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## Formulation and Evaluation of Semi Solid Dosage Forms Based On Naturally Occurring Analgesic Agent Camphor

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### ABSTRACT

Oral analgesics are commonly prescribed for the treatment of acute and chronic pain, but these agents often produce adverse systemic effects, which some times are severe, so topical administration of analgesics is an alternative method. The aim of present work is to develop semi solid preparations of natural analgesics like camphor. Three different strengths were prepared which are 25mg, 50mg, 100mg in two different bases that are hydrophilic and hydrophobic. All the prepared formulations were evaluated for PH, spreadability, diffusion studies. The selected formulations were evaluated for in-vivo studies in comparison with marketed preparations. The finalized preparation was kept for stability studies according to ICH guidelines.

**Keywords:** Pain, Camphor, Ointment.

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## INTRODUCTION

Pain: pain is an unpleasant neurophysiological sensation leading to discomfort it results from stimulation of specialized nerve endings which are particular evoked by tissue damage or injury.it interferes with an individual quality life and normal body functions. As it is a subjective experience therefore the medical diagnosis is challenging and it is characterized in different ways like duration, severity, type of the pain location of pain in the body and cause of pain.

Physiology of pain: Buck and paice in 1994 coined the name “nociception” for physiological process of pain. pain is caused by stimulation of pain receptors which are situated on free nerve endings .receptors that respond to stimuli which are responsible for sensation of pain are known as nociceptors, while the process by which a nociceptor is stimulated (due to chemical, thermal, mechanical or environmental changes) beyond its stimulation threshold is known as nociception. The basic pain mechanism undergoes three events- transduction, transmission and modulation .

The release of neuromodulator is a sensory process, allowing the stimulus to get transferred to an actual nerve impulse. This is known as transduction.

As a result, an action potential gets generated and a pain message is propagated by an impulse along the length of peripheral afferent nerve fibers to dorsal horn of spinal cord, which is called transmission.

Nociceptive impulses can be inhibited or blocked by modulation. This is brought about by the efferent pathway. All these lead to one end result, and the pathway of pain has been initiated and completed ,thus allowing us to feel the painful sensation triggered by the stimulus.

A variety of herbs and essential oils can be used for pain and inflammation associated with sports and exercise, as well as pain and inflammation associated with rheumatism, arthritis, surgery, or other medical conditions.

Till date, the only therapeutic options for treating MSK disorders involve oral or parenteral administration of steroids or non-steroidal anti-inflammatory drugs (NSAIDs).NSAID’s are one of the most commonly prescribed medications for wide range of MSK disorders as they have well established anti-inflammatory and analgesic properties. Application of these agents ranges in treatment of pain due to acute injury to the long term chronic disorders such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and similar degenerative disorders. NSAIDs are known to provide symptomatic relief from pain, allow quicker recovery and return to normal activity.

However, the main limitation of these formulations is extensive hepatic first pass metabolism (limiting the oral bioavailability to 50-60%).<sup>4</sup> Therefore, the drug needs frequent administration (daily dose of 150mg-3 times a day) leading to serious adverse effects such as ulcers, stomach pain, gastrointestinal (GI) disturbances, GI bleeding, dyspepsia, nausea and vomiting.<sup>4</sup> So topical administration of analgesics is an alternative method.

### **Need of herbal medicine:**

A variety of herbs and essential oils can be used for pain and inflammation associated with sports and exercise, as well pain and inflammation associated with rheumatism, arthritis, surgery, or other medical conditions. Herbal drugs are the drugs which occurs naturally from plants, they does not produce any side effects upon topical application.

**Camphor** (*Cinnamomum camphora*) is a white, crystalline substance with a strong odor and pungent taste, derived from the wood of camphor laurel (*Cinnamomum camphora*) and other related trees of laurel family. Camphor tree is native to India, Mongolia, Japan and Taiwan and a variety of this fragrant evergreen tree is grown in Southern United States. Camphor is obtained through steam distillation, purification and sublimation of wood, twigs and bark of the tree. There are many pharmaceutical applications for camphor such as topical analgesic, antiseptic, antispasmodic, antipruritic, antiinflammatory, antiinfective, rubefacient, contraceptive, mild expectorant, nasal decongestant, cough suppressant, etc. Camphor is easily absorbed through the skin, Camphor has several chemical varieties, each with different essential oil compositions. The leaf of *Cinnamomum camphora* contains camphor, as the main component along with cineol, linalool, eugenol, limonene, safrole,  $\alpha$ pinene,  $\beta$ pinene,  $\beta$ myrecene,  $\alpha$ humulene, p-cymene, nerolidol, borneol, camphene and some other components [11]

### **Semi solid dosage forms:**

semi solid dosage forms are the products that are applied to skin to treat a pathological condition and protects from other harmful environment. They are smooth, non-staining and get miscible with skin secretions. Semi solid dosage forms include ointments, creams, gels, Pastes, patches. They may be medicated (containing therapeutic agents) or non medicated (used for their physical effects as protectants, lubricants, and emollients).

### **Ointment:**

ointment is defined as a greasy semisolid preparation meant for external applications to the skin (or) mucous membrane. They usually contain medicaments that are dissolved, (or) suspended (or) emulsified in an ointment base.

## MATERIALS AND METHOD

### Formula for Formulation “A: Hydrophillic

S.No	Ingredients	Quantity in Grams
1	White soft paraffin	25g
2	Propylene glycol	12g
3	Stery alcohol	25g
4	Sodium lauryl sulphate	1g
5	Water	37ml
Total=100g		

### Formula For Formulation “B’: Hydrophobic

S.No	Ingredients	Quantity
1	Hard Paraffin	5g
2	Coetosteryl alcohol	5g
3	White Soft paraffin	85g
4	Lanolin	5g
Total = 100g		

### Procedure for Preparation Of Ointments:

#### Hydrophilic base:

The hydrophilic bases were prepared by melting the steryl alcohol and white soft paraffin at 70 °c. continue heating until the temperature of the mixture is about 75 °c .Add propylene glycol, sodium lauryl sulphate, methyl paraben, propyl paraben, to the water and heat to 75 °. Add aqueous phase to the oily phase with continuous stirring. Switch off the heating and stir continuously until the mixture has congealed.<sup>3</sup>

#### Hydrophobic base:

The hydrophobic bases were prepared by melting the Hard paraffin and cetosteryl alcohol on water bath. To this incorporate white soft paraffin, lanolin. stir until the ingredients are melted.<sup>3</sup>

Different Formulations F1, F2, F3, were prepared by using hydrophilic base. Different Formulations F4, F5, F6,were prepared using hydrophobic base. To the hydrophilic base and hydrophobic base camphor, were added and dissolved at 70 °c in water bath stir continuously until the mixture has congealed.

#### Formulation table:

Ingredients	F1	F2	F3
Camphor	25mg	50mg	100g
White soft paraffin	1.25mg	1.25mg	1.25mg
Propylene glycol 12g	0.62ml	0.62ml	0.62ml
Stery alcohol	1.25mg	1.25mg	1.25mg
Sodium lauryl sulphate	0.15mg	0.15mg	0.15mg
Water	1.85ml	1.85ml	1.85ml

Methyl paraben	25mg	25mg	25mg
Propyl paraben	25mg	25mg	25mg
<b>Ingredients</b>	<b>F4</b>	<b>F5</b>	<b>F6</b>
camphor	25mg	50mg	100mg
Lanolin	0.25mg	0.25mg	0.25mg
Hard paraffin	0.25mg	0.25mg	0.25mg
Cetosteryl alcohol	0.25mg	0.25mg	0.25mg
White soft paraffin	4.25mg	4.25mg	4.25mg
Methyl paraben	25mg	25mg	25mg
Propyl paraben	25mg	25mg	25mg

### Camphor calibration curve

#### **Preparation of Buffer (6.4 Phosphate buffer)**

6.8 g of potassium dihydrogen orthophosphate were weighed and taken in a 1000ml volumetric flask and make the volume to 1000ml with distilled water. 11.6ml of 0.2 m sodium hydroxide is added ,Buffer is prepared.

#### **Procedure:**

#### **Preparation Of Standard Stock Solution**

##### **(1000µg/ml or 1mg/ml):**

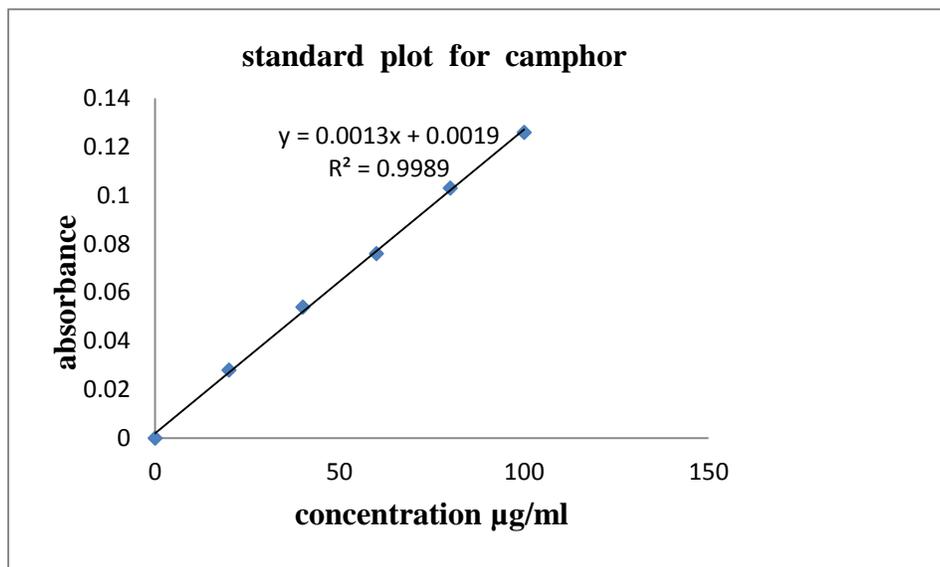
10mg of camphor drug was weighed and transferred into a 10ml volumetric flask, dissolved in ethanol and volume was made upto the mark with phosphate buffer.

##### **Preparation Of Sub Stock Solution(100µg/ml):**

1ml of above stock solution was taken in a 10ml volumetric flask and make the volume upto the mark with buffer (6.4phosphate buffer).

##### **Preparation of Series of Standards:**

From the above stock solution 2,4,6,8,10ml was transferred into separate 10ml volumetric flask and the volume was made up with buffer. This gives 20, 40,60,80,100 µg/ml respectively. The absorbance of the solutions was measured at 290nm using UV-Visible spectrophotometer. A graph was plotted by taking concentration on X-axis and absorbance on Y-axis.



**Figure 1 :Camphor calibration curve**

### **EVALUATION OF THE PREPARED FORMULATIONS:**

#### **pH:**

The pH of various formulations was determined by using Digital pH meter (Digital pH meter 335, Systronics, ). The 0.5 g of the weighed formulation was dispersed in 50 mL of distilled water and the pH was noted.<sup>1</sup>

#### **Homogeneity:**

All the developed ointments were tested for homogeneity by visual inspection. They were tested for their appearance with no lumps<sup>1</sup>

#### **Spreadability:**

The spreadability is expressed in terms of time in seconds taken by two slides to slip off from ointment, placed in between two slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability of ointment. The spreadability was calculated by using the following formula  $S = MxL/T$ .

Where S = spreadability, M = Weight tied to upper slide, L =Length of glass slides and T = Time taken to separate the slides completely from each other.

In this present experiment, M = g,L = cm and T was recorded (Ehrlich and Hunt, 1968).

#### **In-Vitro Release Studies of Prepared ointment**

In-vitro drug release was performed using franz diffusion cell. Dialysis membrane was previously soaked in the respective dissolution medium overnight and used as the permeation membrane. Phosphate buffer pH 6.4 was placed in receptor compartment.

An accurately weighed quantity ( 250mg ) of the formulated ointment was uniformly spread on the dialysis membrane was placed in donor compartment. One side of the cellophane membrane was kept in contact with the medium i.e., Phosphate Buffer pH 6.4 .

The medium was constantly agitated using a magnetic stirrer and the temperature was maintained at a constant of  $37 \pm 1$  °C throughout the operation. Samples of 1 ml volume were then withdrawn from the receptor compartment at intervals of 5 minutes over a period of 1 hour and the amount withdrawn was replaced with fresh volume of the medium. The samples withdrawn were then analysed for the amount of Drug released by UV spectrophotometric method by measuring the absorbance of the samples at particular wavelength against Phosphate Buffer p H 6.4 taken as blank.

#### **Ex-vivo studies:**

Using flow-through diffusion cell or microdialys method; the rate of penetration of the preparation can be estimated. Animal or human skin of definite area should be collected and tied to the holder present in a diffusion cell. The diffusion cell is placed in a fluid bath. Measured quantity of the preparation is applied over the skin and the amount of drug passed into the fluid is measured at regular intervals by analyzing the aliquots of fluid using a spectrophotometer.<sup>11</sup>

#### **In-vivo studies :**

Evaluation of analgesic activity: In the present investigation, analgesic activity of camphor, menthol, thymol was studied by using Eddy's hot plate method using diclofenac sodium as standard drug.

#### **Hot plate induced analgesia**

The animals were placed individually in hot plate regulated at a temperature ( $55 \pm 2$  °C) before the treatment and its reaction time was determined. After noting the initial reaction time, the treatment was given to each mouse. Then the mice were placed on the Eddy's hot plate under regulated temperature and the licking of the forepaws was recorded as the hot plate latency with the help of a stop-watch. The mice were divided into four groups with (n=6) and treated with the respective solutions as given below

Group-I: served as control(hydrophobic) .

Group-II: served as control (hydrophilic)

Group-III: served as standard & received diclofenac.

Group-VI: : served as camphor hydrophobic.

Group-V: served as camphor hydrophilic

#### **Tail flick method using immersion of tail:**

Mice of 100mg weight were used, rat is placed into cage in such a way that their tail hangs freely. distal 5cm of mice is marked and immersed into a cup of warm water (55°C) for 15 seconds. The reaction time is determined periodically after administration of test drug.

#### Stability studies:

The stability studies were carried out in all formulations at different temperature conditions (45°C) for 3 months. All the evaluation parameters i.e. , pH, viscosity ,spreadability, consistency and phase separation were studied at different time intervals i.e., 15, 30, 60 and 90th days

## RESULTS AND DISCUSSION:

#### Physical Appearance:

Various formulations of the prepared ointment were inspected visually for their colour, homogeneity, consistency. The results are tabulated in Table 1. The results indicate that all the prepared formulations F1 to F6 were observed for physical appearance and all the formulations were appeared to be white and good.

**Table 1: Physical appearance for all the formulations**

S. No.	Formulation Code	Colour	Homogeneity	Consistency
1	F1	White	Good	++
2	F2	White	Good	++
3	F3	White	Good	++
4	F4	White	Good	++
5	F5	White	Good	++
6	F6	White	Good	++

#### Determination of pH:

The pH of the ointments were determine by using a calibrated pH meter. The readings were taken as an average of three sample readings. The pH values exhibited by the ointments were tabulated in the table 2 , and are found to be in the range of 6.09 to 6.53. Hence all the formulations were in the normal pH range of the skin and would not produce any skin irritation

**Table 2: PH of the formulations**

S. No.	Formulation Code	pH*
1	F1	6.36±0.3
2	F2	6.27±0.1
3	F3	6.39±0.6
4	F4	6.53±0.5
5	F5	6.09±0.18
6	F6	6.34±0.2

#### Spreadability:

Pharmaceutical semisolid preparations include ointments, cream, emulsion, gel, and rigid foams. Their common property is the ability to cling to the application surface for a reasonable period of time before they are washed off or worn off. They usually serve as vehicles for topically applied drugs, as emollients, or as protective. The spreadability of all the prepared formulations was evaluated and spreadability range for F1 to F6 is 11 to

**Table 3: Spreadability of the all formulations**

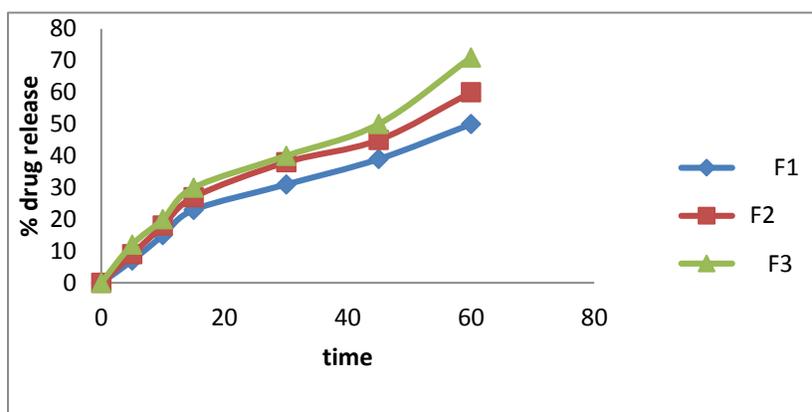
S. No.	Formulation Code	Spreadability*
1	F1	11gm.cm/sec
2	F2	12gm.cm/sec
3	F3	13.5gm.cm/sec
4	F4	12gm.cm/sec
5	F5	14gm.cm/sec
6	F6	12gm.cm/sec

#### IN-VITRO DRUG RELEASE FOR HYDROPHILLIC FORMULATIONS:

All the formulations were evaluated for drug release studies in in vitro conditions. the in vitro studies showed that F1 to F3 was observed to be within 50 to 71 range f3 is giving 71% drug release within 60 minutes.

**Table 4: In-vitro drug release of camphor from hydrophilic formulations**

Time	F1	F2	F3
0	0	0	0
5	7	9	12
10	15	18	20
15	23	27	30
30	31	38	40
45	39	45	50
60	50	60	71

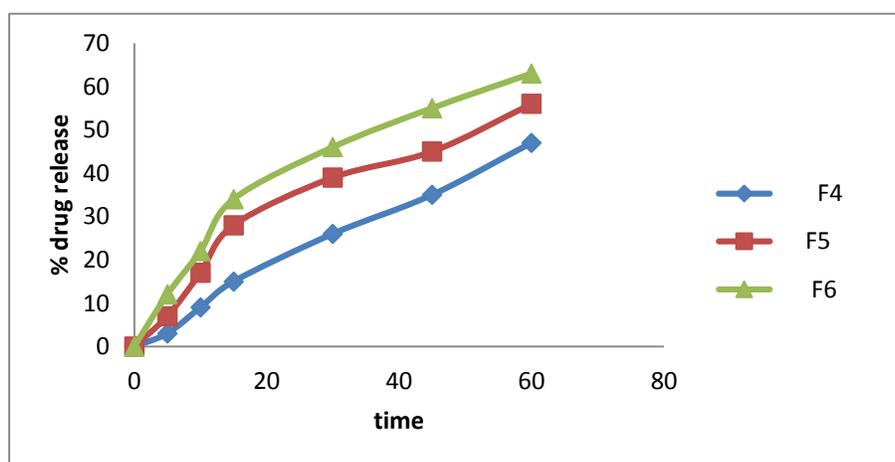


**Figure 2: Graph showing percentage drug release in-vitro drug release for hydrophilic formulations**

IN-VITRO DRUG RELEASE FOR HYDROPHOBIC FORMULATIONS: all the formulations were evaluated for drug release studies in in vitro conditions. the intro studies showed that F4 to F6 was observed to be within 47 to 63 range f6 is giving 63% drug release with in 60 minutes

**Table 5: In-vitro drug release of camphor for hydrophobic formulations**

Time	F4	F5	F6
0	0	0	0
5	3	7	12
10	9	17	22
15	15	28	34
30	26	39	46
45	35	45	55
60	47	56	63



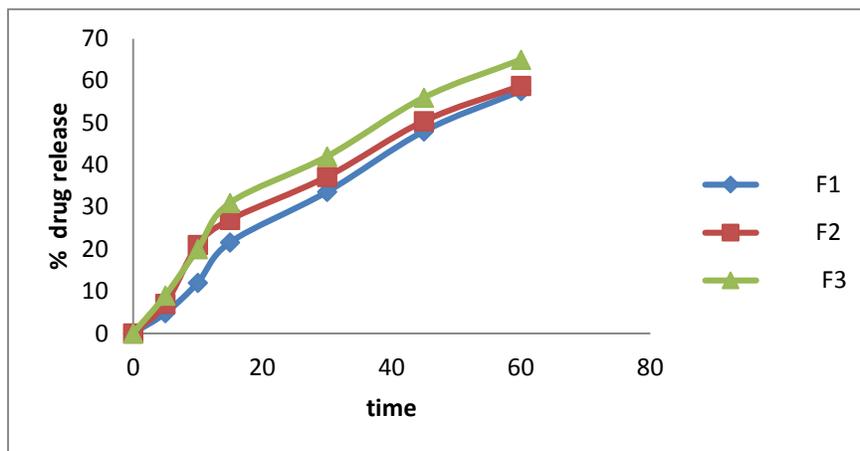
**Figure 3: Graph showing percentage drug release in-vitro drug release for hydrophobic formulations**

EX-VIVO PERMEATION FOR HYDROPHILLIC FORMULATIONS:

For the prepared ointment formulation drug release pattern was studied using franz diffusion cell and goat skin. The results from the table indicate that formulation f6 showed higher drug release of 86 followed by formulation f1, f2, f3, F4, f5, respectively

**Table 6: ex-vivo studies for hydrophilic formulations**

Time	F1	F2	F3
0	0	0	0
5	4.8	7	9
10	12	21	20
15	21.6	27	31
30	33.6	37.2	42
45	48	50.4	56
60	57.6	58.8	65

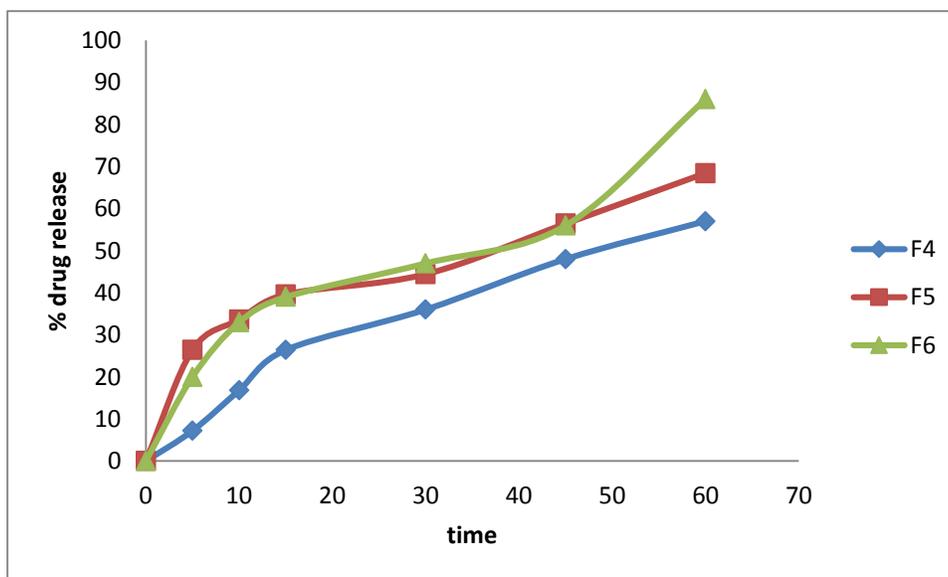


**Figure 4: Graph showing percentage drug release ex-vivo studies for hydrophilic formulations**

EX-VIVO PERMEATION FOR HYDROPHOBIC FORMULATIONS: in ex-vivo studies F6 is showing better release pattern.

**Table 7: ex-vivo studies for hydrophobic formulation**

Time	F4	F5	F6
0	0	0	0
5	7.2	26.4	20
10	16.8	33.6	33
15	26.4	39.6	39
30	36	44.4	47
45	48	56.4	56
60	57	68.4	86



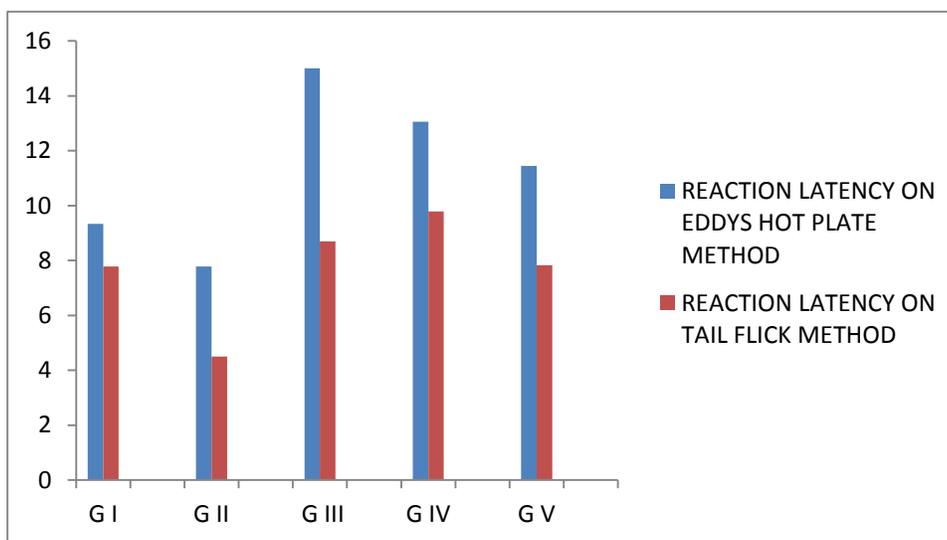
**Figure 5 Graphs showing percentage drug release for ex-vivo studies for hydrophobic formulations**

### IN-VIVO STUDIES FOR PREPARED FORMULATIONS:

The reaction latency on Eddy's hotplate increased significantly with topical application of hydrophobic formulations and with Standard formulation.

**Table 8: Showing reaction latency time**

S.No	Groups	Reaction latency in on Eddy's hot plate(Seconds)	Tail flick latency in tail immersion test(Seconds)
1	Group I (Hydrophobic control)	9.33± 0.74	7.78 ±5.78
2	Group II	7.78± 0.76	4.5±0.69
3	Group III	15 ±0.00 <sup>##</sup> *	8.7±0.46* #
4	Group-VI	13.06± 3.16*	9.78 ± 1.61*
5	Group-	11.44 ± 0.46 <sup>#</sup>	7.83 ± 0.28



**Figure 6: showing bar diagram on eddys hot plate method and tail flick method.**

Ex-vivo and in-vivo results are in accordance with each other .in in-vivo as well as ex-vivo conditions f6 is only showing the better result it can be attributed that hydrophobic bases are better in compliance with skin secretions .that's why hydrophobic bases are showing better release in ex-vivo and in-vivo conditions.

#### Stability studies:

The prepared formulations were packed in aluminum collapsible tubes (5 g) and subjected to stability studies at 45 °C /75% RH for a period of 3 months using stability chamber.

**Table 9: showing pH values of stability studies**

Time	pH			
	0 days	After 1 month	2 months	3 months
F1	6.36± 0.03	6.40	6.48	6.48
F2	6.42± 0.03	6.63	6.64	6.65
F3	6.40± 0.02	6.4	6.6	6.63
F4	6.51± 0.04	6.51	6.52	6.51
F5	6.54 ±0.02	6.51	6.51	6.54
F6	6.39±0.08	6.39	6.41	6.42

**Table 10: showing % drug release of stability studies**

% Drug Release		After 1month	After 2 months	After 3 months
Formulations	0	40°C/	40°C/	40°C/
	days	75% RH	75% RH	75% RH
F1	50	50	49	48
F2	60	60	59	58
F3	71	71	70	69
F4	47	47	46	46
F5	57	57	56	55
F6	63	63	62	61

F1 to f6 formulations were exposed to stress conditions and were tested for stability for three months. all the formulations were found to be stable. There was no change in color and there was a negligible difference in values of pH, drug and drug release.

#### CONCLUSION:

All the prepared formulations were found to be good in physical appearance, spreadability, and pH. When evaluated for in-vitro drug release ,the formulation F3 has shown the better release profile of camphor. The prepared formulations were subjected to ex-vivo and in-vivo studies, which revealed that the formulation F6 is showing better release profile in terms of analgesic activity. F6 formulation is hydrophobic base consisting of 100mg of camphor, this can be attributed to the fact that lipophilic nature of skin secretions will aid in the penetration of drug easily which will help in showing better analgesic properties.

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