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Effect of propylene glycol, poly ethylene glycol 400 and pH on the release and diffusion of Ibuprofen from different topical bases

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الخلاصة:

هذه الدراسة اجريت لإيجاد تأثيرالبروبلين كلايكول والبولي اثيلين كلايكول 400 والاس الهيدروجيني على تحرر و نفاذ الإيبوبروفين مِنْ القواعدِ الموضعية المختلفةِ. تم وضع 5 % إيبوبروفين في القواعدِ التاليةِ ونسبةِ التحررمن هذه القواعد كَانتَ حسب التسلسل الاتي:

صوديوم كاربوكسي مثيل سليلوز الصيغة –4> الميثيلِ سليلوز الصيغة –3> هلامِ الكاربومير الصيغة –1> المستحلبِ الصيغة–2. لقد تم تجربة تأثير التركيز 10% و 30% وال 40% من البروبلين كلايكول كما في الصيغِ 5 و 6 و 7 ولقد وجد ان 40 % أعطىَ التحرر الأعلى. في نفس الوقتِ تم تجربة التركيز 40 % من البروبلين كلايكول كما في الصيغ8و9 و10 وكانت الصيغة–10 فقط من أعطت تأثيرا هاما بالإضافة إلى الصيغة 7 , أما باقي الصيغ فلم تعطي أي تغيير في تحرر الايبوفرين . يالاضافة إلى البروبلين كلايكول، إلاثيلين كلايكول 400 أُضيفَ كما في الصيغِ 11و 12 وهذا المزيج أدى إلى زيادة تحرر إلايبوبروفين. تم اختيار الصيغة–1 لتغيير الاس الهيدروجيني إلى 6,5 و 8 وكان الأخيرِ أعطىَ التحرر الأعلى مما أدى إلى اختيار الصيغِ 11 و12والصيغةِ ذات الأس الهيدروجيني 8 و تم إخضاعهم لاختبار النفاذ باستخدام جلد الفار المستأصل.ومن جهة أخرى، أجريت دراسة سريريه تمهيدية نُفّذتْ مَع 20 مريضِ والنتيجةِ كَشفت أن 65 % من المرضى أعطوا رَدّاَ إيجابيَا جيدَا.

Abstract

This study was carried out to find the effect of propylene glycol (PG), poly ethylene glycol 400(PEG 400) and pH on the release and diffusion of Ibuprofen from different topical bases. 5% Ibuprofen was incorporated in the following bases and the release rate from these bases as in the following order: NaCMC formula-4> methyl cellulose formula -3 > carbomer gel formula-1 > emulsion base formula-2.

The effect of propylene glycol concentrations 10%, 30% and 40% applied as in formulas 5, 6 and 7 which 40% gave the highest release, in the same time 40% of propylene glycol added as in formulas 8, 9 and 10 and only formula 10 gave significant effect and in addition to formula 7 while others had no change

in Ibuprofen release. In addition to that, poly ethylene glycol 400 has been added as in formulas 11 and 12 and this combination increased the Ibuprofen release. Formula -1 has been chosen to study the effect of pH change (6.5 and 8) on the release process, since pH 8 gave the highest release leading to select the formulas 11, 12 and formula with pH 8 and applied them to the diffusion test by using excised mouse skin. On the other hand, preliminary clinical study was carried out with 20 patients and the result revealed 65% of the patients gave good positive response.

Introduction:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs worldwide and are responsible for approximately one-quarter of all adverse drug reaction reports. NSAIDs are widely prescribed for patients with rheumatic disease. Considering the fact that most inflammatory diseases occur locally and near the surface of the body, topical application of NSAIDs on the inflamed site can offer the advantage of delivering a drug directly to the disease site and producing its local effect, so preparing Ibuprofen topical preparation will help to overcome NSAIDs problems [1].Ibuprofen is mainly used in the treatment of mild to moderate pain related to dysmenorrhoea, headache, migrane, postoperative, and dental pain and in the management of spondylitis, osteo-arthritis, rheumatoid arthritis, and soft tissue disorders and has also antipyretic properties. Ibuprofen is regarded one of the safest NSAIDs available [2,3].

This study included the incorporation of Ibuprofen in different topical bases and studying the release of drug from these bases, investigating the effect of PG concentration on the Ibuprofen release, the effect of penetrating enhancers combination of PG and PEG 400 and pH on the Ibuprofen releasing rate from the bases. Then selected the formulas with a significant effect subjected to diffusion study through mouse skin.

Materials and Methods:

Ibuprofen was gifted from Al-Hukamaa pharmaceutical Industries, (cetyl alcohol, sodium lauryl sulphate , glycerol, diethyl ether and sodium carboxy methyl cellulose low viscosity grade) by BDH chemical LTD.Pool ,England. Triethanolamine by Hopkins and Williams LTD. England. Poly ethylene glycol 400 and propylene glycol by Merk-Schuchardt, Germany. White bees wax by May and Bake. LTD, Dagenham, England. Carbomer 940 by Goodrich, U.S.A.

Preparation of bases:

According to the quantities of contents in table -1as following:

1- Emulsion base was prepared by melting the white bees wax and cetyl alcohol with aid of water bath at 75º C, in the same time and at the same temperature in a separate beaker, sodium lauryl sulphate and propylene

glycol were added to the water then aqueous phase was then added to the oil phase with stirring until congealing.

2- NaCMC gel was prepared by wetting NaCMC with glycerin and the mixture poured gradually to previously warmed water at 70ºC with stirring until forming gel.
3- methyl cellulose gel was prepared by adding methyl cellulose to the water then kept in fridge to get a gel.
4- carbomer gel was prepared by gradually adding carbomer to the water with mechanical stirring until getting dispersion of the polymer then drops of triethanolamine was added to get gel [4].

The formulas were prepared and kept for 24 hours.

Physical examination

The prepared formulas were inspected visually for their color, homogeneity, consistency, spreadability and phase separation. The pH values of the prepared formulas were measured by pH meter (pH -2C- china) [5].

Solubility study:

Excess amount of the Ibuprofen was added to the different mediums as shown in(Table -3), mixed and left in a shaking water bath at 25ºC for 24 hours and then stored for a further 24 hours without agitation, Then filtered and the absorbance of the filtrate was measured spectrophotometrically at 265 nm [6].

Preparation of the Diffusion Membrane:

The mouse (4-6 week old male) was sacrificed by ether inhalation, and then the skin was shaved lightly with an electrical clipper taking care to prevent any damage to the skin. A rectangular section of abdominal skin was excised from the animal using a sharp blade and then applied the defating procedure.

The in Vitro Release and Diffusion of Ibuprofen:

A test tube with 2.5 cm in diameter was filled with 2gm of each base. The mouth of the test tube was covered with filter paper which was secured in place with a rubber bad while in diffusion test a 1gm of base was introduced in a test tube with a diameter of 1.4 cm and the epidermal surface of mouse skin was stretched over the mouth of the test tube and legated with a cotton thread [7]. In both testes the release cell and diffusion cell were then inverted and immersed in 500 ml and 350 ml of phosphate buffer (pH 7.4) respectively which placed in a beaker of the dissolution apparatus. The system maintained at 37ºC and the buffer solution was stirred at 100 r.p.m during the 6 hours of the study. Samples of 5 ml were pipetted from the collecting medium after 1, 2,3,4,5 and 6 hours replaced with an equal volume of freshly prepared phosphate buffer (pH 7.4) at 37ºC. The samples were then analyzed spectrophotometrically (UV- 165 OPC Shimadzu) for their drug content at 265 nm.

Effect of Penetration Enhancers and pH on the Release and Diffusion of Ibuprofen from Topical Bases:

The effect of addition of different concentrations of propylene glycol and PEG 400 according to the(Table -2) on the release and diffusion of Ibuprofen

and studying the effect of pH by adjusting the pH of the base by triethanolamine buffer on the release and diffusion of Ibuprofen.

Effect of initial drug concentration:

The effect of initial Ibuprofen on the release from the base by using other two drug concentrations 10 and 15% beside 5% [8].

Calculation of cumulative drug release:

The amount of Ibuprofen in the total receptor solution was determined from a calibration curve. The cumulative drug permeated (Q_n) corresponding to the time of the n^{th} sample was calculated from the following equation [9]:

$$Q_n = V_R C_n + \sum_{i=0}^{n-1} V_s C_i$$

Where Cn and Ci are the drug concentrations of the receptor solution at the time of the n^{th} sample and the i (the first) sample, respectively and V_R and V_S are the volumes of the receptor solution and the sample, respectively.

Release kinetics:

To study and characterize the drug release mechanisms from formulas, the Korsmeyer –Peppas model was applied:

$$M_t / M_\infty = K \times t^n$$

Where Mt is the amount of released drug at time t, M∞ is the overall amount of the drug, k is the constant incorporating structural and geometric characteristics of the controlled release device, and n is the release exponent indicative of the drug release mechanism. The rate constant *k* and the diffusional exponent *n* can be obtained from the intercept and the slope of a plot of *log*M_t / M_∞ versus *log* t respectively.

When $n \leq 0.5$ corresponds to a Fickian diffusion, and if $0.5<n<0.89$ corresponds to anomalous transport, $n \geq 0.89$ indicates to a zero order or case II transport where, anomalous transport is due generally to the swelling of the system in the solvent before the release takes place in addition to polymer relaxation while, case II represents polymer relaxation [10,11,12].

Preliminary Clinical Study:

It was done under the supervision of Dr. Abdalkareem Alsaffar (Consultant-sport medicine –Rheumatologist—Iraqi football team doctor).

Twenty patients of different cases and age were selected. The gel was applied at the pain area once daily for one week with the observation for pain relief.

Statistical Analysis:

Student t-test was used to determine the relation between 2 parameters.

Result and Discussion:

Physical examination:

The prepared formulas colors were white except the formulas with pH 6.5 and 8 were transparent gel. They were easily spreadable with good adhesion. The pH values of all formulas ranged from 4.77 to 6.77 except the formula with pH 8, which all of them did not show any skin irritation upon application to skin.

Release and diffusion studies:

(Figure -1) shows that the release rate decreased in the following order NaCMC gel (formula-4)> methyl cellulose gel (formula-3) > carbomer gel (formula -1) > emulsion base (formula-2).

This could be due to using of low grade of NaCMC and low concentration of methyl cellulose which led to higher release than that 1%carbomer not less. Ibuprofen is practically insoluble in water so water phase of emulsion contained fewer drug available to release and Ibuprofen partitioning in the oil phase giving the slowest release.

The effect of PG concentrations on the release of Ibuprofen from the carbomer gel shown in (figure-2), the release of Ibuprofen increased with an increasing in PG concentration as in the following rank: formula- 7> formula-6> formula-5> formula-1.

Formula 7 showed only a significant effect due to the addition of PG ($p < 0.05$) while the others did not have a significant effect. The effect of addition an increasing amount of propylene glycol on the release of Ibuprofen harmonized with the result of Ibuprofen solubility study as in (Table -3).

So, studying the effect of addition 40% of PG to the other bases (formulas 8, 9 and 10) as shown in (Table -2) and (figure 3, 4 and 5). PG did not have any effect on the release from the NaCMC and methyl cellulose gel and this may be due to precipitation of Ibuprofen in both formulas excluding the solubilizing effect of PG as shown in table-3 which led J.Aukauru *et al* prepared Ibuprofen as an ointment [13].

Emulsion base had a significant effect ($p <0.05$) with the addition of 40% PG. The result agreed with (Table -3).

Then addition of PEG 400 in the presence of PG to the formulas 11 and 12 also gave a significant effect ($p <0.05$) and increased the Ibuprofen release may be due to this combination increased the solubility of Iburofen as shown in figures 6 and 7 also table 3 revelead the same impact. A similar impact had been gotten by Aukunuru et al [13].

Effect of pH on the release of Ibuprofen shown in figure 8, where the pH adjusted in formula -1by triethanolamine buffer to pH 6.5 and 8 and the pH 8 formula gave higher release than formula with pH 6.5 and both formulas gave significant effect ($p < 0.05$). A close result was reported by Potthast *et al* [6].

Formulas 11,12 and the formula with pH 8 (showed a significant effect by synergetic the effect of PG and PEG 400 combinations and the pH effect respectively) have been subjected to the diffusion test using a mouse skin as shown in (figure- 9).

Effect of initial Ibuprofen concentration:

Then the effect of different concentrations of Ibuprofen incorporated in carbomer gel with pH 8 shown in figure 10 and 11. The formula with 15% concentration of Ibuprofen showed highly significant effect ($p < 0.001$) in the releasing process compared with 5% Ibuprofen formula. The results revealed that increasing the drug concentration, resulted in increasing the cumulative amount released. The cumulative amounts released at 6 hrs were 93.625, 155.7 and 312.5 mg/cm^2 for gel prepared with 5, 10, and 15% Ibuprofen, respectively. Close parallel result was reported by Fergany [14].

Release kinetics:

The kinetic analysis of the Ibuprofen release and diffusion presented in (Table 4 and 5). The consistence is very obvious when the discussion is related to the cumulative amount to each formula. On the other hand and according to Korsmeyer-Peppas model, the changing in transport mechanism of formula - 1 from case II to the anomalous by addition of 10% and 30% PG in formulas 5 and 6 respectively, it may be due to PG is hygroscopic material (15) and this led to the diffusion of water from the surroundings to the polymer into the base and resulted into the swelling of the system and then relaxation (anomalous) but, the solubilizing effect of PG made the drug ready to release and overcome the swelling happened due to the addition of PG as shown in (Table -3) [10]. The transport mechanism of formula -7 with 40% PG was case II, means that 40% PG affected on the polymer structure and led to relaxation and chain disentanglement, which showed the same effect on the transport mechanism in formulas 8 and 9, but had no effect on release rate due to Ibuprofen precipitation. The transport mechanism of formula -2 did not change after addition of 40% PG (formula -10) but, it had a significant effect on the release rate due to increase in the Ibuprofen solubility as shown in (Table-3). Since the mechanism of formula -11 changed from case II to anomalous (swelling and relaxation), this may be due to presence both hygroscopic materials PG and PEG 400 [15], that led to diffusion of water to the formula and as mentioned previously the solubilizing effect of the combination of PG and PEG overcame the swelling of polymer. Also the transport mechanism of formula 12 changed from anomalous to fickian after addition of PEG 400 that seemed increasing or expanding the layers in the same base. But increasing in the release rate may be due to decrease in the hydrophobicity of the base and increase the porosity of the base resulted in ready release of the soluble and insoluble drug (11). Changing the pH of formula 1 from 5.6 to 6.5 and 8 did not change the transport mechanism (case II). (Table -5) shows the diffusion kinetic parameters since all formulas followed fickian transport mechanism.

Preliminary clinical study:

The clinical effects of Ibuprofen 5% gel with pH 8 have been tested in a group of 20 patients. (Table -5)- revealed that 35% of the patients showed mild positive response while other cases showed good positive response (relief pain and better range of movement). This indicates that Ibuprofen has good release from the selected topical formula and good diffusion through the skin.

Formula no.	**1**	**2**	**3**	**4**
Iboprofen	5gm	5gm	5gm	5gm
Carbomer 941	1gm			
Triethanolamine	Few drops			
White bees wax		1 gm		
Cetyl alcohol		15 gm		
S.L.S		2 gm		
PG		10 gm		
PEG 400				
Methyl cellulose			2 gm	
Na.CMC				5 gm
Glycerol				15 gm
EDTA	0.1%	0.1%	0.1%	0.1%
H_2O	to 100 gm	to 100 gm	To 100 gm	to 100 gm

Table-1: formulas compositions

Formula no.	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Ibuprofen	5 gm	5 gm	5 gm	5gm	5gm	5gm	5gm	5gm
Carbomer 941	1 gm	1 gm	1 gm				1gm	
triethanolamine	Few drops	Few drops	Few drops				Few drops	
White bees wax						1gm		1gm
Cetyl alchol						15gm		15gm
S.L.S						2gm		2gm
PG	10	30gm	40gm	40gm	40gm	40gm	40gm	40gm
PEG 400							6gm	6 gm
Methyl cellulose				2gm				
Na.CMC					5gm			
Glycerol					15gm			
EDTA	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
H_2O	to100 gm	to100 gm	to100 gm	to100 gm	to100 gm	to100 gm	to100 gm	to100 gm

Table-2: formulas of Ibuprofen

Composition of solvents	Solubility mg\ml
10%PG +90% H2O	1.25
30%PG +70% H2O	1.7
40%PG +60% H2O	2.46
40%PG +6% PEG 400 +54% H2O	3.714

Table-3: Solubility of Ibuprofen

Formula no.	n	log k	R2	Transport mechanism	Cumulative amount
F1	1.07	-4.49	0.9847	Case II	35.975
F2	0.625	-3.94	0.923	Anomalous	8.8651
F3	0.8024	-3.386	0.987	Anomalous	93.375
F4	1.2	-4.2	0.994	Case II	103.75
F5	0.747	-3.58	0.97	anomalous	39.125
F6	0.703	-3.42	0.964	anomalous	49.36
F7	1.036	-3.92	0.9795	Case II	83.025
F8	1.4	-5	0.91	Case II	82.06
F9	1.07	-3.9	0.9714	Case II	101.33
F10	0.789	-3.68	0.90	anomalous	51.675
F11	0.878	-3.48	0.951	anomalous	104.1
F12	.0.41	-2.6	0.817	Fickian	57.175
pH 6.5	0.914	-3.7	0.98	Case II	83
pH 8	1.05	-3.9	0.918	Case II	93.625

Table-4: Release Ibuprofen parameters

Formula no.	n	Log k	R2	Transport mechanism	Cumulative amount
Formula of pH 8	0.485	-2.6	0.9876	Fickian	55.7
Formula 11	0.497	-2.9	0.9755	Fickian	51.975
Formula 12	0.478	-2.99	0.9609	Fickian	25.975

Table-5: Diffusion kinetic parameters of Ibuprofen

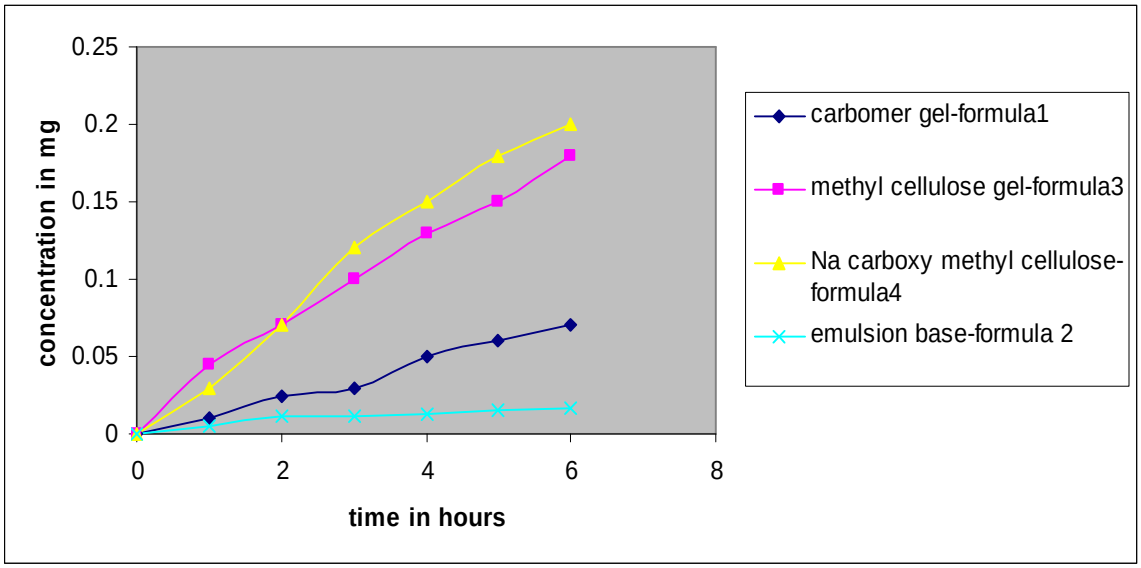

Figure-1: Effect of Different Bases on The Release of Ibuprofen

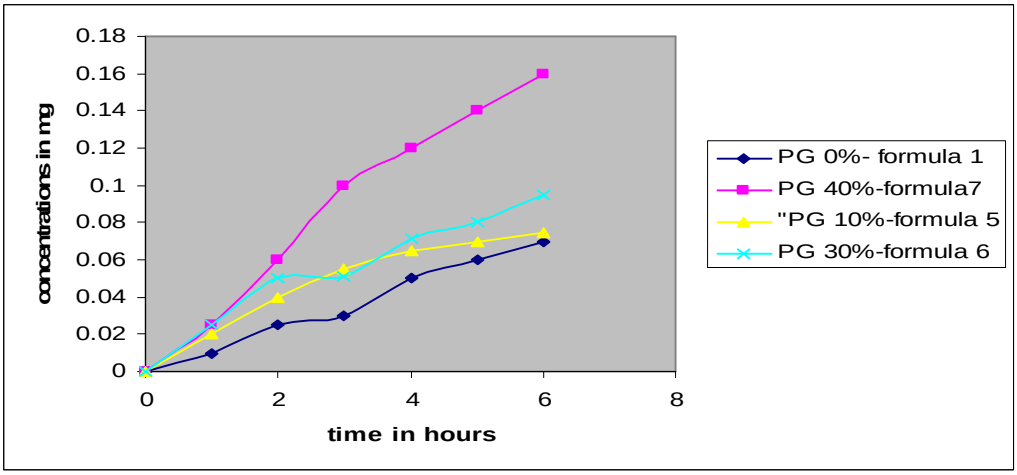

Figure-2:Effect of Diffrrent Propylene Glycol Concentration on The Release Of Ibuprofen From Carbomer Gel.

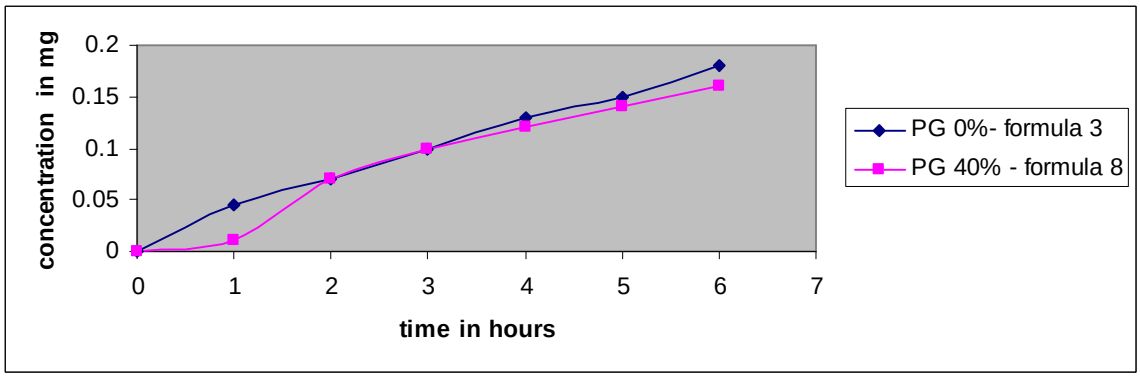

Figure-3 Effect of 40% Propylene Glycol on The Release of Ibuprofen From Methyl Cellulose Gel.

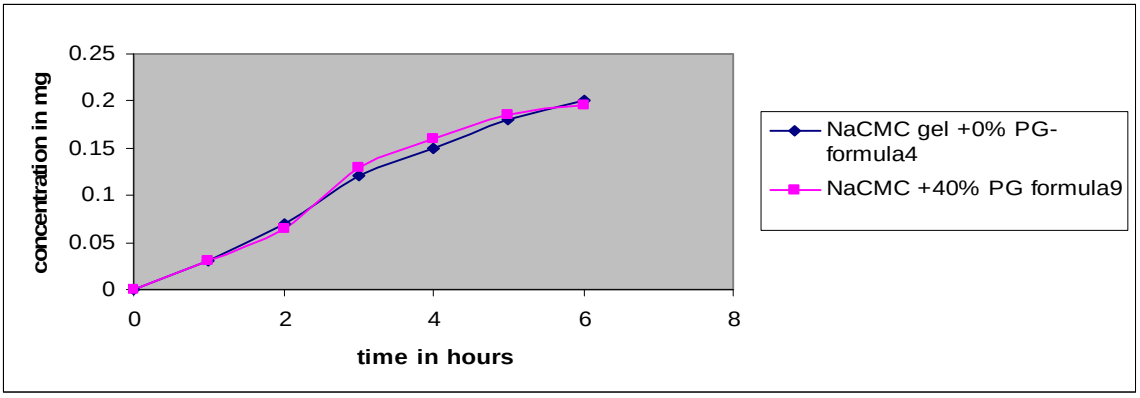

Figure-4: Effect of 40% PG on The Release Of Ibuprofen From Sodium CMC Gel.

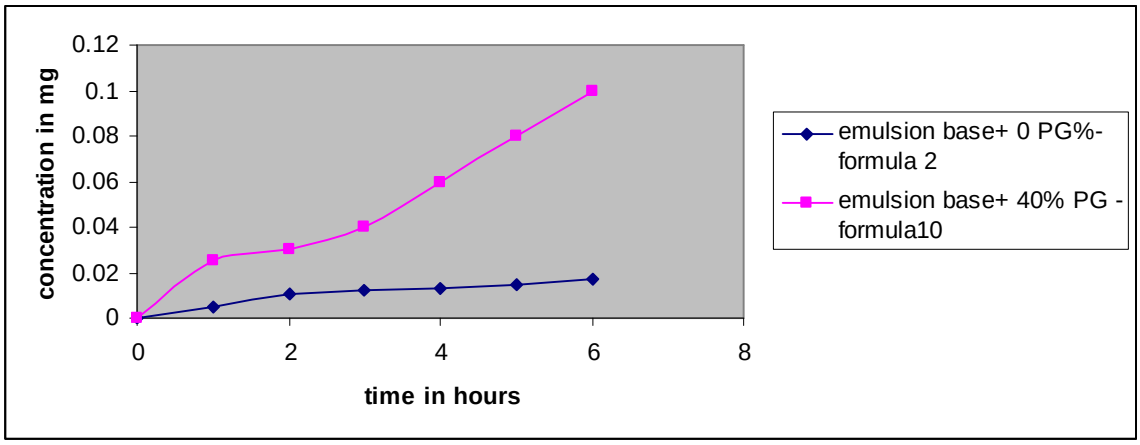

Figure-5: Effect of 40% PG on The Release of Ibuprofen From Emulsion Base.

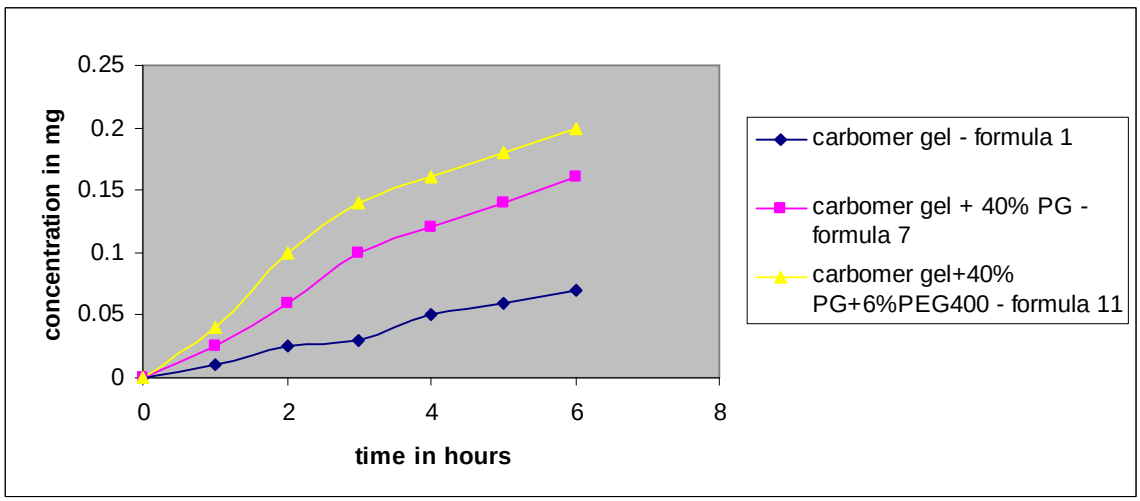

Figure-6: Effect of PG + PEG 400 on The Release of Ibuprofen From Carbomer Gel.

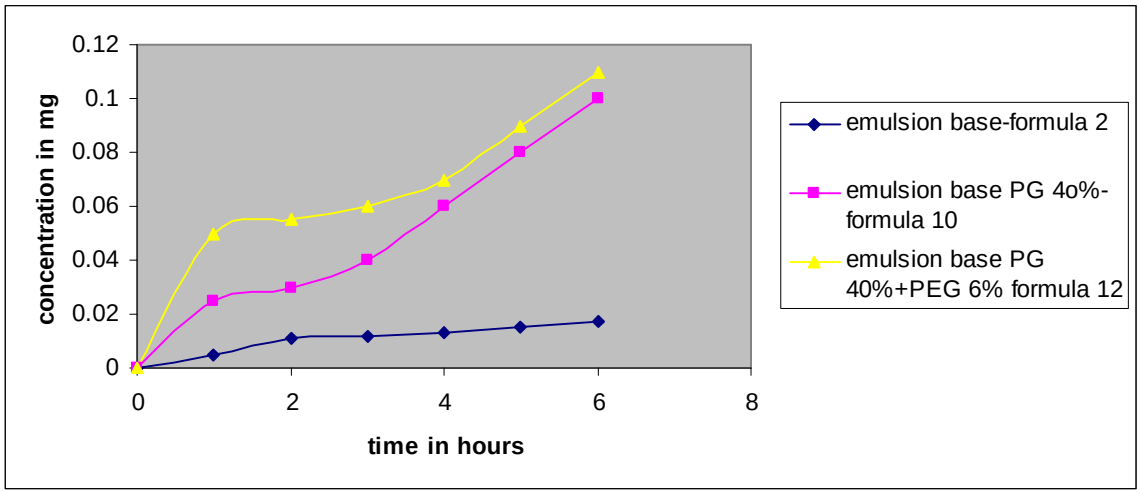

Figure-7: Effect of PG +PEG 400 On the Release Ibuprofen From Emulsiom Base.

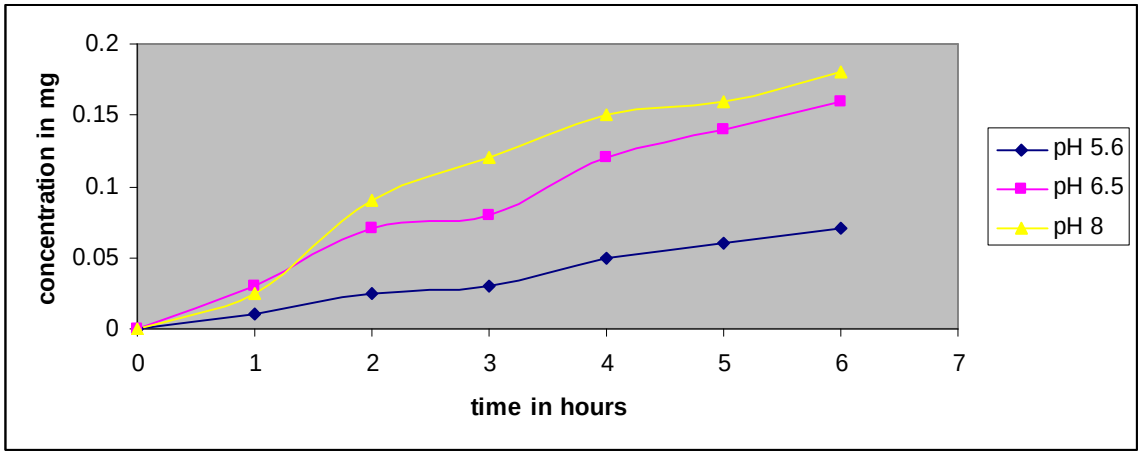

Figure-8: Effect of pH on the release of ibuprofen from carbomer gel

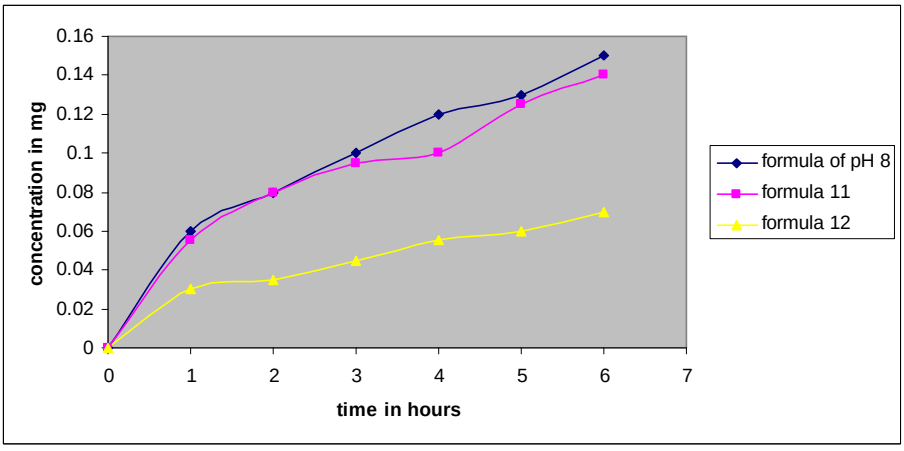

Figure -9: The diffusion of ibuprofen 5% through mouse skin via selected formulas.

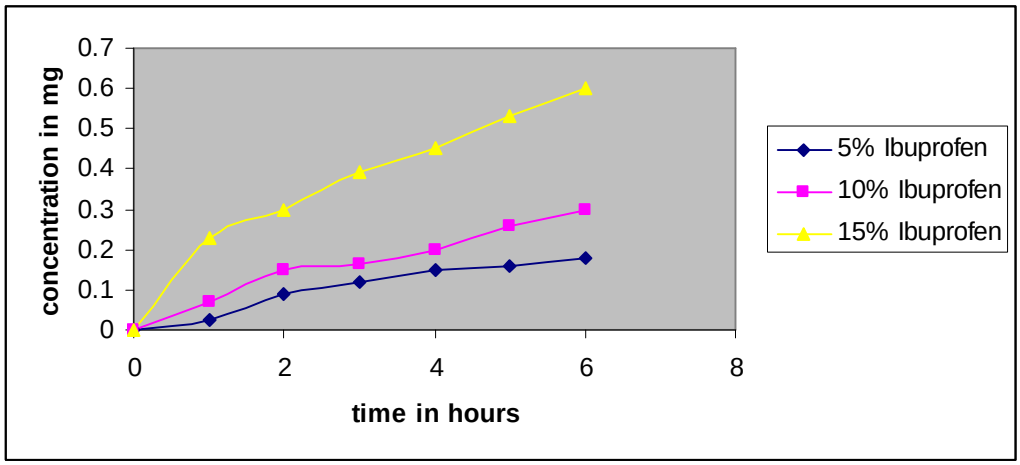

Figure-10: Effect of different ibuprofen concentrattions on the release from carbomer formula with ph 8.

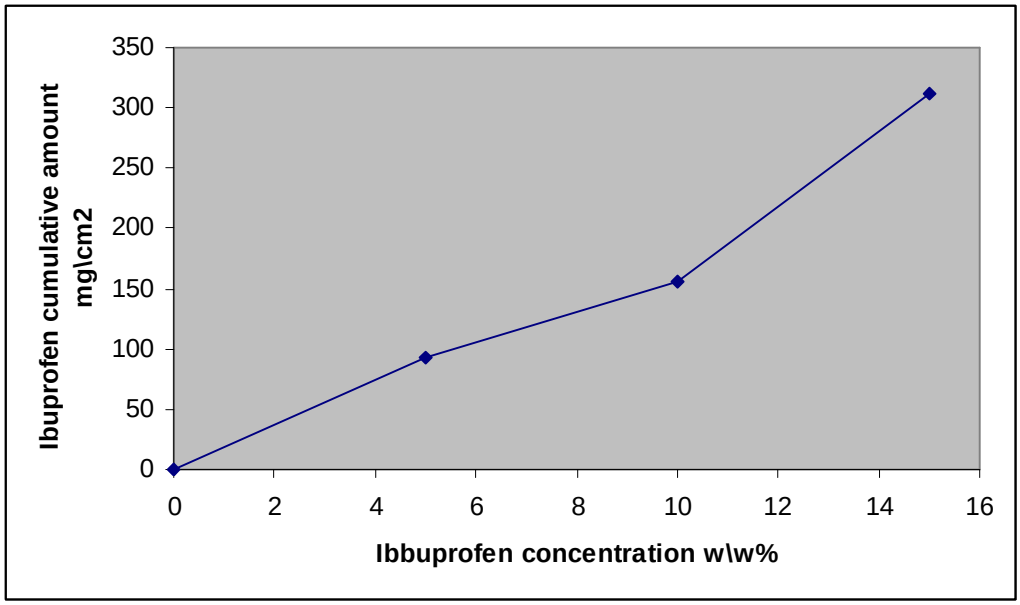

Figure-11: The Effect of Initial Drug Concentration on The Amount of Ibuprofen Released in The Release Study.

No. of cases	The case	Response
2	Supraspinates tendentites	Good +ve response
2	Osteoarthritis of knee joint	Mild +ve response
5	Sport injury	Good +ve response
5	LBP	Mild +ve response
2	Knee joint pain	Good +ve response
2	Muscle spasm (neck)	Good +ve response
2	Frozen shoulder	Good +ve response

Table 6- The preliminary clinical study of Ibuprofen 5%w/w gel.

Conclusion:

The results indicated that topical preparation of Ibuprofen could be an effective topical dosage form beside its oral dosage form in inflammatory conditions with the possibility of less systemic side effects.

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I would like to thank Dr. Abdalkareem Alsaffar (Consultant-sport medicine –Rheumatologist—Iraqi football team doctor) for his help in preliminary clinical study. Deepest gratefulness to the pharmacists Hadeel Hareth and Nora Zawar for their help and support.

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