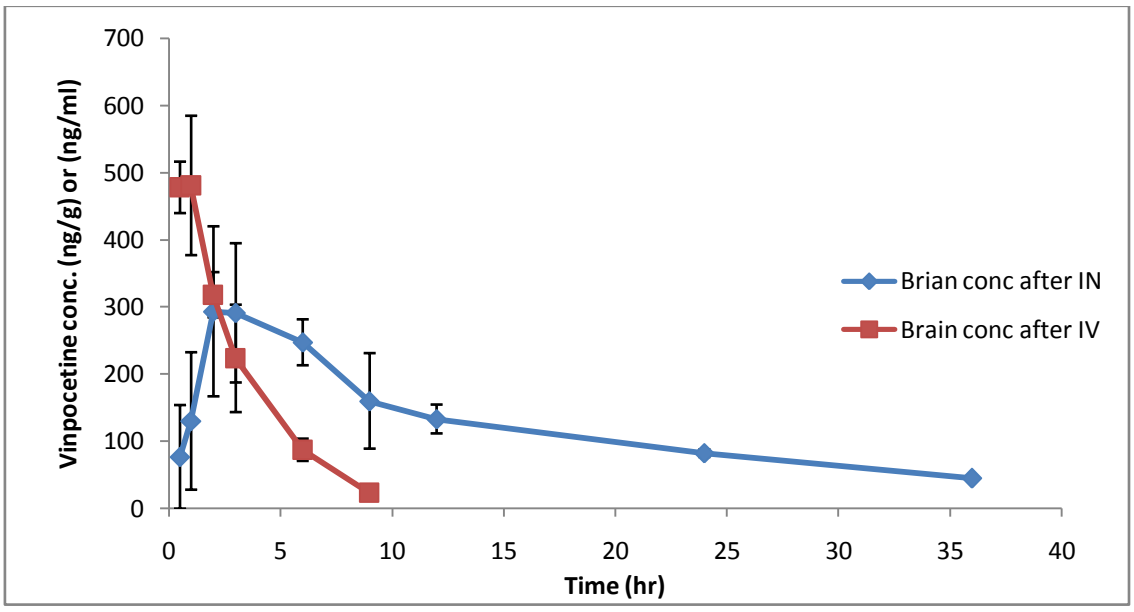

Figure 14: Brain concentration of Vinpocetine after IV bolus Vinpocetine solution and IN Vinpocetine SLNs bioadhesive nasal gel formula G10.

Conclusion

The use of Vinpocetine SLNs in the form a bioadhesive nasal gel effectively increased the nose to brain delivery in comparison of using Vinpocetine solution intravenously also the presence of the drug in the form of SLNs effectively sustained its release pattern and finally the extremely small size of the prepared Vinpocetine SLNs allowed for an effective escape from the RES allowing for long residence time in vivo.

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Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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