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THE EFFECT OF VARIOUS VEHICLES ON *IN-VIVO* PERFORMANCE OF INDOMETHACIN FROM DIFFERENT TOPICAL FORMULATIONS

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ABSTRACT

Indomethacin is a non-steroidal anti-inflammatory agent (NSAIDs) with anti-inflammatory activity. Topical non-steroidal anti-inflammatory drugs (NSAIDs) are applied to the skin in the forms of gels, and cream in the region where pain is experienced. The aim of this study was to determine the effect of various vehicles containing an anti-inflammatory agent and to establish and optimal and stable system for cutaneous application. Ointments and gels are semisolid dosage forms intended for topical application. They may be applied to the skin, or used nasally, rectally and etc. Topical cutaneous applications minimize first pass effect and avoid harsh gastric condition. Two vehicle systems were evaluated, which includes emulsion O/W (cream) and gel, all of them containing indomethacin. The investigation of the vehicle systems was characterized by suitable in-vivo studies. Studies on *in-vivo* performance of indomethacin cream showed a decrease in 9 % of paw size after inducing inflammation while for indomethacin gel was 5%. The developed indomethacin cream and gel was stable for at least a period of 1 month. In conclusion, a stable cream and gel formulations containing indomethacin was successfully developed. Considering all the studies on the effect of various vehicles on the pharmaceutical availability, the cream formulation had been shown comparatively better performance than gel formulation, with no significance difference

observed ($p > 0.05$). Further research, such as proper parameters and release study maybe further required and conducted to support these findings.

KEYWORDS: Topical formulation, Indomethacin, NSAIDs and Stability study.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) present an important therapeutic class used to relieve pain and inflammation. NSAIDs can be further classified based on their chemical structure: salicylates, propionic, acetic, enolic (Oxicam) and fenamic acid derivatives; selective cyclooxygenase-2 (COX-2) inhibitors, sulphonanilides and others.[1]

Indomethacin is a non-steroidal anti-inflammatory agent (NSAID) with anti-inflammatory activity. Its pharmacological effect is thought to be mediated through inhibition of the enzyme cyclooxygenase (COX), the enzyme responsible for catalyzes the rate-limiting step in prostaglandin synthesis via the arachidonic acid pathway.[2]

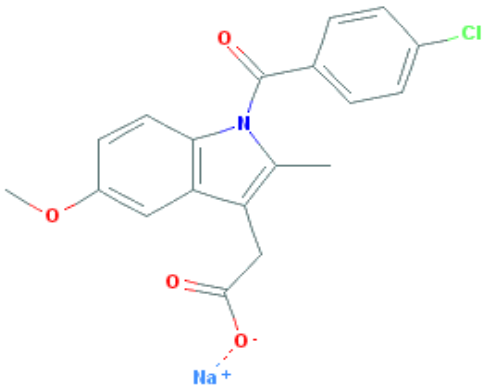

Figure 1: Structure of Indomethacin[2]

Topical non-steroidal anti-inflammatory drugs (NSAIDs) are applied to the skin in the forms of gels, and cream in the region where pain is experienced. The attraction of topical application of NSAIDs is that blood concentration are typically less than $1/20^{th}$ of those found with oral NSAIDs, minimizing the risk of serious harm.[3]

Ointments and gels are semisolid dosage forms intended for topical application. They may be applied to the skin or used nasally, rectally and etc. Most of these preparations are used for the effects of the therapeutic agents they contain.[4]

Topical preparations are used for both local and systemic effects. Systemic drug absorption should always be considered when using topical products if the patients are pregnant or nursing, because drugs can enter the fetal blood supply and breast milk and be transferred to the fetus or nursing infant.[1]

Generally, if comparison can be done between both emulsion and gel, there's a distinct differences that can be identified. An emulsion is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout a vehicle in which it is immiscible. In emulsion terminology, the dispersed phase is the internal phase, and the dispersion medium is the external or continuous phase.[4]

Emulsion with an oleaginous internal phase and an aqueous external phase are oil-in-water (O/W) emulsions. Conversely, emulsions having an aqueous internal phase and an oleaginous are termed water-in-oil (w/o) emulsions. Because the external phase of an emulsion is continuous, an o/w emulsion maybe diluted or extended with water or an aqueous preparation and a w/o emulsions, with an oleaginous or oil miscible liquid. Generally, to prepare a stable emulsion, a third phase, an emulsifying agent is necessary. Emulsions may also be used to deliver multiple active pharmaceutical ingredients of differing solubility's, or present on ingredients in a format that improve patient compliance for aesthetic reasons. However, as emulsions are inherently unstable, understanding the theoretical factors influencing emulsion stability is critical to the emulsion formulation.[5]

Gel on the other hand, are semi-rigid systems by which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macro-molecules of the dispersed phase. A high degree of physical or chemical cross-linking may be involved. The increased viscosity caused by the interlacing and consequential internal friction is responsible for the semisolid state.[4]

A gel may consist of twisted matted strands often wound together by stronger types of van der Waals forces to form crystalline and amorphous region throughout the system, such as tragacanth and carboxymethylcellulose. Some gel systems are as clear as water, and other are

turbid, since the ingredients may not be completely molecularly dispersed or they form aggregates, which disperse light. The concentration of the gelling agents is most likely less than 10% usually in 0.5 to 2.0% range with some exceptions. Gels are considered colloidal dispersions, since they contain particle of colloidal dimensions.[6]

MATERIALS AND METHODS

Materials

White petroleum, sodium lauryl sulphate, purified water, cetomacragol, glycerin, indomethacin (Indomen®, YSP), carbopol® 934, triethanolamine.

Apparatus

Beaker 1000ml, measuring cylinder 25ml, scott bottle 1000ml, mortar & pestle, pipette 5ml, conical flask 250ml, syringe 1cc, needle 27g, Porcelin dish.

Preparation of the cream

The preparation of creams will be done using the wet gum method. This preparation shall use the proportion of 4:2:1 ratio of the oil, water and emulsifier. The fatty phase shall be melt and the aqueous phase also shall be heated separately. The 1 part gum is triturated with 2 parts water to form a mucilage. This is generally form by trituration emulsifying agent with the water. Then, the 4 parts oil is added slowly, in portions, while triturating. After all the oil is added, the mixture is triturated for several minutes to form the primary emulsion. After all of the oil is added, the mixture is thoroughly mixed for several minutes to ensure uniformity. This follows by adding in all the solid substances such as preservatives, stabilizers and other excipients which are dissolved and added to the primary solution.

Cream Formulations

Table 1: Cream Formulation 1

Constituents	Percentage (%)
White Petroleum	25
Sodium Lauryl Sulphate	1
Purified Water	36
Cetamacragol	25
Glycerin	12
Indomethacin	1

Table 2: Cream Formulation 2

Constituents	Percentage (%)
White Petroleum	25
Sodium Lauryl Sulphate	3
Purified Water	34
Cetamacragol	25
Glycerin	12
Indomethacin	1

Table 3: Cream Formulation 3

Constituents	Percentage (%)
White Petroleum	25
Sodium Lauryl Sulphate	3
Purified Water	34
Cetamacragol	25
Glycerin	12
Indomethacin	1
Methylparaben	0.025
Propylparaben	0.030

Preparation of gel

The preparation of gel involves the use of polymer and in here; Carbapol®934 shall be used. Appropriate quantity of Carbapol®934 shall be soaking in water for a period around 2 hours. The Carbapol®934 then shall be neutralized with Triethanolamine (TEA) which is an alkalizing agent. Specific amount of drug shall be then dissolve in appropriate and pre-weight amounts of propylene glycol. This mixture which is form is stir gently with a spatula until a homogeneous gel is form. This sample is allow to equilibrate for at least 24 hours at room temperature prior to being evaluated by different testing

Gel Formulations

Table 4: Gel Formulation 1

Constituents	Percentage (%)
Carbapol®934	2
Water	10
Ethanol	qs 87
Indomethacin	1
Methylparaben	0.025
Propylparaben	0.030

Table 5: Gel Formulation 2

Constituents	Percentage (%)
Carbapol®934	2
Water	10
Ethanol	qs 87
Indomethacin	1
Methylparaben	0.025
Propylparaben	0.030
Triethonalamine (TEA)	3 Drops

Evaluations Tests

Physical and Stability Examination

The physical stability of the formulation was determined during the 1 month at storage and room temperature. This latter shall be conducted while changing the temperature at prescribed time intervals.

Thus, the sample shall be kept over at room temperature for a period of 1 month. This cycle was done for both the cream and gel formulation and the samples shall be left for 24h at room temperature. The physical condition of the samples shall be evaluated visually. The consideration of the physical stability includes the homogeneity, consistency, phase separation and the colour of both the formulation.

pH Determination

The pH will be measured for both the formulation using a pH meter, which is calibrate before each use with a standard buffer solution at pH 4, 7 and 9. The electrode shall be inserted into the sample 10 minutes priors to taking reading at room temperature. The formulation also shall be inspected whether any colour changes during the storage period as well as the homogeneity.

***In-Vivo* Study**

The Wistar strain albino rats of either sex were weighed and randomly divided in to four groups of four. First group not being treated served as control group. The second, third and fourth group was induced with inflammation by injecting with 0.1 ml of 3% formalin in distilled water in subplantar region of right hind paw. The third group was treated with indomethacin cream formulation while the fourth group was being treated by the indomethacin gel formulation.

Both the cream and gel applied to the injected site of the right hind paw. The paw size inflammation was being examined and carefully measured by using vernier calipers at the period of one hour on each group each up to the third hour after administration of both the formulation.

Data Analysis

The result for the study was recorded and analyzed via SPSS v20 (Statistical Product and Service Solution). Statistical evaluation of the results for pH value was carried out using Student's t-test at the significance level of $\alpha = 0.05$. The tables and figures show the mean values (x) and standard deviation (SD).

RESULTS AND DISSCUSSION

Cream and Gel Formulation

Based from the preparation of both the cream and gel formulation, it was identified that the appropriate preparation with acceptable appearance with consistence content and no phase separation was cream formulation 3. This formulation consist of white petroleum 25%, sodium lauryl sulphate 3%, purified water 35%, cetamacragol 25%, glycerin 12%, indomethacin 1%, methylparaben 0.025%, propylparaben 0.030%.

Figure 2 Indomethacin Cream

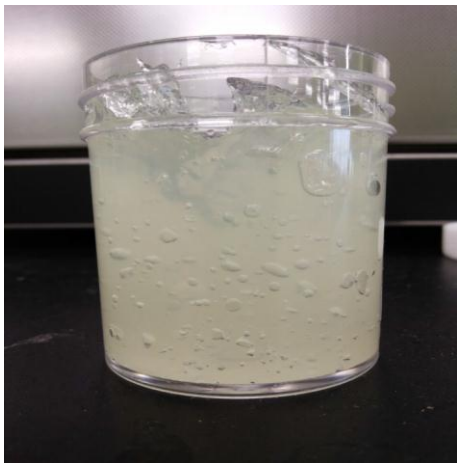

Figure 3 Indomethacin Gel

For the gel formulation, it was identified that the appropriate preparation with good appearance was gel formulation 2. This formulation consist of carbopol ® 934 2%, water 10%, indomethacin 1%, methylparaben 0.025%, propylparaben 0.030% and triethonalamine (TEA) 3 drops.

Table 6: Physical and Stability Examinations

Durations		Colour	Consistency	Phase Separation	Homogeneity
Week 1	**Cream**	White	Consistent	None	Homogenous
	Gel	Translucent			
Week 2	**Cream**	White	Consistent	None	Homogenous
	Gel	Translucent			
Week 3	**Cream**	White	Consistent	None	Homogenous
	Gel	Translucent			
Week 4	**Cream**	White	Consistent	None	Homogenous
	Gel	Translucent			

pH Determination

Table 7: pH Value of Gel

Weeks	1st Reading	2nd Reading	3rd Reading	Average
1	5.29	5.29	5.32	5.30
2	5.12	5.12	5.14	5.13
3	5.10	5.12	5.09	5.10
4	5.08	5.07	5.07	5.07

Table 8: pH Value of Cream

Weeks	1st Reading	2nd Reading	3rd Reading	Average
1	5.83	5.85	5.85	5.84
2	5.45	5.44	5.47	5.45
3	5.34	5.32	5.32	5.33
4	5.32	5.32	5.33	5.32

Table 9 Comparison between pH of Cream and Gel against Period of Time

Week	Cream		Gel		P Value
	Mean	± SD	Mean	± SD	
1	5.84	0.01	5.30	0.02	0.000
2	5.45	0.02	5.13	0.01	
3	5.33	0.01	5.10	0.02	
4	5.32	0.01	5.07	0.01	

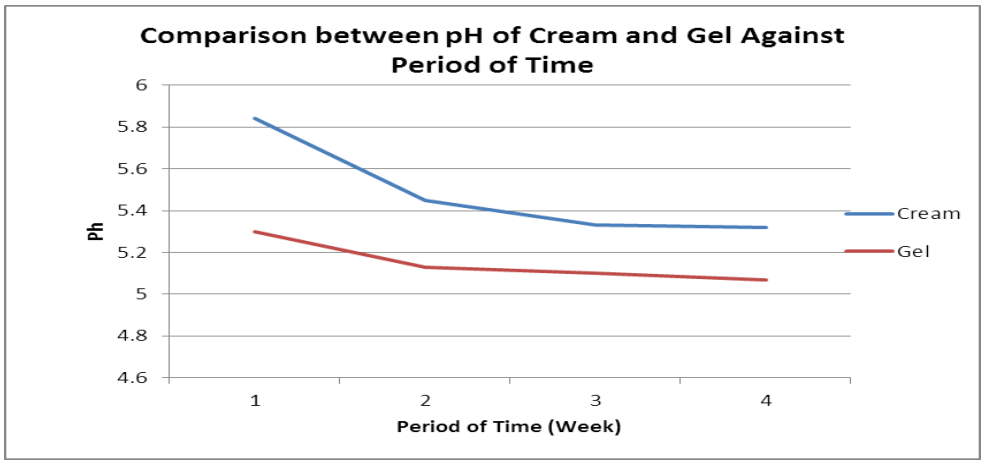

Figure 4: Comparison between pH of cream and gel against period of time

The pH of the skin was estimated between broad ranges of 4 to 7. It was shown that both the cream and gel formulation was between the range of the pH for the skin. Both the formulation was analysed weekly and clarified that both are still within the range upon storage of four weeks. Upon analysis, it shows the result was statistically significant ($p < 0.05$).

***In-Vivo* Study**

Rats with Controlled Condition

Table 10: Rats Paw Size to Different Hour of Controlled Condition

Animals		0 Hour	1st Hour	2nd Hour	3rd Hour
Rat 1	**Paw Size (cm)**	1.31	1.31	1.31	1.31
Rat 2		1.25	1.25	1.25	1.25
Rat 3		1.27	1.27	1.27	1.27
Rat 4		1.29	1.29	1.29	1.29
Mean		**1.28**	**1.28**	**1.28**	**1.28**

Table 11: Inflammation Percentage to Different Hour of Controlled Condition

Animals		0 Hour	1st Hour	2nd Hour	3rd Hour
Rat 1	**Paw Size (%)**	100	100	100	100
Rat 2		100	100	100	100
Rat 3		100	100	100	100
Rat 4		100	100	100	100
Mean		**100**	**100**	**100**	**100**

Rats with Formalin Injection

Table 12: Rats Paw Size to Different Hour of Formalin Injection

Animals		0 Hour	1st Hour	2nd Hour	3rd Hour
Rat 1	**Paw Size (cm)**	1.24	1.46	1.42	1.42
Rat 2		1.04	1.54	1.54	1.49
Rat 3		1.16	1.61	1.65	1.63
Rat 4		1.21	1.49	1.49	1.51
Mean		**1.16**	**1.53**	**1.53**	**1.5125**

Table 13: Inflammation Percentage to Different Hour of Formalin Injection

Animals		0 Hour	1st Hour	2nd Hour	3rd Hour
Rat 5	**Paw Size (%)**	100	117.7	114.5	114.5
Rat 6		100	148.1	148.1	143.3
Rat 7		100	138.8	142.3	140.5
Rat 8		100	123.1	123.1	124.8
Mean		**100**	**131.9**	**132.0**	**130.8**

Comparison between Induced Inflammation by Controlled and Formalin

Table 14: Injection Condition based on Time and Paw Size

Hour	Control		Formalin Inj		P Value
	Mean	± SD	Mean	±S D	
0	100	0.00	100.0	0.00	0.024
1st	100	0.00	131.9	14.01	
2nd	100	0.00	132.0	15.82	
3rd	100	0.00	130.8	13.56	

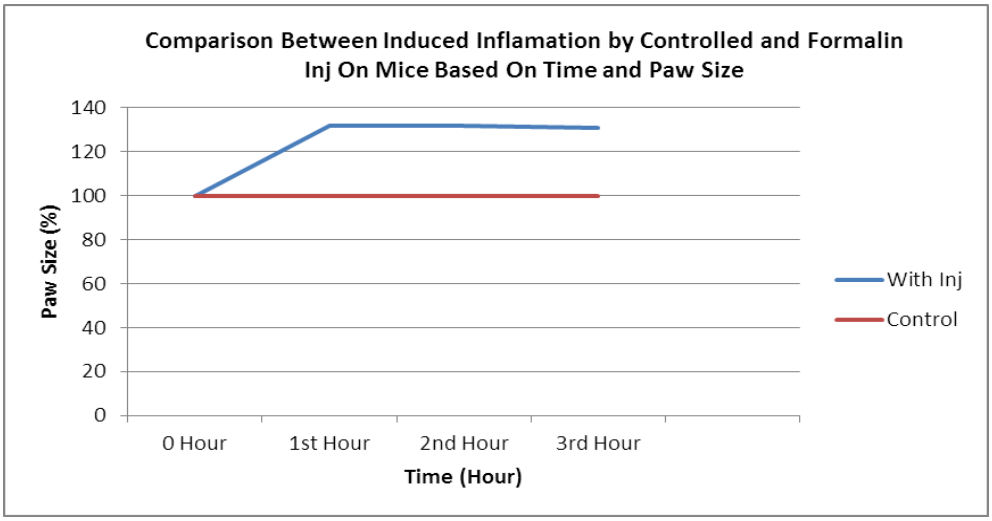

Figure 5: Comparison between induced inflammation by controlled and Formalin injection on mice based on time and paw size.

The paw size that was injected was the right side paw and measured with vernier calipers. From the table, it was shown that the paw size of the formalin induced increased up to 14.8% in the first hour followed by reduced to 5.9% in the second hour and 3.3% in the third hour. On the other hand, there was no recorded increase in paw size due to inflammation for the controlled.

Rats Treated with Cream Formulation

Table 15: Rats Paw Size to Different Hour Treated with Cream Formulation

Animals		0 Hour	1st Hour	2nd Hour	3rd Hour
Rat 1	**Paw Size (cm)**	1.25	1.44	1.35	1.29
Rat 2		1.33	1.56	1.42	1.38
Rat 3		1.29	1.45	1.34	1.32
Rat 4		1.27	1.45	1.33	1.32
Mean		**1.29**	**1.48**	**1.36**	**1.33**

Table 16: Inflammation Percentage to Different Hour Treated with Cream Formulation

Animals		0 Hour	1st Hour	2nd Hour	3rd Hour
Rat 1	**Paw Size (%)**	100	115.2	108	103.2
Rat 2		100	117.3	106.8	103.8
Rat 3		100	112.4	103.9	102.3
Rat 4		100	114.2	104.7	103.9
Mean		**100**	**114.8**	**105.9**	**103.3**

Rats Treated with Gel Formulation

Table 17: Rats Paw Size to Different Hour Treated with Gel Formulation

Animals		0 Hour	1st Hour	2nd Hour	3rd Hour
Rat 1	**Paw Size (cm)**	1.35	2.00	1.89	1.87
Rat 2		1.38	1.89	1.84	1.79
Rat 3		1.25	1.74	1.72	1.71
Rat 4		1.32	1.86	1.85	1.85
Mean		**1.33**	**1.87**	**1.83**	**1.81**

Table 18: Inflammation Percentage to Different Hour Treated with Gel Formulation

Animals		0 Hour	1st Hour	2nd Hour	3rd Hour
Rat 1	**Paw Size (%)**	100	148.1	140	138.5
Rat 2		100	137.0	133.3	129.7
Rat 3		100	139.2	137.6	136.8
Rat 4		100	140.9	140.2	140.2
Mean		**100**	**141.3**	**137.8**	**136.3**

Table 19: Comparison between Gel and Cream Effectiveness on Rats Based on Time and Paw Size

Hour	Gel		Cream		P Value
	Mean	**±SD**	**Mean**	**±SD**	
0	100	0.00	100.0	0.00	0.127
1st	141.3	4.81	114.8	2.04	
2nd	137.8	3.21	105.9	1.88	
3rd	136.3	4.61	103.3	0.73	

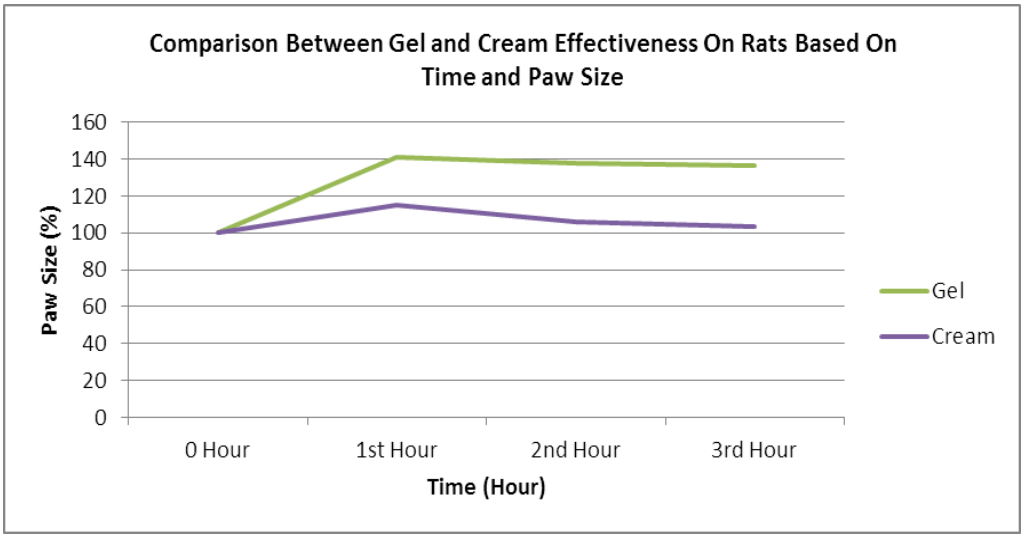

Figure 6: Comparison between gel and cream effectiveness on mice based on time and paw size

The paw size that was injected was the right side paw and measured with vernier calipers. From the table, the paw size of the indomethacin cream treated group, upon the formalin induced increased up to 14.8% in the first hour followed by reduced to 5.9% in the second hour and 3.3% in the third hour. The indomethacin cream was applied on the first hour after the formalin injection. On the other hand, it was shown that the paw size of the indomethacin gel treated group, upon the formalin induced increased up to 41.3% in the first hour followed by reduced to 37.8% in the second hour and 36.8% in the third hour. The indomethacin gel was applied on the first hour after the formalin injection.

DISCUSSIONS

Based on the studies done shown that both formulations are stable and formulated properly. Each component of the pharmaceutical cream and gel plays a crucial role in their development. In the cream formulation, the white petroleum acts as an ingredient in lubricant formulations for medicated confectionery together with mineral oil. Sodium lauryl sulfate is an anionic surfactant employed in a wide range of nonparenteral pharmaceutical formulations and cosmetics. Cetamacragol are generally used as ointment base with glycerin as solvent or co-solvent. In gel on the other hand, the Carbapol®934 was being used as a gelling agent. Topical ethanol solutions are used in the development of transdermal drug delivery systems as penetration enhancers with methylparaben and propylparaben as preservative.

A one month physical stability analysis shows that the cream and gel with indomethacin have a stable consistency at room temperature. Upon 1 month, both the cream and gel maintain the colour of which white for the cream and translucent for the gel. Both the formulation are consistent and smooth with each of their constituents. No phase separation was observed for a period of one month. Both the formulation also was homogenous upon storage and spread equally upon administration to the intended site.

The pH of both formulation also was examined for the period of 1 month. The pH of the skin was estimated between broad ranges of 4 to 7. It was shown that both the cream and gel formulation was between the ranges of the pH for the skin. Both the formulation was analysed weekly and clarified that both are still within the range upon storage of four weeks. At the first week, the pH of the cream was 5.84 and gel was 5.30. After the one month period, the value drop to 5.32 for the cream and 5.07 for the gel. Considerably, the value was still between the normal human range skin pH. Upon analysis, it shows the result was statistically significant ($p < 0.05$).

In-vivo study was done on both the gel and cream formulation. Upon comparison between controlled group versus formalin injection group shows that the formalin injection induced an inflammatory response which causes an inflammation on the rat paw after few hours of injection with the highest percentage increase was at the 1st hour after administration of formalin injection. Analysis testing was done using student-t test which shown a result of P value of 0.024. This shows that result was statistically significant.

A comparable study was done on both the indomethacin cream and gel, and it shows that both the formation of gel and cream with active ingredient indomethacin reduces the inflammation induced formalin. Both the indomethacin cream and gel formulation was applied on the first hour after the formalin injection. Both the formulation was applied on the injected site by rubbing gently on the site of affected region for a few seconds to increase the surface area as well as faster absorption of the topical formulations. Although the cream had shown a better performance but by using student t-test, the analyze values shows an obtained P-value of 0.127. This shows the result was not statistically significant.

An in-vitro studies was supposed to be conducted to achieve a more consistent as well as more theoretically better results, but due to some limitations which includes time constrain and limited sources, this cannot be conducted. With the in-vitro application studies, we will

be able to study drug release profile and have a better understanding regarding topical formulation application. A study regarding this should be done in the future to have a better understanding.

CONCLUSIONS

A stable cream and gel formulations containing indomethacin was successfully developed. Considering all the studies on the effect of various vehicles on the pharmaceutical availability, the cream formulation had been shown comparatively better performance than gel formulation on reducing inflammation in formalin induced inflammation on rat paw, with no significance difference observed ($p > 0.05$). The limitation of this study is due to the lack supplier of the materials needed to conduct the study. The limitation of time also one of the difficulties in completing and exploring the preparation as well as the evaluation studies. Further research can be done to further study regarding different topical formulation with main interest on pharmaceutical gel as well cream containing indomethacin.

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