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FABRICATION OF TOPICAL BACLOFEN LOADED EMULGEL: CHARACTERIZATION, OPTIMIZATION USING 2^3 FULL FACTORIAL DESIGN AND IN VIVO ANTI-INFLAMMATORY ACTIVITY

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Baclofen is a GABA-B receptors agonist and possesses anti-inflammatory properties. It has many gastrointestinal side effects and narrow therapeutic index. Thus, the objective of this study was to produce emulgel for the topical delivery of baclofen so as to evade its side effects. Emulgel containing 1% baclofen were fabricated, evaluated and optimized applying full factorial design (2^3). Liquid paraffin concentration, cremophor RH 40 concentration, and penetration enhancers type was selected as independent variables in the current study to determine the influence of them on the percentage release of baclofen after 30 minutes. The anti-inflammatory activity of the optimal baclofen emulgel was assessed employing the carragenan-induced rat paw edema method. The formulation E5 was established to fulfill the maximum requisite of an optimum formulation with desirability value of 0.982. The mean percentage inhibition value of E5 after 1 hour of application was significantly higher than Baclofen® tablet, baclofen hydrogel and Voltaren® emulgel. The % relative bioavailability of E5 was 108.9%, 99.8% and 138.6% relative to Baclofen® tablet, Voltaren® emulgel and baclofen hydrogel respectively. Therefore, baclofen emulgel can be utilized as an effective anti-inflammatory for topical drug delivery.

***Key Words**: Baclofen, emulgel, topical drug delivery, rat paw edema*

INTRODUCTION

Emulgel are gellified emulsions, either of the water in oil or oil in water type. They possess a great patient acceptability as they have the privileges of both gels and emulsions. Hence, it was recently utilized as vehicles to transport both hydrophobic and hydrophilic drugs to the skin[1]. Emulgels have gained importance in topical drug delivery because they are convenient due to absence of greasiness, easily removable, non-staining, easily spreadable, emollient and long shelf life[2-4].

Baclofen, molecular weight of 213.66 g/mol, is a mostly odorless and white (or off-white) crystalline powder. It is insoluble in chloroform, very slightly *soluble* in methanol and slightly *soluble* in water. Baclofen is agonist of GABA-B receptors[5]. It is used to diminish muscle spasm and pain particularly in spinal cord lesions in states such as multiple sclerosis or paraplegia[6]. Recently, Baclofen prominently relieved symptoms of inflammation in addition to mobilization of lymphocytes, monocytes and neutrophils into the skin[7]. Oral administration of baclofen usually prompts constipation, vomiting, insomnia, urinary frequency, drowsiness, tinnitus, hypotension, dizziness, sedation, weakness, fatigue, elevate liver enzymes and elevate of blood sugar[8]. It possesses a short biological half-life and a very narrow therapeutic index with inter individual variability in pharmacokinetics and pharmacodynamics. This side effects of oral administration of baclofen restricted its use and

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increasing the dose may lead to elevated risk of adverse effects and toxicity; so, the main objective in this work was to fabricate topical baclofen emulgel by carbopol 940 as gelling agent using 2^3 full factorial design to demonstrate the recent property of the GABA-B receptor in the inflammation as a potential new therapeutic target to treat inflammatory skin diseases.

MATERIALS AND METHODS

Materials

Baclofen was gained from Misr Pharmaceutical Co. (Cairo, Egypt). Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) was acquired from BASF (Schwarzheide, Germany). Isopropyl myristate (IPM), olive oil, span 20, liquid paraffin and carbopol 940 were acquired from Sigma Aldrich (USA). Propylene glycol was obtained from Fluka AG (Buchs, Switzerland).

Experimental design

A full factorial design using 2 levels of 3 independent variables, namely liquid paraffin concentration (X_1), cremophor RH 40 concentration (X_2) and penetration enhancers type (X_3), was applied in the current study to determine the influence of these independent variables on the percentage release of baclofen after 30 minutes (dependent variable) as shown in Table 1. Eight baclofen emulgel formulations were prepared by using all possible combinations of different levels of the experimental variables. Design-Expert® software (version 7; Stat-Ease, Inc., Minneapolis, MN, USA) was employed for constructing the design and making the interpretation by fitting appropriate regression models to empower navigation of the experimental space[9]. One factor plots were obtained with the help of the software and significance level was established at $P<0.05$.

A polynomial regression first-order equation also created by this experimental design was as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}(X_1X_2) + b_{13}(X_1X_3) + b_{23}(X_2X_3) + b_{123}(X_1X_2X_3)$$

Where Y is the response (dependent variables); b_0 is the intercept demonstrating the arithmetic average of the outcomes of the experimental runs; b_1-b_3 are the coefficients assessed from the noticed experimental values of Y; and X_1, X_2, and X_3 represent the independent variables. The terms b_{12}, b_{13}, b_{23}, and b_{123} represent the interaction terms. Coefficients with one factor mean the impact of this factor on the response while the coefficients with more than one factor denote the interaction between those factors.

Preparation of baclofen topical emulgel formulations

First, the gel base was fabricated by soaking carbopol 940 in a beaker containing hot purified water (70 °C) then pH was adapted to 6 to 7 by triethylamine (TEA). In another beaker, baclofen dissolved in propylene glycol and cremophor RH 40 and added to the carbopol 940 gel base with continuous stirring until homogenous mixture was formed without any lumps. Span 20, liquid paraffin, propanol and penetration enhancers (IPM or olive oil) were mixing together to form the emulsion oil phase and heated to 70 °C and then added to the aqueous phase with continuous stirring until cooled to room temperature to obtain the emulgel[10]. The composition of various baclofen topical emulgel formulations was given in Table 2.

Table 1: The factorial design plain (2^3) for the fabrication of baclofen topical emulgel

	Unit	Symbols	Applied levels	
			Low	High
Independent variables				
Liquid paraffin concentration	%	X_1	5	7.5
Cremophor RH 40 concentration	%	X_2	1	1.5
Penetration enhancers type	-	X_3	IPM	Olive oil
Dependent variable			**Goal**	
Percentage release after 30 min	%	Y1	Maximize	

Table 2: The composition of baclofen topical emulgel formulations (% w/w), and their evaluation tests.

Formulation Code	Composition (% w/w)*				Spreadability (cm)	Drug Content (%)	pH
	Liquid paraffin	Cremophor RH 40	IPM	Olive oil			
E1	5	1	-	10	6.7±0.10	99.9±0.05	5.8±0.05
E2	5	1.5	-	10	6.9±0.06	100.7±0.04	6.61±0.34
E3	7.5	1	-	10	6.8±0.12	98.5±0.12	6.15±0.09
E4	7.5	1.5	-	10	6.1±0.05	96±0.06	6.5±0.11
E5	5	1	10	-	7.8±0.06	101.9±0.23	5.8±0.10
E6	5	1.5	10	-	7.7±0.07	99.4±0.07	5.6±0.05
E7	7.5	1	10	-	7.5±0.04	99.1±0.06	5.5±0.02
E8	7.5	1.5	10	-	7.2±0.15	97.5±0.115	5.3±0.12

***** All formulations contain 1% baclofen, 1% carbopol 940, 1% span 20, 5% propylene glycol, 2.5% propanol, 0.03% methyl paraben, 0.01% propyl paraben and purified water to 100%. Data are presented as mean average value (±SD, n=3).

Evaluation of the prepared baclofen topical emulgel formulations

Physical examination

The fabricated baclofen emulgel formulations were visually inspected for their consistency, homogeneity, color and phase separation[11&12].

Test for spreadability

Spreadability was decided using the following technique; 0.5 g emulgel was placed between two glass slides then a weight of 500 g was permitted to rest on the upper glass for 5 min. The formed circle diameter was estimated and utilized as relative values for spreadability[4&13&14].

Determination of the pH

The pH values of 1% aqueous solutions of the fabricated baclofen emulgel formulations were gauged using a pH meter (3310, Jenway, UK) standardized by pH 4 and pH 7 standard buffers solution before use[15].

Determination of the drug content

The drug content was evaluated by dissolving 0.1 g of the prepared emulgels in 50 ml methanol. The concentration of this solution was decided spectrophotometrically (Shimadzu, model UV-1601 PC, Kyoto, Japan) at 266 nm after filtration through Millipore filter (0.45µm). The percentage of the drug content was determined applying the following equation:

$$\%\ \text{Baclofen in emulgel} = \frac{\text{concentration of baclofen in emulgel}}{\text{calculated concentration of baclofen}}\ \text{X}\ 100$$

Rheological study

The viscosity of the different baclofen emulgels at minimum (η_{min}) and maximum (η_{max}) rates of shear was measured at 25 ± 1.0 ºC applying a cone and plate viscometer with a spindle 52 (Model DV-I, programmable rheometer, spindle CP-52, USA)[16-18].

In vitro drug release study

USP dissolution tester (apparatus II, Pharma Test, Type PTW, Germany) was used for the in vitro release studies[15]. One gram of baclofen topical emulgel was applied onto a glass plate with 4.2 cm diameter then coated with cellulose nitrate membrane with pore size 0.45 mm (Sartorius stedium, Germany) and clasped with each otherby blaster[9]. It was then immersed in the vessel of dissolution tester containing 250 ml of phosphate buffer pH 5.5 at 37 ± 0.5 °C and 50 rpm. At specified time intervals over one hr., aliquots were withdrawn and instantly substituted with fresh release medium. The baclofen concentration in the collected samples was decided spectrophotometrically at 266 nm. The mean percent of baclofen released was plotted as a

function of time. The drug release data were exposed to zero order, first order and Higuchi equations in order to determine the mechanism of drug release.

Optimization of baclofen topical emulgel

Optimization was done to find the level of the independent variables (X_1, X_2, and X_3) that produce emulgel with high % release by using the point prediction method of the Design Expert software[8].

In vivo bioavailability study

Evaluation of anti-inflammatory activity

The anti-inflammatory activity of baclofen was assessed by carrageenan-induced rat paw edema model[19] to determine the activity of the optimized baclofen emulgel. Various materials have been employed to induce edema but the most widely utilized in this category is carrageenan prompt edema as a means of assaying anti-inflammatory drugs. Carrageenan is a mixture of polysaccharide composed of sulfated galactose units. The animal protocol was approved by Research Ethics Committee (REC) at Faculty of Pharmacy, Cairo University. Male albino rats weighing 150-180 g were used for this study and divided into 5 groups, each consisting of 6 animals. The animals were housed in standard metal cages in an air-conditioned room at 20-25 °C, 55±5% humidity, and provided with standard laboratory diet and water ad libitum.

Group I (control) received carrageenan only without treatment for comparison. Group II received oral treatment of the commercial Baclofen® tablet. Group III, IV and V received topical application of the commercial Voltaren® emulgel, 1% baclofen hydrogel and optimized baclofen emulgel (E5) respectively on the right hind paw of rats half an hour before subplantar injection of carrageenean[20].

Rats were marked on the hind paw just beyond the tibiotorsal junction, so that every time the paw could be dipped in mercury column up to fixed mark in order to ensure constant paw volume. Carrageenan suspension (0.1 ml, 1% w/v in deionized water) was injected in the subplantar section of the right hind rat paw. Before carrageenan injection, immediately after carrageenan injection and after 1, 2, 3, 4, 5, 6, 7 and 8 hrs. carrageenan injection, the paw edema volume was measured by mercury displacement method using plethysmometer (UGO Basile, model no. 21025 Comerio, Italy)[4&21]. The mean percentage inhibition of inflammation of treated groups was calculated by comparing with that of mean percentage inhibition of inflammation of control group applying the following equation[22&23]:

$$\% \text{ Inhibition of drug} = (Vc\text{-}Vt/Vc) \times 100$$

Where Vc is paw volume of the control group and Vt is paw volume of the treated groups.

Pharmacodynamic parameters analysis

The pharmacodynamic parameters were analyzed utilizing Kinetica® software (version 5, Thermo Fisher Scientific Inc., Waltham, MA) to assess the relative bioavailability of optimized baclofen emulgel compared with the commercial Baclofen® tablet, baclofen hydrogel or Voltaren® emulgel.

Statistical analysis

One way ANOVA followed by LSD was performed using the statistical software of statistical package for social sciences (SPSS®, Chicago, IL) version 14. Difference was considered significant at $P< 0.05$.

RESULTS AND DISCUSSION

Evaluation of the prepared baclofen topical emulgel formulations

Physical examination

Baclofen emulgels E1-E4 containing olive oil were yellowish white while E5-E8 containing IPM were white creamy with smooth texture and glossy homogeneous appearance. No phase separation was detected in all the formulated emulgels.

Test for spreadability

The spreadability is an important gauge for ease and uniform of application of topical formulations. Spreadability of various baclofen emulgel formulations were ranged from 6.1 ± 0.05 cm to 7.8 ± 0.06 cm as shown Table 2. Needless to say that the greater the diameter, the better the spreadability[24].

Determination of the pH

Skin compatibility is the primary requirement for a good topical formulation[25]**.** The physiologic accepted range of pH for topical formulation was 4-7 units[26]. The value of the pH of all emulgel formulations was

ranging from 5.3 ± 0.12 to 6.61 ± 0.34 which considered acceptable to avoid the risk of skin irritation (Table 2).

Determination of the drug content

The percentage of baclofen in different emulgel formulations was calculated and found in the range of 96.0 ± 0.06 % to 101.9 ± 0.23%. The results are presented in Table 2.

Rheological study

Rheological properties are essential in the various pharmaceutical areas as it helps to monitor the influence of the vehicles consistency on the release of drug from the formulations and investigate the stability of formulations[27]. Minimum rate of shear (1 rpm) was used to reflect the viscosity at rest and viscosity at maximum rate of shear (100 rpm) reflect viscosity during manufacturing process and the rubbing of the product on the skin[28]. The viscosity data (η min and η max) are represented in Figure 1. In our study, baclofen emulgel formulations exhibited non-Newtonian, pseudoplastic flow with thixotropy as the viscosity reduced upon shear rates increased as shown in Figure 2 (Rheogram of E5 is a representative example). The same result was observed by Naga Sravan Kumar Varma *et al.*[10]. Thixotropic, or time-dependent flow happens scince the gel needs a finite time to reconstruct its original structure that breaks down during continuous shear measurements. Needless to say that thixotropy is a necessary feature for topical application of semisolid drug carriers[29], to deliver an initially thick product as a thinner, easily spreadable material.

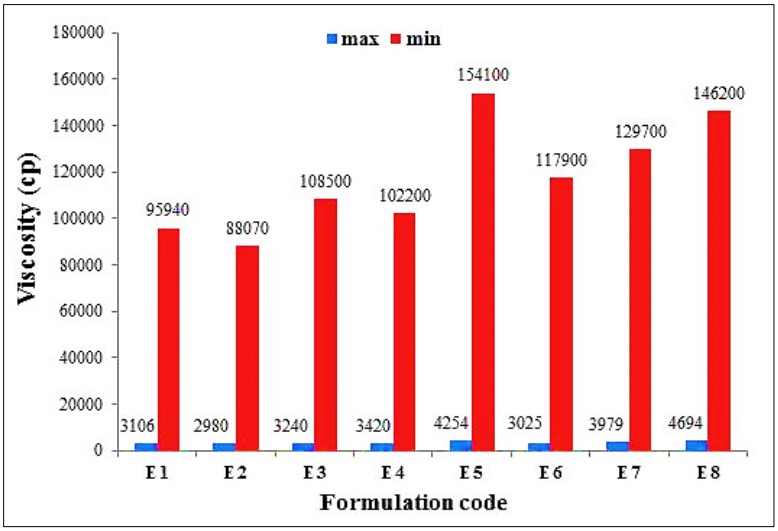

Fig. 1: Viscosity values of the prepared baclofen topical emulgel formulations at high shear rate (100 rpm) and low shear rate (1 rpm) (mean ±SD, n=3).

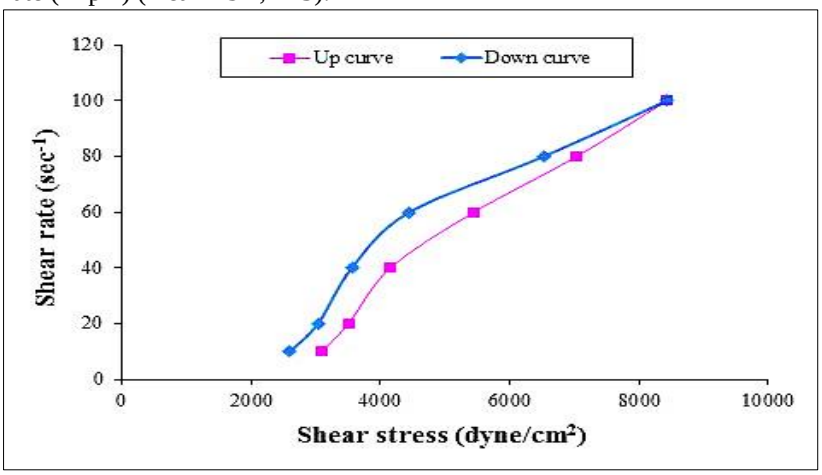

Fig. 2: Rheogram of E5 baclofen topical emulgel formulation (representive example) (mean ±SD, n=3).

In vitro drug release study

The drug should be first released from the vehicle, and then it can be partitioned into or absorbed by the skin or gastrointestinal tract[30] so evaluation of the in vitro drug release is an essential step. The in vitro release profile of baclofen from different emulgel formulations was illustrated graphically in Figure 3. The emulgel formulations could be arranged according to the percentage of baclofen released after 30 minutes in the following order: E5 > E6 > E7 > E1 > E8 > E2 > E3 > E4. The mechanism of drug release from all emulgel formulations was found best fitting to Higuchi diffusion model with a correlation coefficient ranging from 0.911 to 0.992. This finding shows that the rate-controlling stage in the release process was diffusion of the dissolved drug through the gel network to the external media[31].

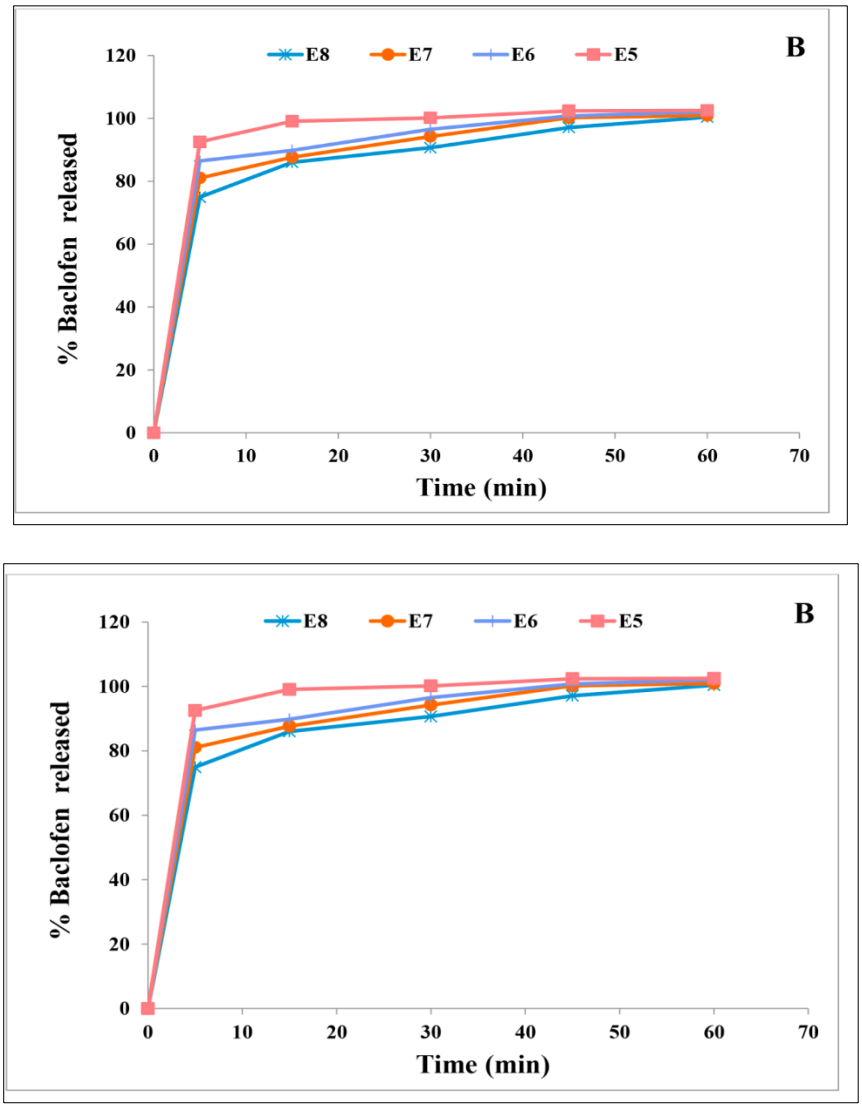

Fig. 3: In vitro release profile of baclofen topical emulgel formulations: (A) formulations prepared with olive oil and (B) formulations prepared with IPM (mean ±SD, n = 3).

Analysis of mean percentage release data after 30 minutes

The effect of different independent variables, namely liquid paraffin concentration (X_1), cremophor RH 40 concentration (X_2) and penetration enhancer type (X_3) on the percentage release of baclofen from emulgels was assessed using the software Design-Expert®. The ANOVA study of the the percentage release data after 30 minutes was illustrated in Table 3. It was found that all variables (X_1, X_2 and X_3) affected significantly on the percentage release after 30 minutes.

Effect of the liquid paraffin concentration on the percentage release after 30 minutes

It was found that, the percentage release after 30 minutes of emulgels prepared with high concentration of liquid paraffin showed the lowest release as present in Figure 4a. This might be due to reduce the hydrophilicity of the emulgel at a high concentration of liquid paraffin which, result in, retard the penetration of the release medium into the emulgel and diffusion of the drug from the emulgel. This result was in accordance with Abd El-Bary et al. and Mohamed[31&32] who found that high concentration of liquid paraffin led to delay the drug release from its emulgel formulations.

Effect of the cremophor RH 40 concentration on the percentage release after 30 minutes

Figure 4b shows that as cremophor RH 40 concentration was increased, the percentage of baclofen released was decreased. This might be due to the enhancement of the thermodynamic activity of the drug in the emulgel at lower content of surfactant[33]. Similar result were reported by Rhee et al., and Kogan et al., who stated that the elevation in the surfactant concentration caused a decrease in the release of ketoprofen and carbamazepine from MEs respectively[34&35].

Effect of the penetration enhancers type on the percentage release after 30 minutes

The transport of the drugs through the skin was reported as an effective therapy for local dermatologic and systemic disorders. However, little drugs can overcome the impermeable barrier function of human skin to exogenous substances. So, we add penetration enhancer to topical preparation to enhance baclofen penetration into skin layers especially stratum cornum.

It was found that, the percentage release after 30 minutes of emulgels prepared with olive oil was significantly less than that prepared with IPM as shown in Figure 4c as IPM fluidizes the lipid bilayer of stratum corneum and hence decreases the resistance, resulting in the increase permeation of the drug across the skin. These outcomes are in accordance with the studies done by Khan et al. who found IPM to be effective enhancer for the *in vitro* skin permeation of Sumatriptan Succinate than olive oil[36].

Table 3: ANOVA analysis of the percentage release of baclofen topical emulgel formulations after 30 min.

Source	Sum of Squares	Df	Mean Squares	F-Value	P-Value
Model	361.71	7	51.67	139.03	< 0.0001*
A: Liquid paraffin	116.11	1	116.11	312.41	< 0.0001*
B: Cremophor RH 40	29.54	1	29.54	79.49	< 0.0001*
C: Penetration enhancers type	210.51	1	210.51	566.41	< 0.0001*
AB	0.23	1	0.23	0.61	0.4583
AC	1.640E-003	1	1.640E-003	4.413E-003	0.9487
BC	4.88	1	4.88	13.14	0.0067
ABC	0.44	1	0.44	1.17	0.3105
Pure Error	2.97	8	0.37		
Cor Total	364.69	15			

***** Significant difference.

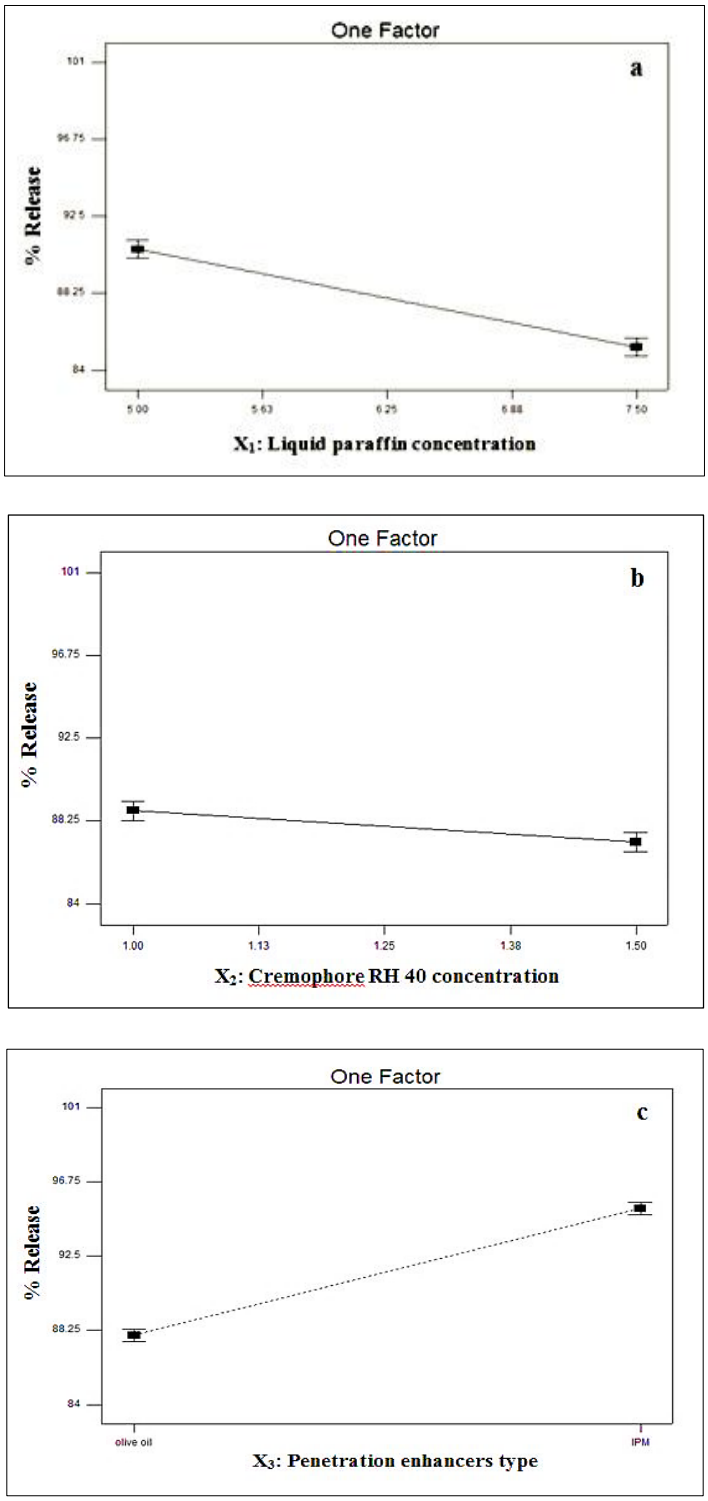

Fig. 4: One factor plot of the effect of independent variables on the percentage release after 30 min (Y1), (a) effect of liquid paraffin concentration (x_1), (b) effect of cremophor RH 40 concentration (x_2) and (c) effect of penetration enhancers type (x_3).

Optimization of baclofen topical emulgel

The optimum independent variables values were attained based on the criterion of desirability using the Design-Expert® software. The formulation E5 was established to fulfill the maximum requisite of an optimum formulation with desirability value of 0.982. So, the formulation E5 was selected for in vivo study.

In vivo bioavailability study

Evaluation of anti-inflammatory activity

Carrageenan-induced rat paw edema is the most common and reliable screening model of acute inflammation. It is considered as a highly predictive model of anti-inflammatory drug activity in human inflammatory disease. The generation of the edema in the paw of the rat after injection of carrageenan has been attributed to the release of histamine and serotonin, increased vascular permeability extends, and swelling due to the release of a prostaglandin substance and the migration of leukocytes into the site of inflammation[37]. So, the anti-inflammatory activity of the optimized baclofen emulgel E5 was assessed by carrageenan-induced rat paw edema model. The mean percentage inhibition curve of each group were illustrated Figure 5. It was found that the mean percentage inhibition value of E5 after 1 hour of application (10.1%) was significantly ($P< 0.05$) higher than Baclofen® tablet (0.30%), baclofen hydrogel (0.37%) and Voltaren® emulgel (9.26%).Also, the mean percentage inhibition value of E5 after 8 hour of application (52.03 ± 0.8%) was significantly ($P< 0.05$) higher than Baclofen® tablet (50.03± 0.2%) and baclofen hydrogel (43.86 ± 0.11%) whereas, a non-significant difference between E5 (52.33 ± 0.51%) and Voltaren® emulgel (52.66 ± 0.21%).

Pharmacodynamic parameters analysis

Bioavailability assessment is useful in defining the safety of the drug products, the effect of changes in the physicochemical properties of the drug substance, the effect of added additives and the effect of route of administration on the pharmacokinetics and pharmacodynamics of the drug. Bioavailability studies are used to define. Thus, assessment of bioavailability of drugs is very essential to detect the extent of success of the new formulations.

After topical application of the optimized baclofen emulgel E5, the value of $AUC_{(0-8)}$ was found to be 232.01 ± 10.85 and its % relative bioavailability was 108.9%, 99.8% & 138.6% when compared with Baclofen® oral tablet, Voltaren® topical emulgel and baclofen topical hydrogel respectively (Table 4). This result showed that the optimized baclofen emulgel E5 was effective as marketed Voltaren® topical emulgel formulation. These results elucidated the incredible impact of emulgel and its constituent in enhancing the anti-inflammatory activity of baclofen. So, baclofen emulgel can be utilized as an anti-inflammatory for topical drug delivery.

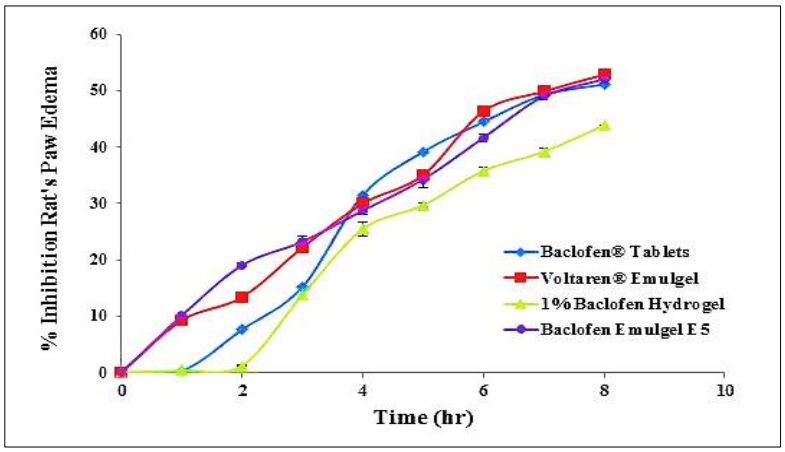

Fig. 5: Anti-inflammatory activity of the tested formulations by the carrageenean-induced hind paw edema method (mean ±SD, n=3).

Table (4): Pharmacodynamics parameters and relative bioavailability of E5 formulation.

Pharmacodynamics Parameter	Optimized baclofen emulgel (E5)	Baclofen® oral tablet	Voltaren® topical emulgel	Baclofen topical hydrogel
$AUC_{(0-8)}$	232.01±10.85	213.04±7.5	232.46±11.16	167.31±6.08
% Relative Bioavailability of E5	-	108.9	99.8	138.6

Conclusion

1% baclofen emulgel were prepared, evaluated and optimized applying a 2^3 full factorial design. Baclofen emulgel formulations exhibited non-Newtonian, pseudoplastic flow with thixotropy. The percentage release of emulgels prepared with olive oil was significantly less than that prepared with IPM. E5 was established to fulfill the maximum requisite of an optimum formulation since it had the maximum percent release and maximum desirability. Carrageenan induced paw edema revealed that baclofen emulgel can be used as an effective anti-inflammatory for topical drug delivery.

REFERENCES

1. N. M. Daood, Z. E. Jassim, M. M. Gareeb and H. Zeki "Studying the effect of different gelling agent on the preparation and characterization of metronidazole as topical emulgel", ***Asian J Pharm Clin Res***, 12(3), 571-577 (2019).
2. P. A. Gayatri, Krisnawati, M. Sahlan, D. K. Pratami and R. Widayati "Stability of zoledronate gel emulsion in virgin coconut oil", ***Int J App Pharm***, 11(1), 201-206 (2019).
3. C. Parlina, E. Purwaningsih, A. Jusuf and R. Widayati "Impact of zoledronate bisphosphonates gel in virgin coconut oil on the increase of apoptosis osteoclast", ***Int J Appl Pharm***, 9(2), 24-27 (2017).
4. R. Khullar, D. Kumar, N. Seth and S. Saini "Formulation and evaluation of mefenamic acid emulgel for topical delivery", ***Saudi Pharm J***, 20(1), 63-67 (2012).
5. S.C. Sweetman. Martindale: The Complete Drug Reference. London, England, UK: Pharmaceutical Press, 1887-1890 (2011).
6. A. Dario, M.G. Di Stefano, A. Grossi, F. Casagrande and G. Bono "Long-term intrathecal baclofen infusion in supraspinal spasticity of adulthood", ***Acta Neurol Scand***, 105(2): 83–87 (2002).
7. B. Duthey, A. Hubner, S. Diehl, S. Boehncke, J. Pfeffer and W. Boehncke "Anti-inflammatory effects of the GAPAB receprtor agonist baclofen in allergic contact dermatitis", ***Exp Dermatol***, 19(7), 661-666 (2010).
8. M. Nabi-Meibodi, B. Navidi, N. Navidi, A. Vatanara, M. Reza Rouini and V. Ramezani "Optimized double emulsion-solvent evaporation process for production of solid lipid nanoparticles containing baclofene as a lipid insoluble drug", ***J Drug Del Sci Tech***, 23(3), 225-230 (2013).
9. S. M. Soliman, N. S. Abdelmalak, O. N. El-Gazayerly and N. Abdelaziz "Novel non-ionic surfactant proniosomes for transdermal delivery of lacidipine: optimization using 2^3 factorial design and in vivo evaluation in rabbits", ***Drug Delivery***, 23(5), 1608-1622 (2016).
10. V. Naga Sravan Kumar Varma , P. V. Maheshwari, M. Navya , S. C. Reddy, H. G. Shivakumar and D. V. Gowda "Calcipotriol delivery into the skin as emulgel for effective permeation", ***Saudi Pharm J***, 22(6), 591-599 (2014).
11. N. Kasliwal, D. Derle, J. Negi and J. Gohil "Effect of permeation enhancers on the release and permeation kinetics of meloxicam gel formulations through rat skin", ***Asian J Pharm Sci***, 3(5), 193-199 (2008).
12. Y. Shen, X. Ling, W. Jiag, S. Du, Y. Lu and J. Tu "Formulation and evaluation of Cyclosporin A emulgel for ocular delivery", ***Drug Deliv***, 22(7), 911-917 (2015).
13. Y. G. Bachhav and B. P. Vandana "Microemulsion based vaginal gel of fluconazole: Formulation, in vitro and in vivo evaluation", ***Int J Pharm***, 365(1-2), 175-179 (2009).
14. S. M. Soliman, N. S. Abdelmalak, O. N. El-Gazayerly and A. E. A. Abd El-Rehim "Formulation of microemulsion gel systems for transdermal delivery of celecoxib: in-vitro permeation, anti-inflammatory activity and skin irritation tests", ***Drug Discov Therap***, 4(6), 459-471 (2010).
15. D. Shankar, S. Gajanan, J. Suresh and G. Dushyant "Formulation and Evaluation of Luliconazole Emulgel for Topical Drug Delivery", ***Int Res J of Science & Engineering***, A3: 85-90 (2018).
16. E. Khalil, U. F. Schaefer and A. Sallam "Release characteristics of diclofenac diethylamine from emulgels containing Pluronic F127", ***J Drug Del Sci Tech***, 16(5), 381-387 (2006).
17. G. Bonacucina, M. Cespi and G. F. Palmieri "Characterization and stability of emulsion gels based on acrylamide/sodium acryloyldimethyl taurate copolymer",

AAPS PharmSciTech, 10(2), 368-375 (2009).
18. B. Behera, D. Biswal, K. Uvanesh, A. K. Srivastava, K. Bhattacharya Mrinal, K. Paramanik and K. Pal "Modulating the properties of sunflower oil based novel emulgels using castor oil fatty acid ester: Prospects for topical antimicrobial drug delivery", ***Colloids Surf B Biointerfaces***, 128, 155-164 (2015).
19. C. A. Winter, E. A. Risley and G. W. Nuss "Carrageenan induced oedema in hind paws of the rats as an assay for anti-inflammatory drugs", ***Proc Soc Exp Biol Med***, 111, 544-547 (1962).
20. B. N. Dhavan "Organization of biological screening program for natural products. Use of Pharmacological Techniques for the Study of Natural Products", Proceedings of UNESCO-CDRI Work-shop. Central Drug Research Institute Lukhnow, 3-29 (1992).
21. P. Crunkhorn and S. C. Mencock "Mediators of inflammation induced in rat paw carregeenan", ***Br J Pharmacol***, 42, 371–402 (1971).
22. M. A. El-Nabarawi, E. R. Bendas, M. S. El-Ridy, G. A. Abdel-Jaleel and S. M. Nasr-Alla "Formulation and evaluation of topical niosomal gel of baclofen", ***J Chem Pharm Res***, 7(1), 277-288 (2015).
23. M. K. Jeengar , S. V. Rompicharla , S. Shrivastava , N. Chella , N. R. Shastri , V. G. Naidu and R. Sistla "Emu oil based nano-emulgel for topical delivery of curcumin", ***Int J Pharm***, 506(1-2), 222-236 (2016).
24. K. G. H. Desai "Enhanced skin permeation of rofecoxib using topical microemulsion gel", ***Drug Develop Res***, 63, 33-40 (2004).
25. S. Mittal, A. Mittal and K. Sharma, S. Alam "Proniosomes as a drug carrier for transdermal delivery of candesartan cilexetil", ***IJNST***, 2(2), 1-7 (2013).
26. M. T. Lucero, J. Vigo and M. J. Leon "The influence of anti-oxidant on the spreadability of alpha-tocopherol gels", ***Drug Develop Ind Pharm***, 20(14), 2315-2322 (1994).
27. K. W. Ambade, K. R. Jadhav, M. N. Gambhire, S. D. Kurmi, V. J. Kadam and K. R. Jadhav "Formulation and evaluation of flurbiprofen microemulsion", ***Curr Drug Deliv***, 5, 32-41 (2008).
28. A. E. Ekong, M. Melbouci, K. Lusvardi and P. E. Eraze-Majewicz "In (Handbook of cosmetic science and technology", A. O. Barel, M. Paye and H. I. Maibach, eds., Marcel Dekker, New York and Basel. 384-385 (2001).
29. A. Lippacher, R. H. Muller and K. Mäder "Liquid and semisolid SLN™ dispersions for topical application: Rheological characterization", ***Eur J Pharm Biopharm***, 58, 561-567 (2004).
30. S. Küchler, W. Herrmann, G. P. Minkin, T. Blaschke, C. Zoschke, K. D. Kramer, R. Bittl and M. S. Korting "SLN for topical application in skin diseasesd characterization of drug ecarrier and carrier target interactions", ***Int J Pharm***, 390(2), 225-233 (2010).
31. M. I. Mohamed "Optimization of Chlorphenesin Emulgel Formulation", ***AAPS J***, 6(3), 81-87 (2004).
32. A. Abd El-Bary, S. Shalaby and S. Abd El-Aal "Formulation and stability of chloramphenicol gel and emulgel", ***Bull Fac Pharm***, 39, 89-99 (2001).
33. V. P. Shah "Skin penetration enhancers: Scientific perspectives. In: Drug Permeation Enhancement; Theory and Applications (Hsieh DS, ed.)", Marcel Dekker, New York, USA, 19-24 (1994).
34. Y. S. Rhee, J. G. Choi, E. S. Park and S. C. Chi "Transdermal delivery of ketoprofen using microemulsions", ***Int J Pharm***, 228, 161-170 (2001).
35. A. Kogan, E. Kesselman, D. Danino, A. Aserin and N. Garti "Viability and permeation across Caco-2 cells of CBZ solubilized in fully dilutable microemulsions", ***Colloids Surf B Biointerfaces***, 66, 1-12 (2008).
36. M. W. Khan, N. Ur-Rahman, A. Nawaz and J. A. Khan "Formulation and In Vitro Evaluation of Sumatriptane Succinate Transdermal Patches", ***Lat Am J Pharm***, 33(4), 574-578 (2014).
37. C.A.Winter, E.A. Risley and G.W. Nuss "Carrageenin induced edema in hind paw of the rat as an assay for anti-inflammatory drugs", ***Exp Biol Med,*** 111(3), 544-547 (1962).

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نشرة العلوم الصيدلية
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تحضير مستحلبات هلامية موضعية للباكلوفين: التقييم، التحسين باستخدام ٢٣ تصميم عاملي كامل و تقييم النشاط المضاد للإلتهاب

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يستخدم الباكلوفين فى علاج الألتهاب عن طريق تحفيز مستقبلات حمض الجاما أمينو بيوتيرك (B) وله العديد من الآثار الجانبية المعدية والمعوية. وبالتالي، كان الهدف من هذه الدراسة هو تحضير مستحلبات هلامية للتوصيل الموضعي لعقار الباكلوفين لتجنب آثاره الجانبية. تم تصنيع مستحلبات هلامية محملة بعقار الباكلوفين (١٪) وتقييمها وتحسينها باستخدام تصميم عاملي كامل (٢٣). تم اختيار تركيز زيت البارافين وتركيز الكريموفور ونوع معززات الاختراق كمتغيرات مستقلة في الدراسة الحالية لتحديد تأثيرها على النسبة المئوية لإطلاق الباكلوفين بعد نصف ساعة. تم ايضا تقييم النشاط المضاد للالتهاب للصيغة المثلى للمستحلب الهلامي للباكلوفين بقياس نسبة الانخفاض فى حجم التورم فى قدم الفأر التي يسببها الكاراجينان. تم أختيار الضيغة الهلامية المستحلبة (E5) كأفضل ضيغة أعتمادا على انطلاق الباكلوفين. وجد ان انخفاض حجم التورم فى قدم الفأر لـE5 بعد ساعة واحدة أعلى بكثير من baclofen tablet و baclofen hydrogel و .Voltaren® emulgelكان التوافر الحيوي النسبي لـ E5 كما يلي: ١٠٨,٩٪ و ٩٩,٨ ٪ و ١٣٨,٦ ٪ نسبة إلى Baclofen tablet و Voltaren® emulgel و baclofen hydrogel على التوالي. لذلك يمكن استخدام المستحلب الهلامي للباكلوفين كمضاد فعال للالتهابات لتوصيل الأدوية الموضعية.