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Research Article

Preparation of Idebenone as A Thermosetting Nasal Gel for Better Bioavailability and Histopathological Effect

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Abstract:

Background: Idebenone is an extensively metabolized drug with poor water solubility that is used to treat Leiber's hereditary optical neuropathy.

Objective: This study aims to prepare idebenone nanoemulsion as a poloxamer-based nasal gel to overcome the extensive rate of hepatic metabolism for better bioavalability and lower histopathological effect on the nasal mucosa.

Methods: The formulation strategy was based on eliciting mutual concentration reduction between the nanoemulsion and the carrier gel by setting their gelation temperature between 30-32°C to overcome the mucociliary dose washout. The o/w nanoemulsions rely on cremophor EL and transcutol as an emulsifying system to stabilize idebenone-loaded lemongrass oil. The spontaneous emulsification method was used to prepare nanoemulsions that were characterized by zeta sizer while the thermosensitive hydrogels were prepared using the cold method. In-vitro dissolution test and ex-vivo permeation study through excised sheep nasal mucosa were performed to evaluate the enhanced permeation ratio, rate of permeation, and permeation coefficient. The histopathological effect of direct application on sheep nasal mucosa was studied using optical microscopy to evaluate cellular toxicity.

Results: The formula prepared from NE1 with poloxamer 407: poloxamer188 in concentrations 10:3% w/w respectively, showed almost complete drug release in 120 minutes due to complete polymers blend erosion. Furthermore, thermosensitive nano-emulgel at a temperature of gelation 31.8°C was obtained at much lower concentrations of poloxamer 407 (10%) compared to previous studies. Nanoemulsions retained their globular size below 100nm due to further gel entrapment stabilization.

Conclusions: Drug permeation through excised sheep nasal mucosa elicited an increase in enhanced permeation ratio to 20.3 times and other flux kinetics parameters compared to those of IDB oil dispersion. Direct cellular toxicity showed a minor inflammatory response characterized by serous infiltration of inflammatory cells and edema. In contrast, most of the epithelial cells retained their histological characteristics compared to control slides.

Keywords: Bioavailability; Idebenone; Nanoemulsion; Permeation.

Introduction

Nasal drug delivery offers an optimal chance for certain drugs of low oral bioavailability to be absorbed effectively via the nasal route. The highly vascularized mucosa is characterized by appreciable blood flow rate, adequate surface area, and low enzymatic activity; therefore, good plasma concentration can be attained (1). However, nasal drug administration faces several challenges, of which mucociliary clearance is the most important. This process takes between 12 and 15 minutes (2) and can be a major reason for the dose washout of poorly formulated nasal preparations.

Poloxamers are a group of thermosensitive polymers that are described as having lower critical solution temperature i.e. they form gel on heating. They are composed basically of polyethylene oxide residue, denoted by (X), and polypropylene oxide residue, denoted by (Y). They are usually present as -(X-Y-X)$_n$ or -(Y-X-Y)$_n$ triblock copolymers in different ratios and molecular weights (Figure 1).

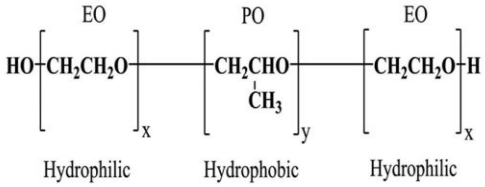

Figure (1): General chemical formula of poloxamers triblock co-polymer (3)

Idebenone (IDB) is a synthetic derivative of natural Co-Q10, a natural co-enzyme of mitochondrial cytoplasm involved in electrons shuttle during ATP production process. Idebenone is a yellow-orange crystalline powder with no offensive odor or taste with a melting point between (52-55°C)(4). It has two polymorphs with different diffraction patterns denoted by A and B of which type (A) is the most

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predominant polymorph. It is practically insoluble in water but freely soluble in methanol, ethanol, oils (log P=3.865). Idebenone was assigned by European medical agency (EMA) as a treatment for Leiber's hereditary optic neuropathy (LHON) (5,6), an autosomal recessive neurodegenerative disease of mitochondrial origin that is characterized by gradual loss of visual acuity ending with complete blindness and this disease has no approved treatment yet other than IDB(7). Although IDB is almost completely absorbed from GIT it has low aqueous solubility as it belongs to the class II of the biopharmaceutical classification system (BCS) but its extensive rate of metabolism reduces the drug's oral bioavailability to less than 1% (8).

This study aims to utilize several well-characterized IDB nanoemulsions (NEs) from previous work to formulate the drug as a thermosensitive nasal gel (NG). Those NGs were supposed to prolong dose residency time and decrease surfactant toxicity through overall dilution, circumventing the extensive hepatic metabolism and increasing the transmucosal permeation of the drug. Consequently, an increase in drug bioavailability with decreased cellular toxicity would be anticipated.

Materials and methods

Materials

Idebenone was purchased from (XI'An Geekee Biotech Co, Ltd, China). lemongrass oil (LGO), was purchased from (Shaanxi Guangie Technology Co.,Ltd, China). Cremophor EL® (CrEL) was purchased from (Shanghai Taijie Chemical Co., Ltd, China). Transcutol P® (TC) was purchased from (Dayhang Chemicals Co., Ltd Hangzou, China. Poloxamer 407 (P407), poloxamer 188 (P188), NaCl, KCl, $CaCl_2$, Na_2HPO_4, and KH_2PO_4 were purchased from (Green land chemical comp.U.K) and de-ionized water (DIW) was purchased from a local manufacturer.

chloroform, n-hexan, ethyl acetate and most organic solvents and

2.2 Methods

2.2.1 Preparation IDB-loaded nanoemulsion

Three well-characterized NE formulas were used to prepare a set of drug-loaded NEs as shown in table (1) using a self-emulsification method at which an oily phase, made of the drug in the oil, was added gradually under continuous stirring at 300rpm to the already prepared aqueous phase which is formed by dissolving the stated amount of CrEl and TC in the DIW.

Table (1): Formulas of Drug-Loaded Nanoemulsions

Drug-loaded NE compositions were expressed as part (gram)

Code	CrEL	TC	IDB:	LGO	DIW	Total
NE1	48.9	6.1	10	10	25	100
NE2	52	13	10	10	15	100
NE2	57.7	7.3	10	10	15	100

Preparation of thermosensitive nasal gels

Poloxamer 407 in three concentrations 10, 11, and 12 w/w% was used as the gel backbone. Poloxamer 188 can raise the temperature of gelation (Tgel) of P407, therefore, P188 at three ratios 1, 2, and 3% w/w with each P470 percentage ratio was used to prepare nine thermosensitive polymer blend of P407:P188 hydrogels (HGs) (10:3), (10:2), (10:1), (11:3), (10:2), (10:1), (12:3), (12:2), and (12:1). A quantity equal to 0.1g of IDB-loaded NE1, NE2, and NE3 were cross-mixed with 0.4g of (P407:P188) polymer blends percent ratios (10:3, 10:2, 10:1, 11:3, 11:2, 11:1, 12:3, 12:2, 12:1 w/w) using a magnetic stirrer to prepare 9 drug-loaded thermosensitive nasal gel (NG) formulas as shown in table (2)

Table (2) The Final compositions of the nasal gels formulas expressed as the percentage ratio

ME code	Gel code	Nasal Gel code	CrEL	TC	LGO	IDB	P407	P188	DIW	Total
NE1	10:3	NG1(10:3)	9.78	1.22	2	2	8	2.4	74.6	100
	10:2	NG1(10:2)	9.78	1.22	2	2	8	1.6	75.4	100
	10:1	NG1(10:1)	9.78	1.22	2	2	8	0.8	76.2	100
NE2	10:3	NG2(10:3)	10.4	2.6	2	2	8	2.4	72.6	100
	10:2	NG2(10:2)	10.4	2.6	2	2	8	1.6	73.4	100
	10:1	NG2(10:1)	10.4	2.6	2	2	8	0.8	74.2	100
NE3	10:3	NG3(10:3)	11.54	1.46	2	2	8	2.4	72.6	100
	10:2	NG3(10:2)	11.54	1.46	2	2	8	1.6	73.4	100
	10:1	NG3(10:1)	11.54	1.46	2	2	8	0.8	74.2	100

Characterization of the IDB-loaded nasal gels

Determination of temperature of gelation

The Tgel values were determined by using the tube inversion method. This method involves the loading of 1g of each NG into (2ml) sealable Eppendorf tubes and mounting them into a thermo-regulated water bath G.F.L, Karl Kolb, Germany. The temperature increased from 10°C to 34°C at a rate of 0.5 degrees/min. The Tgel can be determined by tilting the tube 90° every minute and the temperature at which the meniscus of the gel stands still without movement is recorded as the Tgel(8).

Determination of average globule size and polydispersity index (PDI)

The mean globule diameter of the prepared drug-loaded NE1, NE2, and, NE3 as well as the prepared NGs was determined using Zetasizer (Nano ZS red label, Malvern, UK) operated at 25°C, the angle of incident light was 173° and equipped with an optical filter(9). Samples of NGs were diluted 100 times by using ultra-purified cold water to allow free Brownian motion and to avoid multiple diffractions and were introduced to Zetasizer by disposable polystyrene cells(10).

Determination of Zeta potential: Using DTS 1070 zeta-cell, samples prepared as in the previous section were introduced into the Zetasizer to measure the potential of the diffused layer (zeta potential) that reflects NE electrostatic stability (11)

Morphological characterization by Transmission electron microscope (TEM): A drop of well-characterized NG was diluted and left to dry onto carbon-coated copper grids and negatively stained for 10 s with 2% filtered aqueous sodium phosphotungstate adjusted to pH 7.0. Using filter paper, the excess staining solution was removed from the grid and the sample was observed with a Philips 208S transmission electron microscope operated at 80 kV. (12)

In-vitro drug release of the nasal gels and release kinetics: A membrane-less model was applied to the USP type II dissolution apparatus to determine the drug release profile in which the prepared NGs were introduced directly to the dissolution media (200 ml simulated nasal fluid (SNF) with 1% Tween 80) without dialysis membrane(13). This approach can be achieved by using a 5ml test tube of 1cm diameter that is thermally equilibrated at 34°C in a water bath, as shown in figure (2), then 0.5 grams of tested NG equivalent to 10mg IDB was loaded into the tube and left 10min to ensure complete sol-gel transformation. The tube was fixed to the wall of the dissolution jar using double-sided adhesive tape. Aliquots of 1 ml were withdrawn at different periods (0, 0.25, 0.5, 1, 1.5, 2, 2.5, and 3h) and were filtered using a 0.45µm syringe filter. The quantity of the drug in each sample was measured using the UV-visible spectrophotometer. The media was replenished with fresh media each time to preserve sink conditions. The results of the permeated drug quantity per unit surface area were plotted versus their corresponding time and dissolution profiles were obtained (14).

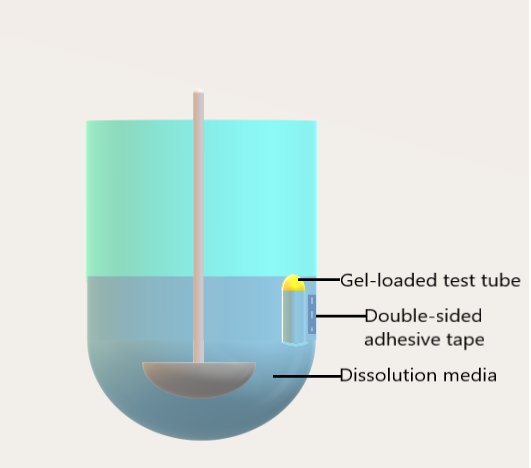


Figure (2): Membrane-less model dissolution test.

Ex-vivo transmucosal permeation through sheep nasal mucosa

Transmucosal permeation through the anterior turbinate mucosa of a recently sacrificed sheep was done to evaluate the permeation parameters after the formulation as NG. The excised mucosa was cut, washed with phosphate buffer saline (PBS), and preserved and cooled at 4°C until mounted on a 20ml vertical Franz-diffusion cell that had an effective permeation surface area of 3.14 cm^2. The Franz cell was kept in a thermo-regulated water bath at 34°C to simulate the temperature of the nasal cavity. The lower acceptor chamber was filled with (PBS with 1% Tween 80) without any entrapped air bubbles and stirred at 60 rpm using a magnetic stirrer. The excised mucosa was fixed in such a way that the upper part was facing the donor chamber and was left for 30 min for equilibrium. An amount equal to 0.5g of NG which is equivalent to 10mg IDB was applied into the donor chamber. Aliquots of 1ml from the receptor chamber were withdrawn at predetermined points of time (0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, and 3.0h), filtered using 0.45µm syringe filter and its IDB concentration was measured using UV-visible spectrophotometer. The media in the acceptor chamber was replenished with the same amount of fresh PBS solution each time to preserve sink conditions (15).

Data analysis of ex-vivo transmucosal permeation of nasal gels

The permeation profile across the nasal mucosa was constructed by plotting the cumulative amount of IDB permeated per unit area (Q, µg/cm^2) on the Y-axis against its corresponding time (t, h) on the X-axis (16). This plot was used to obtain the permeation rate or transmucosal flux of IDB at the steady state (Jss, µg/cm^2/h), which was obtained from the slope of the straight linear portion of the regression line equation (1). The lag time (Tlag) was obtained from the intercept of the straight line that represents steady-state regression with the time axis while the permeability coefficient (PC, cm/h), was obtained by dividing the ratio of drug flux (Jss) by the initial concentration (C_0) of IDB in the tested NG formula equation (2) and finally the enhancement

ratio (Er), which was obtained by dividing the permeation rate or flux (Jss) of IDB from the tested NG formula by the flux (Jss) of the pure IDB oily dispersion (control) equation (3).

Jss = dQ / dt ……Equation (1)
PC = Jss /C_0 …….Equation (2)
Er = Jss of IDB (formulation) / Jss of IDB (control)…… Equation (3)

Nasal mucosal histopathology study: Histopathological studies were done on sheep nasal mucosa to study the direct effect of the formulation application on mucosa when administered intranasally. Sheep nasal mucosa was obtained from a recently sacrificed animal from a local slaughterhouse. The excised mucosa was placed in PBS, cleaned, and cut into nine symmetrical pieces. The formulation was applied to 3 pieces and the positive control, 70% isopropyl alcohol, was applied to another 3 pieces while the negative control (PB pH= 6.5) was introduced to the last three pieces. After 1 hour of treatment, all samples were washed using PBS and stored in 10% formalin for 2h. Next, all samples were kept in 70% ethanol at 4°C for dehydration. The samples were then cut into 5µm thickness by using a microtome and were stained with a combination of hematoxylin and eosin (H&E) dye to observe any damage under an optical microscope (17).

Results

Thermal properties of nasal gels and temperature of gelation

The prepared NGs that were made of P407 as gel forming polymer and P188 as a Tgel modulator were translucent and free from flocculation. Poloxamer 407 has a minimum concentration equals 15% (18)

Determination of mean globule size, polydispersity index, and zeta potential

Mean globule size (MGS) obtained from Zetasizer for the plane NE1, NE2, and NE3 were 42.0, 54.56, and 45.65nm with zeta potential values -6.4, -3.2 and -2.8 mV respectively,

Table (3): Temperature of gelation, mean globule size, and zeta potential and pH of the Prepared NGs

NG-code NE(P407:P188)	NG1 (10:1)	NG1 (10:2)	NG1 (10:3)	NG2 (10:1)	NG2 (10:2)	NG2 (10:3)	NG3 (10:1)	NG3 (10:2)	NG3 (10:3)
Tgel (°C)	31.5	31.2	31.8	31.1	31.2	31.5	30.3	32.0	31.7
MGS (nm)	144.8	165.4	154.1	182.2	253.5	163.7	243.9	186.5	185.5
PDI (0-1)	0.31	0.12	0.26	0.24	0.27	0.17	0.25	0.19	0.23
ZP (mv)	0.2	-3.4	-2.7	0.5	-4.64	-2.32	-5.54	-2.42	-5.53
pH	5.8±0.13	5.9±0.08	5.7±0.09	5.8±0.13	5.78±0.11	5.95±0.08	5.68±0.1	5.7±0.11	5.8±0.09

In-vitro drug release of the nasal gels and release kinetics

Nasal gels can maintain their integrity at 34°C therefore NGs were introduced directly to the dissolution media without barrier. Formula NG1(10:3) showed the best release profile with almost complete drug release at minute 120 as shown in Figure (3).

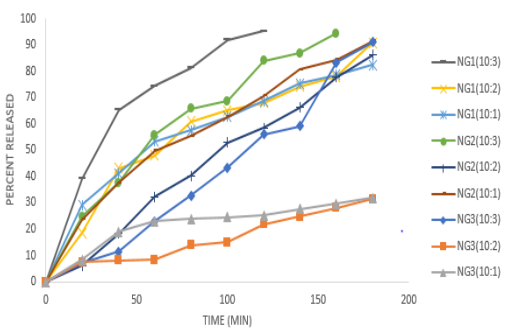


Figure (3): Drug release profile of the selected nasal gels.

In addition, all formulas showed almost no initial burst release despite the membrane-less model used which indicates the drug entrapment inside the carrier gel with no externally adsorbed drug(25).

Transmission electron microscopy (TEM)

The images that are generated by TEM revealed well-characterized rounded micellar configurations that are related to the surfactant-stabilized oil globules. Furthermore, an increase in MGS was noticed as shown in Figure (4) due to the formation of NE.

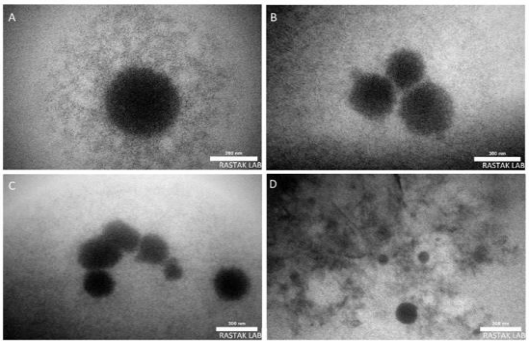


Figure (4): Images from the TEM of the selected formula NG (10:3).

Data analysis of ex-vivo transmucosal permeation of selected nasal gel

The outcome of the permeation study is shown in Figure (5) in which there is an appreciable difference in permeation profile between the formula NG1(10:3) and the oil dispersion of the drug as a control that was obtained from our previous work. The permeation was calculated as enhancement ratio which was equal to 20.3 times with a permeation rate equal to 28.48 µg/cm^2/h, lag time equal 0.57h, and permeation coefficient of 14.24x10^{-4}cm/h.

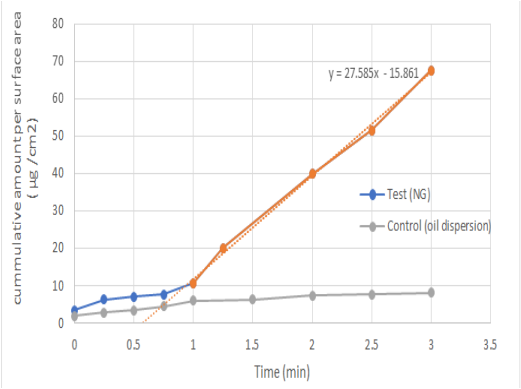
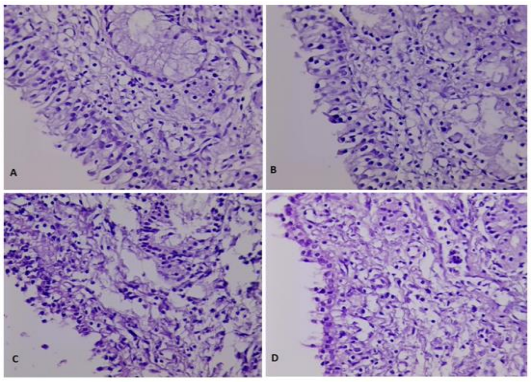


Figure (5): Cumulative IDB permeated per cm^2 versus time profile of NG1(10:3).

As mentioned earlier, the mucociliary wash time is between 12-15min, therefore the transition process from sol to gel is anticipated to prolong the dose residence time more than this period as well as beyond the lag time obtained from the ex-vivo permeation study (0.57h). The longer dose residency



Figure(6): Optical microscopy stained films of standard nasal mucosa (A), Negative control (B), positive control (C) and the selected formula (D).

Discussion:

Below which no gel structure can be formed therefore no gel could be anticipated at the proposed range in this study. However, a remarkable outcome in this study was the formation of thermosetting gel at lower concentrations of P407 equal to 8% unlike the observed effective concentrations (15-30%) that have been used in many previous studies (19,20) . Nasal gels of P407 concentration between (10-12%), regained their ability to form thermo-triggered gels upon the addition of the drug-loaded NE. Consequently, the viscoelastic and thermal properties of the obtained NG were characterizable as shown in Table (2). The Tgel of the NGs that were prepared of P407 at 11&12% w/w were below 30°C therefore out of 27 formulas, 18 were excluded from the study and only nine NGs at P407 equals 10%, shown in table (2), were adapted. Poloxamers have a surface activity that enables them to aggregate in micellar conformation of a hydrophobic core at concentrations above their critical micellar concentrations (CMC) which actually represents the critical gel concentration (CGC) at temperature exceeding the critical micellar temperature (CMT). Cremophre EL is a well-known surfactant that is time serves to offer a better chance for the drug to be absorbed sufficiently.

Histopathological study after nasal mucosa application

Histopathological studies' outcomes are shown in figure (6) where the effect of direct application of NG1(10:3) is shown in (D). Comparing (D) with PBS-treated negative control that has shown almost no destructive effect (B) and propyl alcohol-treated positive control that had a completely destructive effect (C), revealed a minor inflammatory response that was characterized by edematous serous infiltration of fluids and inflammatory cells. The cilia of viable cells were retained normally without ciliary toxicity after an hour of the formula application. However, direct toxicity outcome may offer basic information on the total histopathological changes since it was carried on excised nasal mucosa in which both the mucociliary clearance and blood perfusion are absent. manufactured by the polyethoxylation of 35 moles of castor oil which results in a mixture of different polyethoxylated long chains of (free fatty acids, mono, di, and tri fatty acid glycerol esters and glycerols) as well as unmodified castor oil residuals. This diversity in the composition of long alkyl chain compounds offers the possibility to manipulate and enhance the hydrophobic core radius of poloxamer micelles resulting in a more hydrophobic polymeric aggregation. This heterogenous micellar aggregation can be easily separated from the aqueous phase forming a three-dimensional gel phase at lower CMC value(21,22).. This reduction in the CMC leads to an overall reduction in copolymer concentration used in the formulation and consequently, their toxicity. Furthermore, the addition of the NE to four parts poloxamer HG results in a great reduction (dilution to one-fifth) in total surfactant (CrEL) concentration to less than 10% as well as other NE components (IDB and TC). This reduction in all components helps to decrease the direct toxicity and irritation that could be caused by the surfactant or the drug itself to the nasal mucosa(23). The low globular size indicates the efficiency of the spontaneous emulsification method used for preparation to obtain microemulsion (ME) with MGS below the referential value of 100nm at low PDI. Correspondingly, the results that are related to the prepared NGs showed that the prepared gels didn't retain the globule size below 100nm with a slight increment in diameter and PDI after the incorporation into the gel as shown in Table (3) due to the formation of NEs. Generally, particles with zeta potentials more than +30 mV or less than −30 mV are normally considered stable. Results obtained from measuring the zeta potential varied between (+0.5 and -5.54) which are considered low in defining the stability of NEs within the final product which is maintained by the steric effect imparted by the surfactant side chains rather than electrostatic stabilization(24). The permeation-

enhanced results are attributed to several reasons among which is the tremendous increase in the total surface area of the dispersed oil phase which can profoundly increase the soluble species of the drug that is permeable across the epithelial membrane(26). In addition, the ultra-fine drug-loaded oil droplets that are formed by the action of the emulsifying agent and due to their size and nature can easily permeate through the cellular membrane and cross tight junctions. Another mechanism that could be offered by NE is the permeation enhancement effect of the surfactant that contributes to the higher diffusion rate.

Conclusions

Idebenone can be formulated as NE-based thermosensitive NG that can maintain pharmaceutical stability and appreciable transmucosal permeability at a dose of 5mg/0.25g with permeation rate equal 28.48 μg/cm^2/h, especially when considering the good surface area of the nasal cavity 150-160cm^2 therefore more than 50% of the administered dose can be delivered. Therefore, an increased bioavailability is anticipated through nasal administration of idebenone as nanoemulsion. The basic direct histopathological tests showed retained histological features of the respiratory epithelial mucosa; therefore, further studies on viable animal models are recommended.

Author Contribution:

Study conception & design: (Hussein J. Kadhim). Literature search: (Hussein J. Kadhim). Data acquisition: (Hussein J. Kadhim). Data analysis & interpretation: (Hussein J. Kadhim). Manuscript preparation: (Hussein J. Kadhim, Khalid K Al-Kinani). Manuscript editing & review: (Hussein J. Kadhim, Khalid K Al-Kinani)

References

1. Patel RG. Nasal Anatomy and Function. Facial Plastic Surgery. 2017;33(1): 3–8.

2. Türker S, Onur E, Ózer Y. Nasal route and drug delivery systems., Pharmacy World and Sci. 2004;26:137–42. https://doi.org/10.1023/b:phar.0000026823.82950.ff

. 3. Bodratti AM, Alexandridis P. Amphiphilic block copolymers in drug delivery: advances in formulation structure and performance., Exp Opion D Del. Taylor and Francis Ltd; 2018;15:1085–104. https://doi.org/10.1080/17425247.2018.1529756.

4. Huang Y, Ma M, Zhu X, Li M, Guo M, Liu P, et al. Effectiveness of idebenone nanorod formulations in the treatment of Alzheimer's disease. J Con Rel. 2021 ;336:169–80. https://doi.org/10.1016/j.jconrel.2021.06.024.

5. Catarino CB, Klopstock T. Use of idebenone for the treatment of Leber's hereditary optic neuropathy. J Inborn Errors Metab Screen. 2017; 5:1-8. https://doi.org/10.1177/2326409817731112.

6. Zhao X, Zhang Y, Lu L, Yang H. Therapeutic effects of idebenone on Leber hereditary optic neuropathy. Curr Eye Res. 2020; 45(10):1315–23. https://doi.org/10.1080/02713683.2020.1736307.

7. Varela-Fernández R, Lema-Gesto MI, González-Barcia M, Otero-Espinar FJ. Design, development, and characterization of an idebenone-loaded poly-ε-caprolactone intravitreal implant as a new therapeutic approach for LHON treatment. European Journal of Pharmaceutics and Biopharmaceutics. 2021; 168:195–207. https://doi.org/10.1016/j.ejpb.2021.09.001.

8. Balakrishnan P, Park EK, Song CK, Ko HJ, Hahn TW, Song KW, et al. Carbopol-Incorporated thermoreversible gel for intranasal drug delivery. Molecules. 2015 ;20(3):4124–35. https://doi.org/10.3390/molecules20034124.

9. Bhattacharjee S. DLS and zeta potential - What they are and what they are not?, J of Cont Rel. 2016 ;235: 337–51

10. Sadoon NA, Ghareeb MM. Formulation and characterization of isradipine as oral nanoemulsion. Iraqi J of Pharm Sci. 2020; 29(1):143–53. https://doi.org/10.31351/vol29iss1pp143-153.

11. Hammodi ID, Abd Alhammid SN. Preparation and characterization of topical letrozole nanoemulsion for breast cancer. Iraqi J of Pharm Sci. 2020 ;29(1):195–206. https://doi.org/10.31351/vol29iss1pp195-206.

12. Maccelli A, Vitanza L, Imbriano A, Fraschetti C, Filippi A, Goldoni P, et al. Essential oils: chemical profiles/phytochemical screening, antimicrobial activity and o/w nanoemulsion formulations. Pharmaceutics. 2020 ;12(1):12010007. https://doi.org/10.3390/pharmaceutics12010007.

13. Blanchard J, Almeida H, Desai SD. In vitro evaluation of pluronic F127-based controlled-release ocular delivery systems for pilocarpine . 1998; 87(9):226-230 https://doi.org/10.1021/js970090e.

14. Abdulla NA, Balata GF, El-ghamry HA, Gomaa E. Intranasal delivery of clozapine using nanoemulsion-based in-situ gels: An approach for bioavailability enhancement. Saudi Pharmaceutical J. 2021 ;29(12):1466–85. https://doi.org/10.1016/j.jsps.2021.11.006.

15. Jaiswal M, Kumar A, Sharma S. Nanoemulsions loaded Carbopol® 934 based gel for intranasal delivery of neuroprotective Centella asiatica extract: in–vitro and ex–vivo permeation study. J Pharm Investig. 2016 ;46(1):79–89. https://doi.org/10.1007/s40005-016-0228-1.

16. Abdulbaqi MR, Rajab NA. Apixaban ultrafine O/W nano emulsion transdermal drug delivery system: Formulation, in vitro and ex vivo characterization. Syst Rev in Pharmacy. 2020;11(2):82–94.

17. Nagda CD, Chotai NP, Nagda DC, et al. Development and characterization of mucoadhesive microspheres for nasal delivery of ketorolac. Pharmazie. 2011 ;66(4):249–57. https://doi.org/10.2174/156720112800234503.

18. Chen Y, Lee JH, Meng M, Cui N, Dai CY, Jia Q, et al. An overview on thermosensitive oral gel based

on poloxamer 407. Materials.2021; 14: https://doi.org/10.3390/ma14164522.
19. Dumortier G, Grossiord JL, Agnely F, Chaumeil JC. A review of poloxamer 407 pharmaceutical and pharmacological characteristics., Pharmaceutical Res. 2006; 23(12): 2709–28. https://doi.org/10.1007/s11095-006-9104-4.
20. Giuliano E, Paolino D, Fresta M, et al. Mucosal applications of poloxamer 407-based hydrogels: An overview. Pharmaceutics. 2018; 10:10030159. https://doi.org/10.3390/pharmaceutics10030159.
21. le Garrec D, Leroux JC. Healthcare technology review micelles in anticancer drug delivery. Am J Drug Deliv. 2004;2(1):15-42. https://doi.org/10.2165/00137696-200402010-00002.
22. Letchford K, Burt H. A review of the formation and classification of amphiphilic block copolymer nanoparticulate structures: micelles, nanospheres, nanocapsules and polymersomes., Eur J Pharmaceutics and Biopharmaceutics. 2007; 65: 259–69. https://doi.org/10.1016/j.ejpb.2006.11.009.
23. Xu X, Shen Y, Wang W, Sun C, Li C, Xiong Y, et al. Preparation and in vitro characterization of thermosensitive and mucoadhesive hydrogels for nasal delivery of phenylephrine hydrochloride. European Journal of Pharmaceutics and Biopharmaceutics. 2014 ;88(3):998–1004. https://doi.org/10.1016/j.ejpb.2014.08.015.
24. Souza AG de, Ferreira RR, Aguilar ESF, Zanata L, Rosa D dos S. Cinnamon Essential Oil Nanocellulose-Based Pickering Emulsions: Processing Parameters Effect on Their Formation, Stabilization, and Antimicrobial Activity. Polysaccharides. 2021;2(3):608–25. https://doi.org/10.3390/polysaccharides2030037.
25. Espinoza LC, Silva-Abreu M, Clares B, Rodríguez-Lagunas MJ, Halbaut L, Cañas MA, et al. Formulation strategies to improve nose-to-brain delivery of donepezil. Pharmaceutics. 2019;11(2):11020064. https://doi.org/10.3390/pharmaceutics11020064.
26. Naqvi A, Ahmad M, Minhas MU, Khan KU, Batool F, Rizwan A. Preparation and evaluation of pharmaceutical co-crystals for solubility enhancement of atorvastatin calcium. Polymer Bulletin. 2020 ;77(12):6191–211. https://doi.org/10.1007/s00289-019-02997

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تحضير عقار الايدبنون كجل انفي يتشكل بالحرارة لتوافر حيوي وتأثير نسيجي افضل

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خلفية Idebenoneهو دواء يتم استقلابه على نطاق واسع مع ضعف ذوبانه في الماء ويستخدم لعلاج الاعتلال العصبي البصري الوراثي لليبر. الهدف تهدف هذه الدراسة إلى تحضير مستحلب الإيدبينون النانوي كجل أنفي يعتمد على البولوكسامير للتغلب على المعدل الكبير للاستقلاب الكبدي من أجل توافر حيوي أفضل وتقليل التأثير المرضي النسيجي على الغشاء المخاطي للأنف .
الطرق :استندت استراتيجية العمل إلى تقليل التركيز المتبادل بين المستحلب النانوي والمستحلب النانوي. الجل الناقل عن طريق ضبط درجة حرارة الجيل بين 30-32 درجة مئوية للتغلب على طرد الجرعة الدوائية. تعتمد المستحلبات النانوية على كريموفور اي ال وترانسكيوتول كنظام استحلاب لتثبيت زيت عشبة الليمون المحمل بالإيدبينون. تم استخدام طريقة الاستحلاب التلقائي لتحضير المستحلبات النانوية التي تميزت بمقياس زيتا بينما تم تحضير الهلاميات المائية الحساسة للحرارة باستخدام الطريقة الباردة. تم إجراء اختبار الذوبان في المختبر ودراسة التخلل خارج الجسم الحي من خلال الغشاء المخاطي للأنف للأغنام لتقييم نسبة التخلل المعززة ومعدل التخلل ومعامل التخلل. تمت دراسة التأثير النسيجي المرضي للتطبيق المباشر على الغشاء المخاطي للأنف في الأغنام باستخدام المجهر الضوئي لتقييم السمية الخلوية
النتائج :أظهرت الصيغة المحضرة من NE1 مع بولوكسامير 407: بولوكسامير 188 بتركيزات 10:3% وزن/وزن على التوالي، إطلاقاً كاملاً للدواء خلال 120 دقيقة بسبب التآكل الكامل لخليط البوليمرات. علاوة على ذلك، تم الحصول على مستحلب نانو حساس للحرارة عند درجة حرارة الجيل 31.8 درجة مئوية بتركيزات أقل بكثير من بولوكسامير 407 (10٪) مقارنة بالدراسات السابقة. احتفظت المستحلبات النانوية بحجمها الكروي أقل من 100 نانومتر بسبب زيادة تثبيت الهلام بطريقة الانحباس
الاستنتاجات أدى تغلغل الدواء من خلال الغشاء المخاطي للأنف في الأغنام إلى زيادة في نسبة التخلل المعزز إلى 3.20 مرة وغيرها من المعلمات الحركية للتدفق مقارنة بتلك الخاصة بتشتت زيت IDB. أظهرت السمية الخلوية المباشرة استجابة التهابية بسيطة تتميز بالتسلل المصلي للخلايا الالتهابية والوذمة. في المقابل، احتفظت معظم الخلايا الظهارية بخصائصها النسيجية مقارنة بشرائح التحكم
الكلمات المفتاحية: وافر حيوي، ايدبنون، نانوايملشن، تعابرز