IMPROVEMENT OF THE BIOAVAILABILITY OF BUSPIRONE HCL USING INTRANASAL DELIVERY SYSTEMS

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ABSTRACT

The purpose of the present study was to improve the bioavailability of buspirone hydrochloride using oil-in-water microemulsion, which was suggested to be suitable for intranasal delivery. Different pseudo-ternary phase diagrams were constructed to determine the microemulsion existing zone. The optimized microemulsion system was chosen. Different formulations were thus prepared and they were subsequently characterized for their polarized light microscopy, % transmittance, droplet size, and pH. An optimal microemulsion formulation consisting of 5% isopropyl myristate, 50% water, and 45% (w/w) surfactant/cosurfactant [Tween 80 30%, propylene glycol 15 % at 2: 1 weight ratio] was transparent with % transmittance 99.52 ± 0.43%, mean globule size 35.1 ± 0.5nm, and pH 6.4 ± 0.03, was thus selected for preparation of buspirone microemulsion formulation. Drug release was carried out using modified Franz diffusion cell. Various pharmacokinetic parameters including C_{max}, t_{max} and AUC_{0-t} were determined using Wister albino rats as the animal model. The absolute bioavailability (0–6 h) was 15.85% compared to the intravenous administration in rats, whereas the oral bioavailability of buspirone hydrochloride was 4%. The results confirmed that the suggested intranasal buspirone microemulsion formulations improved to a much promising extent its bioavailability.

Key words: Intranasal delivery (IN); Microemulsion (ME); Buspirone Hydrochloride (BH); bioavailability (BAV).

INTRODUCTION

In recent years, the nasal route has received great attention because of the large surface area of the nasal mucosa and the relatively high blood flow, thereby achieving a rapid absorption and avoiding the hepatic first-pass elimination **(Lin *et al*., 2007)**.

Carrier systems play an important role in the drug delivery to the target site because a dosage form with poor drug delivery can make a useful drug worthless. Microemulsions (MEs) offer an interesting and potentially powerful carrier system for drug delivery because of their high solubilization capacity, transparency, thermodynamic stability, ease of preparation, in addition to the high diffusion and absorption rates **(Jadhav *et al*., 2006; Yin *et al*., 2009)**.

Buspirone HCl (BH), the psychotropic drug with selective anxiolytic properties, belongs chemically to the class of azaspirodecanediones which are not chemically or pharmacologically related to benzodiazepines. It seems to be a promising candidate for the intranasal delivery owing to its extensive first-pass metabolism resulting in the poor oral bioavailability of the pure drug (~ 4%), in addition to a short half-life and the poor lower gastrointestinal tract absorption values **(Galichet, 2004)**. Based on this, the present study aims was to improve BH bioavailability using ME that may help maximize the therapeutic index of the drug, reduce its side effects, its dose and its frequency of dosing that may result in a cost-effectiveness treatment intervention **(Zhang *et al*., 2004)**.

EXPERIMENTAL

Materials:

BH was kindly supplied by Bristol Myers Squibb (Cairo, Egypt). Jojoba oil was kindly supplied by the Egyptian Oil Company (Cairo, Egypt). Isopropyl myristate (IPM), Acetonitrile (HLPC grade), Methanol were purchased from Sigma-Aldrich (St. Louis, USA). Diltiazim (DILT) was kindly supplied by E.P.I.C.O (Cairo, Egypt). Labrafac® Lipophile WL1349 (Labr), Diethylene glycol monoethyl ether "Transcutol®", Caprylocaproyl macrogol-8 glycerides "Labrasol®" were kindly supplied by Gattefosse (Saint-Priest, Lyon, France). Polyethylene 80 sorbitan monooleate "Tween80®" (T80), Isopropyl alcohol, Propylene glycol (PG), Disodium hydrogen phosphate (Na_2HPO_4), Potassium dihydrogen phosphate (KH_2PO_4) were purchased from Adwic and El-Nasr Chemical Co, (Cairo, Egypt).

Equipment:

Horizontal mechanical shaker (Kötterman, Hanigsen, Germany); Biofuge pico micro centrifuge (Heraeus Instruments, Hanau, Germany); UV-visible spectrophotometer (Shimadzu, model UV-1601 PC, Kyoto, Japan); magnetic stirrer with heater (Yellow Line, MGA HS 7, IKA, Germany); cross-polarized light microscopy (Axioskop, Zeiss, Jena, Germany coupled with a photographic camera, Axiocam, Model ICc3, Jena, Germany); Zetasizer (Malvern instruments, Malvern, UK); digital pH meter (Orion, model 420A, USA); centrifuge with cooling (Hermie Labortechnik GmbH, type Z216MK, Germany); vortex shaker (IKA MS3 Digital, Germany); HPLC (Agilent Technolgies 1200 series, Germany).

Methodology:

1. Solubility studies

An excess amount of BH (10 mg) was introduced into each of three different capped vials to which 2 mls of each of the investigated oils (IPM, jojoba oil and labr) were added separately. After sealing the capped vials, the mixtures were mechanically shaken for 48 hours using a horizontal mechanical shaker at 25^{o}C. The mixtures were then allowed to stand for 24 hours for equilibration. Each vial was then centrifuged at 10,000 rpm for 10 minutes using a biofuge pico micro centrifuge, followed by filtration through millipore filter (0.45µm). The amount of BH was determined by UV-visible spectrophotometer at 239nm after proper dilution with isopropyl alcohol **(Vyas *et al*., 2005)**.

2. Construction of pseudo-ternary phase diagram

To explore ME regions; phase diagrams were constructed by water titration method **(Chen *et al*., 2004)**, two surfactants Labrasol® and T80 in combination with Transcutol® and PG respectively as cosurfactants were used with any of the selected oils chosen according to the above mentioned solubility study **(Kumar *et al*., 2009)**. The ratio of oil to the surfactant/cosurfactant mixture (Smix) was varied as follows: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 (w/w). Surfactants were blent with cosurfactants in a fixed weight ratios (1:1 and 2:1) in order to study the effect of surfactant concentration on the phase region. The oil-Smix mixture was titrated with water dropwise with stirring using a magnetic stirrer with heater at 25^{o}C to obtain a transparent ME. After the identification of ME region from the phase diagram, the desired component ratios were selected for ME preparations.

3. Characterization of unloaded microemulsion formulations

3.1. Polarized light microscopy

To verify the isotropic nature of MEs, samples were examined using cross-polarized light microscopy. A drop of the ME was placed between a cover slip and a glass slide and observed under cross-polarized light **(Friberg, 1990; Hathout *et al*., 2010)**.

3.2. Percent transmittance

Transparency of the selected MEs was determined by measuring the percentage transmittance through UV-visible spectrophotometer. Percentage transmittance of samples was measured at 633 nm taking purified water as the blank **(Kawtikwar *et al.*, 2009)**. Triplicate measurements were performed for each sample.

3.3. Determination of the droplet size

The particle size of selected MEs was determined by means of dynamic light scattering using a ZetaSizer **(El-Laithy, 2003)**. The scattering intensity data were obtained from pre-filtered (0.45 µm) MEs **(Delgado-Charro *et al.*, 1997)**. Samples were loaded into 1 cm^3 cuvettes in a thermostated chamber at 25^oC **(Hathout *et al.*, 2010)**. The measurements were performed after diluting each of the samples 100-folds with the continuous phase (Rasal *et al*., 2010). Triplicate measurements were performed for each sample.

3.4. Determination of the pH

The pH measurement was carried out using digital pH meter. Triplicate measurements were performed for each sample.

4. Preparation of BH loaded microemulsion

Buspirone microemulsion was prepared using water titration method. The optimized unloaded ME was chosen to prepare the drug loaded ME formulation in a drug concentration of 1%, (w/w). The formulation was prepared by dissolving the drug in water for the preparation of BHME. The resulting solution was added dropwise to the selected mixture of oil, surfactant and co-surfactant with continuous stirring using a magnetic stirrer with heater at 25^oC.

5. *In-vitro* drug release study

In-vitro release study of ME was carried out by the modified Franz diffusion cell. Dialysis diffusion membrane having molecular weight cut off range of 12000–14000 Da was used where pieces of the membrane were soaked in phosphate buffer, pH 6.8, for 24 hours prior to the experiment. Diffusion cell was filled with phosphate buffer, pH 6.8, and the membrane was then mounted on the cell. The temperature was maintained at 34^oC. After a pre-incubation time of 20 minutes, ME amount equivalent to 10 mg of BH was placed in the donor chamber. Aliquots of one ml samples were withdrawn from the acceptor compartment at time intervals of 5, 10, 15, 30, 45, 60, 120, 180, and subsequently after 360 min. All samples were replaced by equal volumes of fresh phosphate buffer (Rasal *et al*., 2010). The amount of diffused drug was calculated after measuring the absorbance using a UV-visible spectrophotometer at 238 nm as shown in Table 1.

Table (1): *In-vitro* drug release study.

Time (min)	Abs*	Slope	D.F*	Conc*	Conc*Aliq*	Conc*D.M*	Cumulative amount
5	A1	S	D1	(A1/S)*D1	B1	C1	C1
10	A2	S	D2	(A2/S)*D2	B2	C2	C2+B1
15	A3	S	D3	(A3/S)*D3	B3	C3	C3+B2+B1
30	A4	S	D4	(A4/S)*D4	B4	C4	C4+B3+B2+B1
45	A5	S	D5	(A5/S)*D5	B5	C5	C5+B4+B3+B2+B1
60	A6	S	D6	(A6/S)*D6	B6	C6	C6+B5+B4+B3+B2+B1
120	A7	S	D7	(A7/S)*D7	B7	C7	C7+B6+B5+B4+B3+B2+B1
180	A8	S	D8	(A8/S)*D8	B8	C8	C8+B7+B6+B5+B4+B3+B2+B1
360	A9	S	D9	(A9/S)*D9	B9	C9	C9+B8+B7+B6+B5+B4+B3+B2+B1

Abs: absorbance, **D.F:** dilution factor, **Conc:** concentration, **Aliq:** Aliquots of samples were withdrawn from the acceptor compartment at time intervals of 5, 10, 15, 30, 45, 60, 120, 180, and subsequently after 360 min, **D.M:** volume of dissolution medium.

Where, cumulative % of diffused drug = (Sum/B)·100

B: amount of drug placed in donor chamber.

6. Pharmacokinetic studies for buspirone microemulsion

The pharmacokinetic studies of BH were determined for the intranasal delivery of BHME, the results were compared to those obtained from I.V delivery of BH solution (BHS). BHS for I.V delivery was prepared as follow:

BH (10 mg) was added to 25 ml of normal saline (0.9% NaCl) and with continuous stirring. Final concentration was 0.4 mg/ml.

6.1. Animal modeling and drug administration

For all animal studies, the experimental procedures conformed to the ethical principles **(Habashy *et al*., 2005)** where108 Wister Albino rats (aged 4-5 months) and weighing 200 ± 20 g were selected for the study. The animals were randomly divided into 2 groups, each consisting of 54 rats; Group I received IN BHME, and group II received IV BHS. In each group, six rats, per time point, *viz*., 5, 10, 15, 30, 45, 60, 120, 180 and 360 min were used. Aliquots of 10 µl of BHME containing 100µg of BH (equivalent to 1µg/g) were instilled in each of the two nostrils. The conscious rats were held from the back in slanted position during the intranasal administration of the formulation, and the BHME was administered in the openings of the nostrils by means of a micropipette attached with low density polyethylene tube having 0.1 mm internal diameter at the delivery site. For comparison, 0.5 ml of a 0.4 µg/µl of BH in normal saline was injected through the tail vein of the rats (group II).

6.2. Sample preparation for analysis

6.2.1. Plasma Treatment

Blood samples were collected into heparinized tubes. Following centrifugation by using cooling centrifuge at 4000 rpm for 10 min, the resultant plasma was separated and then frozen immediately at –80°C until assayed. 500 µl of each of the plasma samples was mixed with 100 µl of DILT solution (1000 ng/ml), acting as the internal standard (IS). One ml of acetonitrile was finally added. The mixture was then vortex-mixed for 30 sec and subsequently centrifuged at 6000 rpm for 15 min. The supernatant was analyzed for BH content using HPLC.

6.2.2. Chromatographic conditions

The HPLC system consisted of an LC-G 1311A solvent delivery pump equipped with a 20-µl loop and rheodyne sample injector and G1315D diode array detector. The analytical column used was Agilent TC-C_{18} column (250mm×4.6mm I.D, particle size 5µm) at a temperature of 30°C. The mobile phase was acetonitrile and potassium phosphate buffer (10mM) 35:65 v/v at pH adjusted to 4.6 with few drops of ortho phosporic acid. The eluent was monitored at 235 nm, at a flow rate of 1mL/min and the injection volume was 50 µl.

6.3. Pharmacokinetic analysis

The pharmacokinetic parameters of each formulation were calculated using the WinNonlin® program (Version 2, Pharsight Co., Mountainview, CA, USA). The absolute bioavailability following IN administration of BH was estimated using the following equation:

$$\left[AUC_{0-360\text{min}}\ (IN) \Big/ AUC_{0-360\text{min}}\ (IV) \right] \times 100$$

7. Data analysis

All the experiments in the study were performed at least three times and the data were expressed as the mean ± standard deviation (S.D.). A two-tailed unpaired Student's t-test was performed at $p < 0.05$.

RESULTS AND DISCUSION

1. Solubility study

In order to find appropriate oils which can be used for the ME, the solubility of BH was measured in various oils. Solubility study shows that, a slightly higher BH was dissolved in Labr (3.65 ± 0.03) compared to jojoba oil (3.31 ± 0.04). This might probably be due to the higher polarity of the medium chain triglyceride as shown in Figure 1 which therefore possesses higher solubilizing capacity for the polar BH compared to jojoba oil which is composed of a mixture of naturally occuring long chained linear esters as shown in Figure 2. Surprisingly and irrespective of this rule, the long chain triglyceride, IPM as shown in Figure 3, showed the highest solubilizing capacity (4.38 ± 0.01) compared to the two other oils. This result came in accordance with previous studies which demonstrated the ability of IPM to solubilize a variety of drugs with different nature, however, the mechanism is still poorly understood **(Baroli *et al*., 2000; Peltola *et al*., 2003; Djordjevic *et al*., 2004)**.

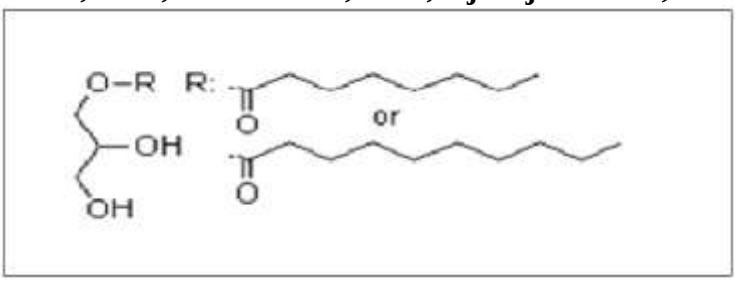

Fig. (1): Chemical structure of labrafac lipophile WL 1349.

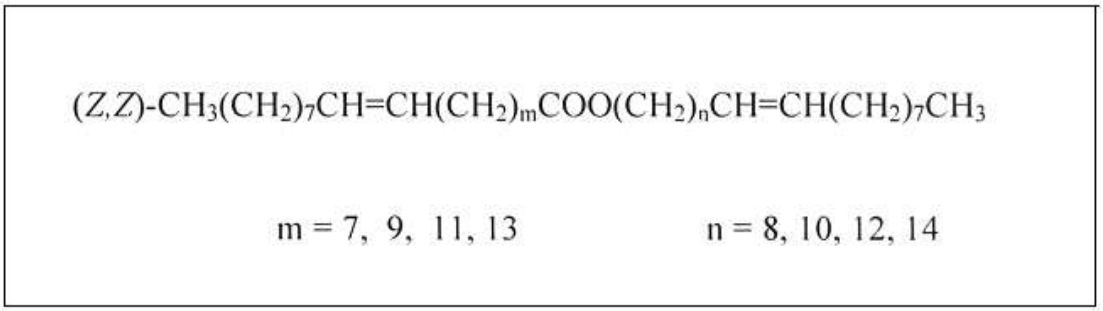

Fig. (2): Chemical structure of jojoba oil.

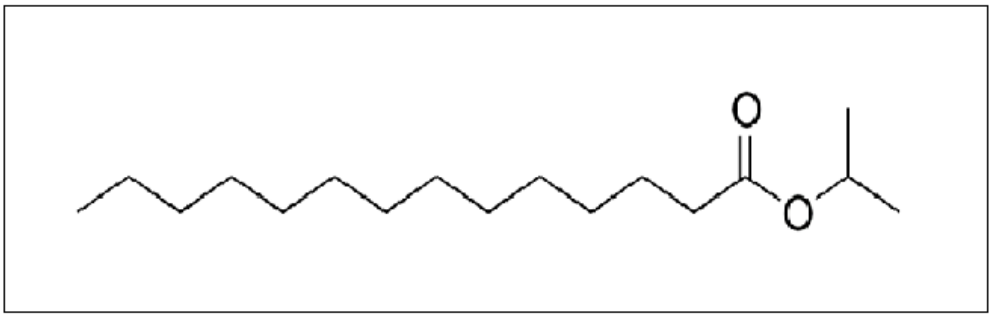

Fig. (3): Chemical structure of isopropyl myristate.

2. Phase behavior

The pseudo-ternary phase diagram of both surfactant/cosurfactant systems (Labrasol®/Transcutol® and T80/PG) at two surfactant/cosurfactant weight ratios (1:1 and 2:1) are presented in Figures (4-7). The ME area is presented in the phase diagrams as shaded region. The rest of the region on the phase diagram represents the turbid conventional emulsions based on visual inspection. The phase diagrams reveal that the existence of the ME area becomes enlarged in case of T80 compared to Labrasol®. This could be attributed to the effect of the hydrocarbon chain length of the oils and surfactants. Labrasol® has shorter hydrocarbon chain than T80 and showed smaller ME area **(Trotta, 1999)**. The influence of relative surfactant:cosurfactant concentrations on the ME isotropic region can be evidently seen from phase diagrams. In both systems the ME region increased in size with the higher surfactant concentration. This increase was toward the oil–water axis, indicating that by increasing the T80 or Labrasol® concentration, the maximum amount of water and oil that could be solubilized into the ME increased.

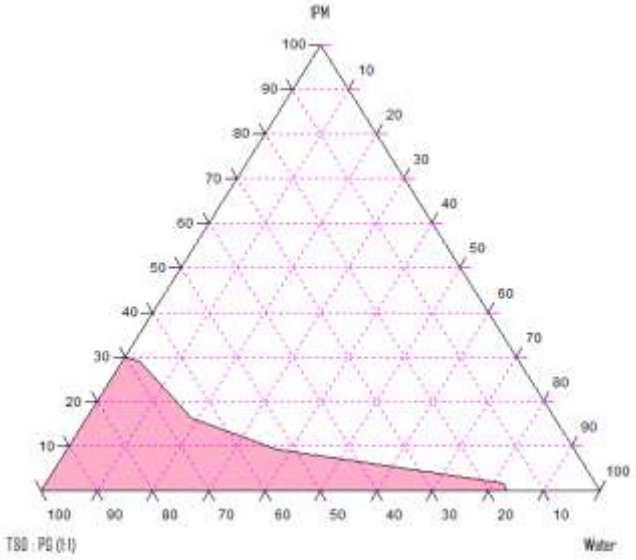

Fig. (4): Pseudo-ternary phase diagram of the microemulsion containing IPM / T80 / PG / Water system where the mixing ratio of T80 : PG is 1:1.

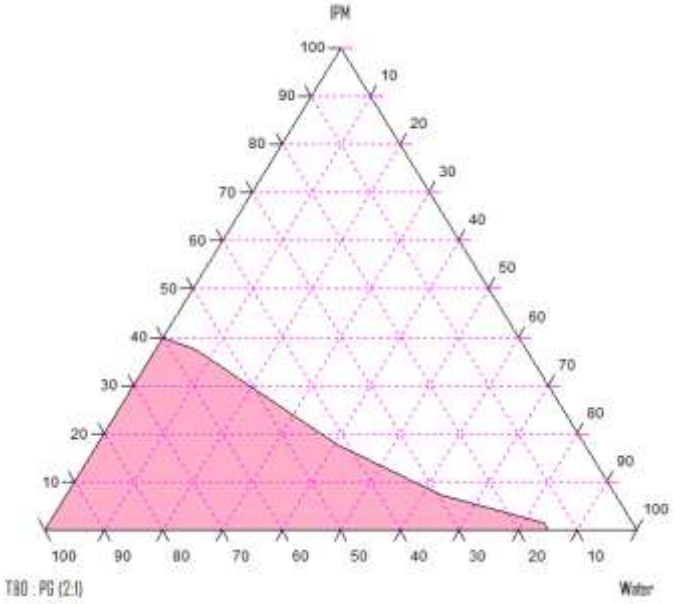

Fig. (5): Pseudo-ternary phase diagram of the microemulsion containing IPM / T80 / PG / Water system where the mixing ratio of T80 : PG is 2:1.

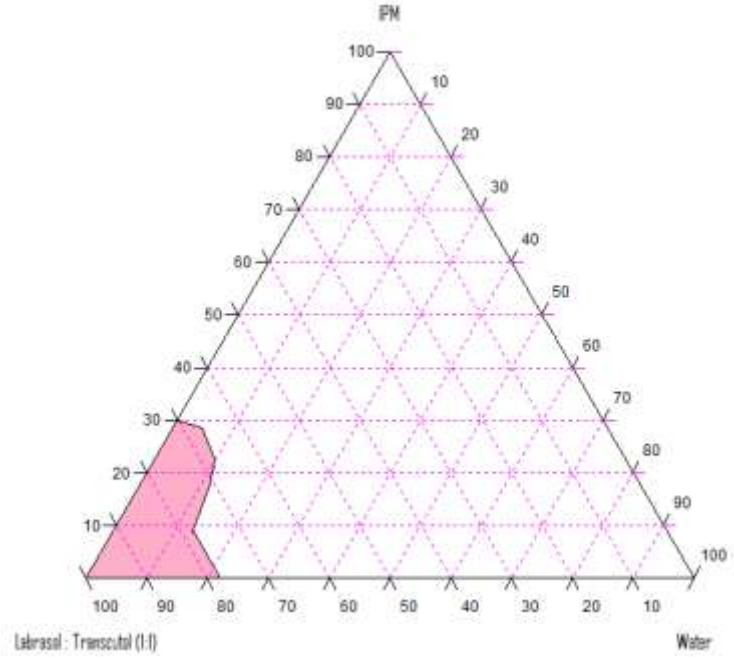

Fig. (6): Pseudo-ternary phase diagram of the microemulsion containing IPM / Labrasol / Transcutol / Water system where the mixing ratio of Labrasol : Transcutol is 1:1.

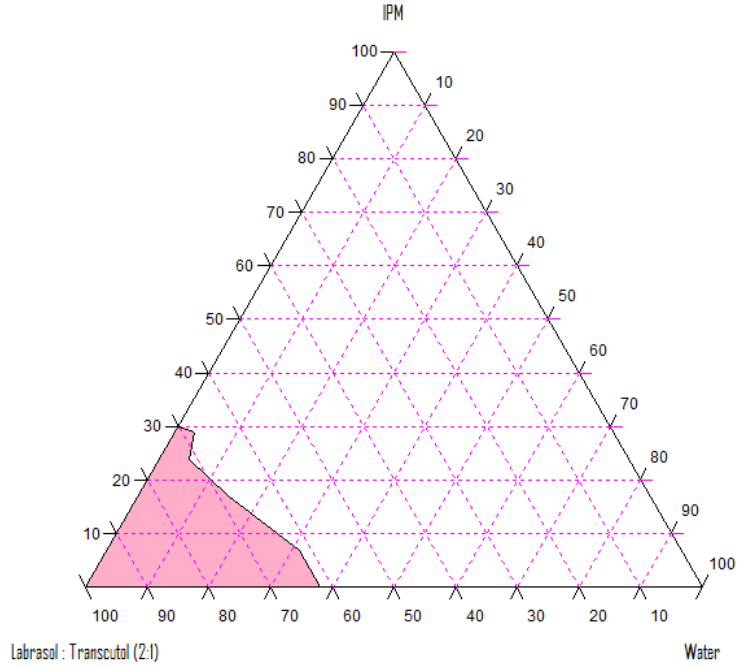

Fig. (7): Pseudo-ternary phase diagram of the microemulsion containing IPM / Labrasol / Transcutol / Water system where the mixing ratio of Labrasol : Transcutol is (a) 1:1, (b) 2:1.

A successful pharmaceutical ME system should not only be stable and transparent, but should also be of relatively low surfactant content and capable of carrying a large amount of drug **(Kamila *et al*., 2009)**. Oil-in-water (O/W) type of ME was suitable for IN delivery as the nasal secretion was aqueous in nature **(Rasal *et al*., 2010)**. From the phase diagrams, the ME system IPM / T80 / PG / water with the ratio surfactant:cosurfactant equal 2:1 had sufficiently large ME domain was chosen to prepare four formulations, names; ME A, ME B, ME C, and ME D as shown in Table 2. These ME formulations were prepared i.e. ME A to ME D in varying concentration of surfactants and water, oil concentration was fixed to 5%.

Table (2): Composition of the prepared microemulsions.

Microemulsion systems	***Oily phase***	***Surfactant***	***Cosurfactant***	***Aqueous phase***
	Isopropyl myristate (%, w/w)	***Tween80 (%, w/w)***	***Propylene glycol (%, w/w)***	***Purified water (%, w/w)***
A	***5***	***30***	***15***	***50***
B	***5***	***36***	***18***	***41***
C	***5***	***40***	***20***	***35***
D	***5***	***45***	***22.5***	***27.5***

3. Characterization of unloaded microemulsion formlations

3.1. Polarized light microscopy

Isotropic material, such as a ME, in contrast to anisotropic liquid crystals, will not interfere with the polarized light **(Friberg, 1990)** and the field of view remains dark. In this context, all the investigated ME fields remained dark under the polarized microscope.

3.2. Percent transmittance

The percentage transmittance for the selected MEs ranged from 99.23±0.18% to 99.52±0.43% as shown in Table (3), indicating transparency and stability of the selected microemulsions **(Formariz *et al*., 2006)**.

3.3. Particle size

All formulae showed a fairly unimodal particle size distribution as shown in Figures (8-11). Data presented in Table (3) show that the lowest particle size value was achieved with ME D containing the highest amount of surfactants and the highest particle size value was achieved from ME A containing the lowest amount of surfactants. As previously reported, the addition of surfactant to ME system causes the interfacial film to condense leading to a reduction in particle size **(Kale and Allen, 1989)**.

3.4. pH

The pH range of the selected MEs was 6.2±0.05 to 6.4±0.03 as shown in Table 3. For intranasal application, the ideal pH of any suggested formulation should be in the range of 4.5 - 6.5 **(Arora *et al*., 2002)**. The main disadvantage of microemulsions in pharmaceutical application is that they usually contain a large amount of surfactants which can cause irritation in the nasal mucosa. In order to select a microemulsion system pharmaceutically acceptable; it is necessary to select such systems which contains the least amount of surfactants to prevent or reduce irritation as possible.

Table (3): Physicochemical parameters of selected microemulsion formulations.

Parameters*	***Microemulsion type***			
	A	***B***	***C***	***D***
% Transmittance	***99.52 ± 0.43%***	***99.32 ± 0.29%***	***99.28 ± 0.15%***	***99.23 ± 0.18%***
Particle size (nm)	***35.1 ± 0.5***	***30.2 ± 0.5***	***28.6 ± 0.4***	***25.7 ± 0.2***
pH	***6.40 ± 0.03***	***6.35 ± 0.07***	***6.30 ± 0.06***	***6.20 ± 0.05***

* Values are mean ± SD., n = 3.

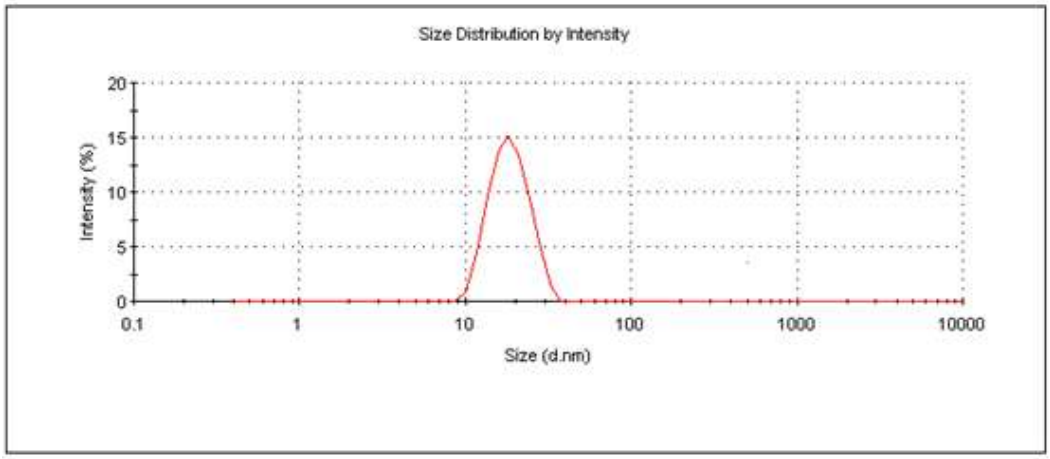

Fig. (8): Particle size distribution of microemulsion A [IPM / Tween80 / Propylene glycol / water (5: 30: 15: 50) (%w/w)].

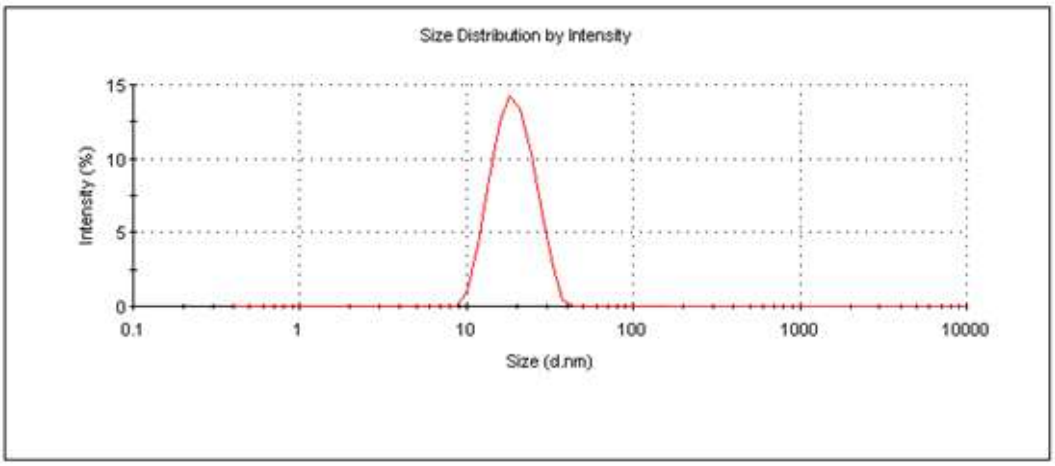

Fig. (9): Particle size distribution of microemulsion B [IPM / Tween80 / Propylene glycol / water (5: 44: 22.5: 27.5) (%w/w)].

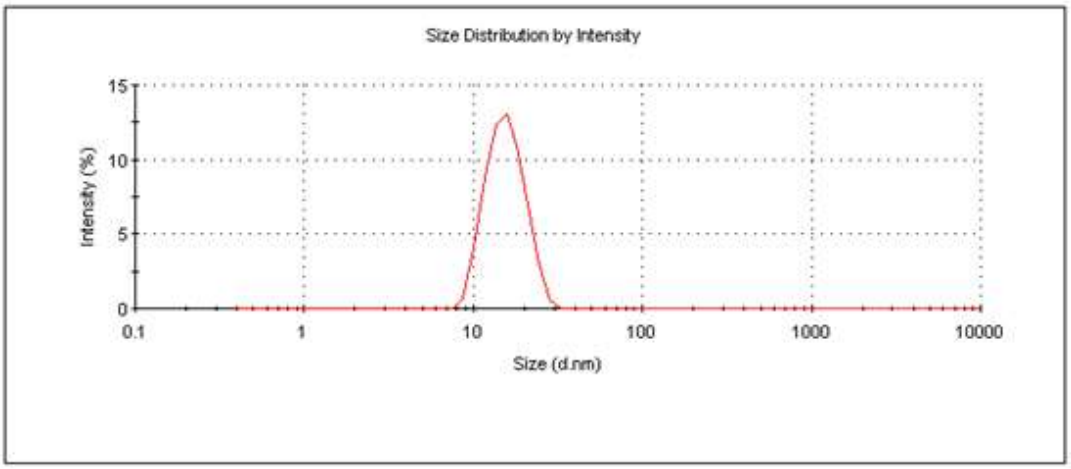

Fig. (10): Particle size distribution of microemulsion C [IPM / Tween80 / Propylene glycol / water (5: 36: 18: 41) (%w/w)].

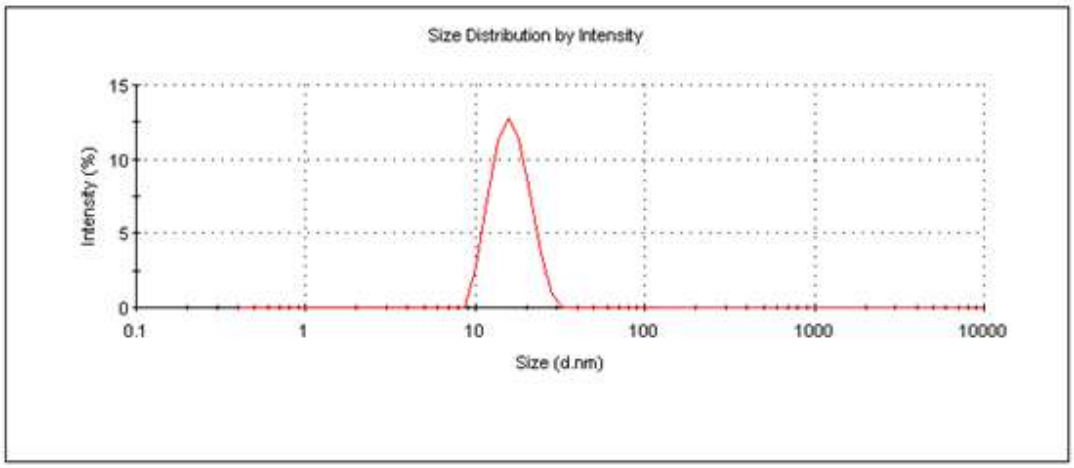

Fig. (11): Particle size distribution of microemulsion D [IPM / Tween80 / Propylene glycol / water (5: 40: 20: 35) (%w/w)].

From the above mentioned results, all prepared MEs showed properties promising for nasal delivery. However, microemulsion A composed of IPM (5%) / Tween80 (30%) / Propylene glycol (15%) / water (50%) with the ratio surfactant:cosurfactant 2:1, contains the least amount of surfactant needed for maximum water solubilization and was therefore selected for preparation of BHME formulation.

4. *In-vitro* drug release study

As shown in Figure 12 and Table 4, buspirone solution showed 100% cumulative drug release after 2 h. The percentage drug release was 100% after 3 h in ME. The inhibition in release of BH by the ME could be due to the high viscosity of microemulsion compared to solution. However, the release rate of the formulation is considered to be decreased with the increase in the viscosity of the formulation, resulting in a delay of the drug's approach to the dissolution medium **(Furubayashi *et al*., 2007)**.

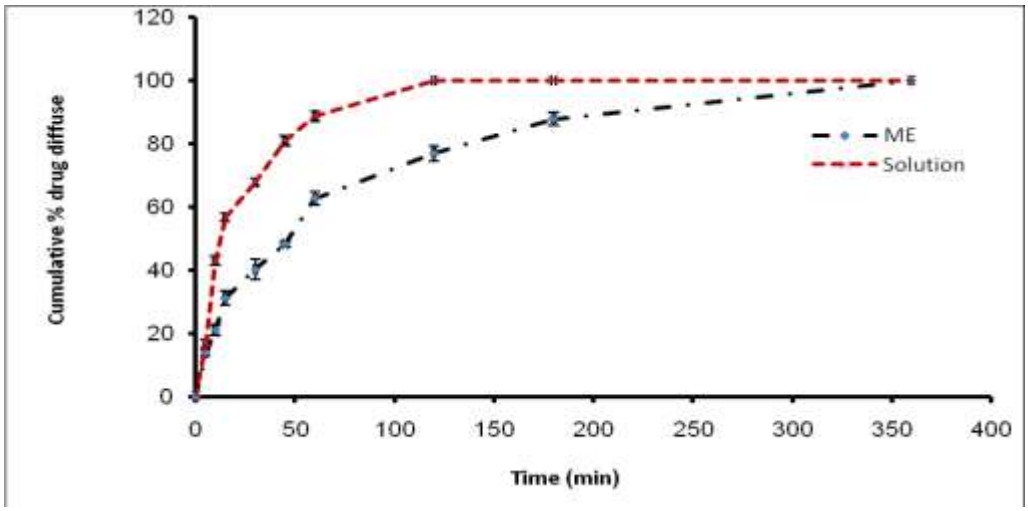

Fig. (12): *In-vitro* drug release profile of buspirone HCl microemulsions.

Table (4): *In-vitro* release of buspirone hydrochloride from solution and microemulsion formulations.

Time (min)	***% Drug released (mean ± S.D.) from:***	
	Solution	***Microemulsion***
5	**16.80 ± 1.10**	**13.83 ± 0.89**
10	**42.97 ± 1.40**	**21.05 ± 1.72**
15	**56.75 ± 1.29**	**31.22 ± 2.36**
30	**67.75 ± 1.11**	**40.25 ± 3.17**
45	**80.94 ± 1.74**	**48.31 ± 0.79**
60	**88.71 ± 1.49**	**62.64 ± 2.13**
120	**100**	**77.01 ± 2.37**
180	**100**	**87.85 ± 2.12**
360	**100**	**100**

5. Pharmacokinetic studies for buspirone microemulsion

The retention time of BH in plasma was 6.6 - 6.9 min, and for the IS, it is 10.3 - 10.5 with a total run time of less than 15 min as shown in Figure 13. The analytical process of BH and IS were resolved with good symmetry. No endogenous interfering peaks were observed in individual blank serum at the retention times of BH and IS, thereby confirming the specificity of the analytical method. The standard plots obtained for plasma samples were linear in the concentration range 1 – 800 ng/ml as shown in Figure 14. The correlation coefficient-values (R^2) determined was 0.9987 for rat plasma. The percentage recovery-values were in the range 92.289 - 98.981 for the BH-spiked plasma as shown in Table 5. The recovery of BH using the described procedure was consistent and efficient. The inter-day accuracy and precision for rat plasma samples were determined on three different days, the percentage coefficient of variance (C.V) was determined by the analysis of three replicates of samples at three different concentrations. The inter-day and intra-day precisions of the samples were satisfactory with coefficient of variation (C.V) less than 15% as shown in Table 6 and Table 7. The limit of quantitation (LOQ) of the method was found to be 1ng/ml for BH in rat plasma with C.V less than 20% and an accuracy of 85 to 110%. The limit of detection (LOD) was determined to be 0.5 ng/ml based on signal-to-noise (s/n) ratio of 3:1.

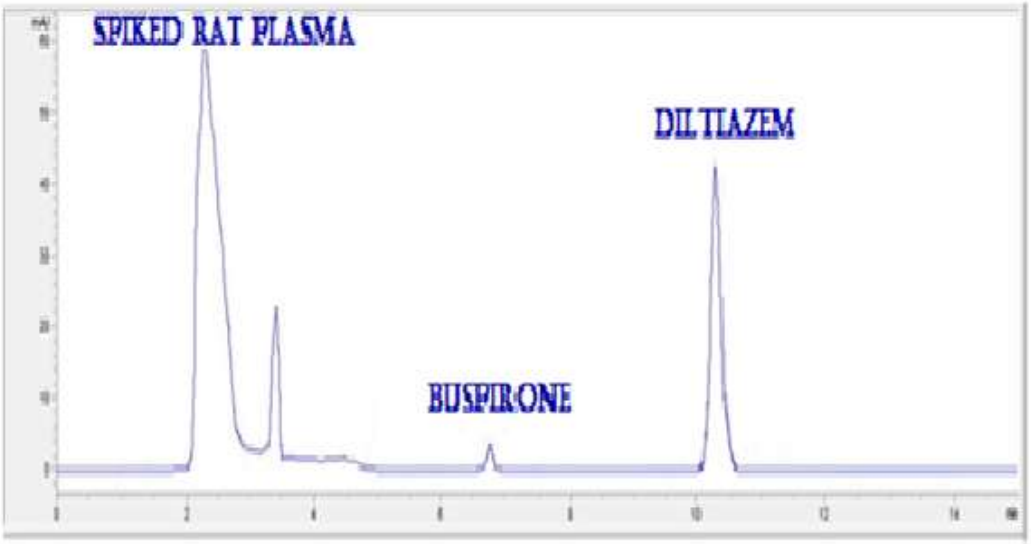

Fig. (13): Representative chromatogram of buspirone HCl and diltiazem in rat plasma.

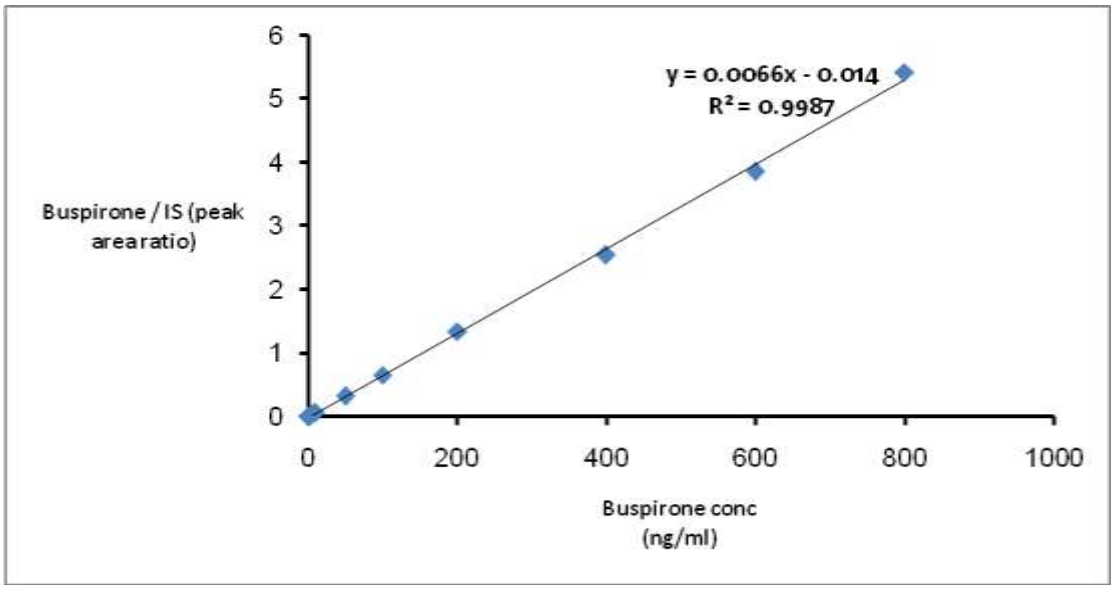

Fig. (14): Calibration curve for buspirone HCl in rat plasma.

Table (5): Recovery data for buspirone from spiked rat plasma.

Spiked conc (ng/ml)	*Measured conc (ng/ml)*			*Mean conc (ng/ml)*	*Recovery (%)*	*SD*	*CV (%)*
	A	*B*	*C*				
1	*0.9676*	*0.9458*	*0.9185*	*0.94395*	*94.395*	*0.0246*	*2.6084*
5	*4.9505*	*4.5085*	*4.4110*	*4.6233*	*92.466*	*0.2874*	*6.2184*
10	*9.5650*	*9.0630*	*9.6580*	*9.4286*	*94.286*	*0.3200*	*3.3946*
50	*49.476*	*44.980*	*48.515*	*48.430*	*96.860*	*2.3676*	*4.8887*
100	*95.760*	*98.250*	*97.500*	*97.170*	*97.170*	*1.2773*	*1.3145*
200	*185.00*	*197.35*	*188.62*	*190.323*	*95.161*	*6.3487*	*3.3357*
400	*392.8*	*388.15*	*378.9*	*386.617*	*96.654*	*7.0757*	*1.8301*
600	*571.9*	*568.5*	*589*	*576.467*	*96.078*	*10.986*	*1.906*
800	*793.9*	*795.4*	*785*	*791.433*	*98.929*	*5.6217*	*0.7103*

Table (6): Intra-day precision and accuracy data for assay of buspirone HCl in rat plasma (n =3).

Spiked conc (ng/ml)	*Measured conc (ng/ml)*			*Mean conc (ng/ml)*	*SD*	*CV%*
	A	*B*	*C*			
2.5	*2.483*	*2.486*	*2.278*	*2.416*	*0.1192*	*4.936*
250	*240.84*	*248.7*	*244.12*	*244.553*	*3.9479*	*1.614*
650	*629.02*	*640.1*	*641.9*	*637.007*	*6.9749*	*1.095*

Table (7): Inter-day precision and accuracy data for assay of buspirone HCl in rat plasma (n = 3).

Spiked conc (ng/ml)	*Measured conc (ng/ml)*			*Mean conc (ng/ml)*	*SD*	*CV%*
	A	*B*	*C*			
2.5	*2.467*	*2.475*	*2.147*	*2.363*	*0.1871*	*7.918*
250	*242.81*	*245.67*	*235.36*	*241.28*	*5.3226*	*2.206*
650	*620.11*	*637.07*	*634.41*	*630.53*	*9.1215*	*1.447*

The mean plasma drug concentration–time profiles after administration of the IV drug solution as well as the IN BHME are illustrated in Figure 15. The corresponding bioavailability and pharmacokinetic parameters in plasma are shown in Table 8. It is evident that (as expected) drug concentration in rat plasma reached its maximum value (C_{max} = 668.07±27.85 ng/ml) following administration of the IV drug solution at first 5 min, whereas it reached its maximum value (C_{max} = 206.69±13.95 ng/ml) following administration of the IN drug microemulsion at 10 min. Moreover, the $AUC_{0-360min}$ values were 51606.27±1617.20 and 8167.51±532.11 ng/ml.min for the IV drug solution and IN drug ME, respectively.

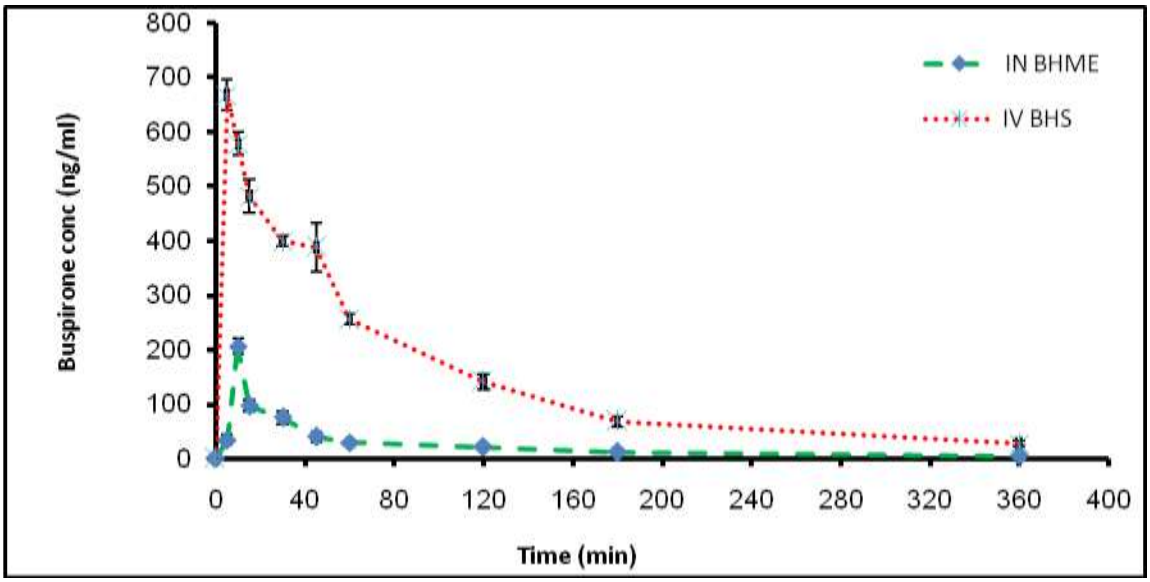

Fig. (15): Plasma concentration–time curve of buspirone HCl after intranasal administration of microemulsion and intravenous administration of solution to rats in a dose of 1 mg/kg

Table (8): Pharmacokinetic parameters of Buspirone HCl after intranasal administration of microemulsion and intravenous administration of solution to rats in a dose of 1 mg/kg.

Pharmacokinetic Parameters	***Formulations***	
	Intranasal buspirone microemulsion	***Intravenous buspirone solution***
C_{max} (ng/ml)	***206.69 ± 13.95***	***668.07 ± 27.85***
t_{max} (min)	***10***	***<5min***
$AUC_{0-360\ min}$ (ng/ml.min)	***8167.51 ± 532.11***	***51606.27 ± 1617.20***
Absolute bioavailability (%)	***15.83 ± 1.03***	***-***
$t_{1/2}$ (min)	***110.46 ± 13.68***	***95.28± 18.57***
MRT(min)	***123.14 ± 10.40***	***113.05 ± 13.95***

Results of C_{max} and $AUC_{0-360min}$ in rat plasma may indicate that there is a correlation between *in-vitro* release studies and amount of the drug transported to the plasma. In our previous *in-vitro* release study (Fig 12) have demonstrated a high release of drug in case of solution and slower diffusion of drug in case of microemulsion formulation, whereas the *in-vivo* studies (Fig 15) showed low values for C_{max} and AUC_{0-360} for IN ME and high values for C_{max} and AUC_{0-360} for IV solution.

Concerning the absolute drug bioavailability it is evident that, drug microemulsion formulation administered intranasally increased the bioavailability about four folds (15.83±1.03%) as shown in Table 8 compared to its oral tablets (~ 4%) (Galichet, 2004), which could be attributed to escaping the first-pass metabolism occuring with peroral drug administration.

The $t_{1/2}$ of 95.28±18.57 - 110.46±13.68 min and the mean residence time (MRT) of 113.05±13.95 -123.14±10.40 were observed irrespective of the routes of administration and the type of the formulations as shown in Table 8.

CONCLUSION

Intranasal buspirone HCl instilled in a microemulsion formula composed of isopropyl myristate (5%), Tween80 (30%), propylene glycol (15%), and purified water (50%), proves safe, viable, and a practically feasible approach for the improvement of the therapeutic effect. Overall, the present study has indicated that the buspirone microemulsion formulations as an efficient as well as efficacious approach for the intranasal delivery of the drug besides being simple and applicable.

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تحسين التوافر الحيوى لهيدروكلوريد البسبيرون باستعمال نظم إيتاء دوائية داخل الانف

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تهدف الدراسة الحالية إلي تحسين التوافر الحيوي لهيدروكلوريد البسبيرون باستعمال المستحلب الميكروني ماء في زيت الذي ذكر أنه يناسب الإيتاء داخل الأنف٠ من أجل ذلك صممت ودرست رسومات بيانية مختلفة للنظام الثلاثي الكاذب لتحديد منطقة تواجد المستحلب الميكروني ومن ثم تم اختيار وتعظيم المستحلب الميكروني الذي صيغت فيه أشكال العقارالمرجوة٠ ولقد وصفت أحوال الصيغ من حيث: خواص استقطاب الضوء المجهرية، النسبة المؤوية للنفاذية، حجم القطيرات، وقيمة الأس الهيدروجيني٠ إثر ذلك أختيرت الصيغة العظمى للمستحلب الميكروني وكانت مكونة من: شمعات الأيزوبروبيل ٥%، ماء ٥٠%، خليط الناشط السطحي مع مرافقه ٤٥% [توين ٨٠ بنسبة ٣٠% + جليكول البروبيلين بنسبة ١٥% أي بنسبة ١:٢ (وزن/وزن) %] وكان متوسط حجم الجسيمات ٣٥,١ ± ٠,٥ نانوميتر، ومقدارالأس الهيدروجيني هو ٦,٤ ± ٠,٠٣، وكان هذا الإختيار موفقا ومناسبا لتحضيرالمستحلب الميكروني لعقار البسبيرون للإستعمال داخل الأنف٠ وقد درس الإنطلاق المعملي باستعمال خلية إنتشار فرانز المعدلة، كما عينت معاير الحركة الدوائية (التركيز الأقصى، زمنه، مساحة تحت منحنى التأثير) طبقا لما هو متعارف عليه في هذا المجال باستخدام فئران فستر البيضاء كنموذج حيوي حيواني في هذه التجارب٠ تبين من التجارب أن التوافر الحيوي (صفر-٦ ساعات) كان في حدود ١٥,٨٥% مقارنا بالحقن الوريدي لمحلول العقار في الفئران، بينما كان التوافر الحيوي لعقار هيدروكلوريد البسبيرون النقي الذي تم اعطاؤه عن طريق الفم مذابا في الماء كان في حدود ٤%٠ وبذلك برهنت النتائج أن إعطاء المستحلب الميكروني لهيدروكلوريد البسبيرون داخل الأنف من شأنه أن يحسن التوافر الحيوي لدواء بصورة واضحة٠

الكلمات المفتاحية: الإيتاء الدوائي داخل الأنف، المستحلب الميكروني، هيدروكلوريد البسبيرون، التوافر الحيوي٠