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FORMULATION AND CHARACTERIZATION OF TOPICAL PROPRANOLOL HYDROCHLORIDE GEL FOR INFANTILE HAEMANGOMIA

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ABSTRACT: Propranolol hydrochloride, a non-selective beta-blocker, has emerged as a first-line treatment for infantile hemangioma due to its vasoconstrictive, anti-antigenic, and pro-apoptotic effects on endothelial cells. This research focuses on the development of topical gel, for the localized treatment of infantile hemangioma, aiming to reduce systemic side effects while enhancing therapeutic efficacy. The formulations were prepared using suitable gelling agents and emulsifying components. Several physicochemical tests were conducted, including spreading ability, viscosity, moisture content, and moisture uptake, to evaluate the formulations' properties. The emulgel demonstrated superior results in terms of spread ability and a balanced viscosity that facilitated both ease of application and prolonged contact with the skin. Moisture content and moisture uptake studies suggested that the emulgel maintained skin hydration better than the aqueous gel. In conclusion, the emulgel exhibited enhanced physicochemical characteristics, making it a more promising option for the topical treatment of infantile hemangioma compared to the aqueous gel. Further clinical evaluations may solidify its potential as an effective and safe therapeutic alternative.

INTRODUCTION: Infantile hemangiomas (IH) are common benign vascular tumors in infants, affecting up to 10% of newborns. Although most hemangiomas resolve on their own, some require treatment due to complications such as ulceration, bleeding, or interference with vital functions like vision or breathing. Propranolol hydrochloride (PH), a beta-blocker initially used for heart conditions, was found to be highly effective in shrinking hemangiomas.

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While oral PH has become the first-line treatment, it carries risks of systemic side effects like hypotension, bradycardia, and hypoglycemia. PH gel, a topical formulation, offers a non-invasive alternative for treating superficial hemangiomas [1]. Applied directly to the lesion, the gel minimizes the risk of systemic side effects while effectively reducing the size, color, and elevation of the tumor. The drug's mechanism includes vasoconstriction, inhibition of angiogenesis, and promoting the death of abnormal cells that form the hemangioma.

While propranolol gel is promising for small and superficial hemangiomas, it may not be as effective for larger or deeper lesions [2]. Research is ongoing to refine its dosage and application. Nonetheless, pH gel represents an important step forward in the safe, localized treatment of infantile hemangiomas

[3]. Aqueous gels and emulgels are popular topical formulations due to their ease of application, smooth texture, and effective delivery of active ingredients. These formulations are used in both pharmaceutical and cosmetic products, offering a versatile and user-friendly approach for topical drug delivery [4]. An aqueous gel consists of a water-based system, where a gelling agent is dissolved to form a structured, semi-solid matrix. Common gelling agents include polymers such as carbomers or cellulose derivatives, which provide stability and enhance the spread ability of the gel [5]. These gels are typically non-greasy, lightweight, and provide a cooling effect upon application, making them ideal for skin conditions requiring moisture retention or quick absorption. Emulgels combine the characteristics of both gels and emulsions [6]. They are formed by dispersing oil droplets within an aqueous gel base, stabilizing the two phases with emulsifiers. This makes emulgels especially effective for delivering both hydrophilic (water-soluble) and lipophilic (oil-soluble) active ingredients. Their dual-phase system ensures better skin penetration, prolonged drug release, and a more pleasant feel on the skin compared to traditional ointments or creams. The preparation of both gels involves a careful process of dissolving the active ingredient in the aqueous phase, incorporating the gelling agent, and ensuring uniform dispersion. Emulgel preparation further requires emulsification of oil into the aqueous phase [7].

MATERIALS: Propranolol hydrochloride is received from Torrent Pharmaceuticals as gift sample. Hydroxy propyl methylcellulose (HPMC) and Carboxymethyl cellulose (CMC) are procured from Maple Biotech. All the chemicals used are of AR grade.

Preparation of rug Loaded Gel:

TABLE 1: FORMULATION TABLE

Type	Formulation	drug (mg)	HPMC (mg)	CMC (mg)	Propylene glycol(ml)	Glycerin (ml)	Liquid Paraffin (ml)	Tween 80 (ml)	Water (ml)
Aqueous	F1	50	200	200	5	5	-	_	5
gel	F2	50	400	400	5	5	_	_	5
Emul gel	F3	50	200	200	5	5	5	0.5	5
	F4	50	400	400	5	5	5	0.5	5

For aqueous gel CMC and HPMC were left to swell overnight by adding water. Afterward, propylene glycol and glycerin were added and allowed to gel. Following gelatinization, the pH solution was added to the polymer solution. Finally, the mixture was stirred for 2 hours at 1000 rpm. For emulgel, CMC and HPMC were left to swell overnight. Then liquid paraffin, tween 80, and propylene glycol were added to the mixture with continuous stirring for 2 hours at 1000 rpm.

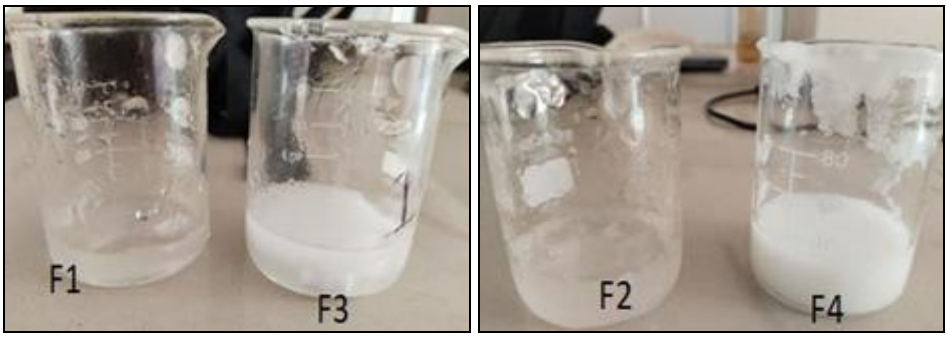

FIG. 1: PICTURE OF DIFFERENT FORMULATIONS

Evaluation:

Spread Ability Study: The parallel plate (PP) method and the slip and drag (SD) method were employed to evaluate the gel's properties an appropriate amount of the gel sample was measured using an analytical balance. A small portion of the gel was placed on a glass slide using a spatula. A second clean glass slide was placed on top, sandwiching the gel between the two slides. A 10-gram weight was applied to the top slide to

ensure uniform pressure. The setup was left to stand for 5 minutes, allowing the gel to spread. Afterward, the slides were carefully separated, and the diameter of the spread gel was measured using a ruler. The spread diameter was recorded, and the spread ability was calculated using the relevant formula [8].

Drug Content Test: A 1g sample of the drug product was weighed using an analytical balance. A standard drug solution of known concentration was prepared using the same solvent as the drug product. The drug product sample was dissolved in a pH 6.8 buffer solution. The sample was then analyzed using a UV spectrophotometer at a wavelength of 289 nm. The absorbance or chromatogram of the sample was compared with that of the standard drug solution to determine the drug content. The percentage of drug content was calculated using the appropriate formula [9].

Viscosity: Viscosity was checked with help of Brook field viscometer using spindle no 22 at various rpm.

pH: To evaluate the pH of aqueous or emulgel formulations using a pH meter, a small amount of the sample was prepared, ensuring room temperature condition. The pH meter was calibrated with standard buffer solutions before use. The electrode of the pH meter was then immersed in the sample, ensuring proper contact with the formulation. The pH meter measures the hydrogen ion concentration in the sample, displaying the pH value.

Moisture Content: The samples were placed in desiccators containing silica gel for 48 hours. Readings were taken at specific intervals during this time [10].

Moisture Uptake: To ensure consistent conditions, Potassium Chloride (KCl) solution was initially placed in desiccators to establish a controlled environment. The four samples were then introduced to the desiccators and left for a period of 48 hours. Throughout this time, readings were taken at predetermined intervals to monitor changes [11].

FTIR: The spectrum provides characteristic peaks, which are analyzed to identify chemical bonds, assess formulation stability, and detect any potential interactions between ingredients or degradation over time [12].

***In-vitro* Release Study:** This study explored the release profile of our drug formulation in a simulated physiological environment. We employed a classic in vitro method, using a paddle apparatus at 37°C and 50 rpm. The drug, carefully weighed at 3 grams, was encapsulated within a cellophane membrane and immersed in 500 ml of pH 6.8 buffer. Samples were collected at specific time intervals over a 7.5-hour period, with the withdrawn volume replaced by drug-free PBS. The absorbance of each sample was measured at 289 nm, allowing us to quantify the drug released. The cumulative release data was meticulously plotted against time, revealing the kinetics of drug release [13].

***Ex-vivo* Permeation Study:** An *ex-vivo* study was conducted to evaluate the release profiles of all formulations using a thin chicken skin membrane in a 100 ml buffer solution with a pH of 6.8. The chicken skin was first secured within a diffusion tube using thread. The samples were then placed in the tube, and the tube was attached to a paddle apparatus. The release study was conducted over a period of 4 hours, with samples collected at predetermined time intervals: 0.25 hours, 0.5 hours, 1 hour, 2 hours, 3 hours and 4 hours [14].

Skin Irritation Study: Model mice (Proposal no. 20/12/IAEC/SPS/SOA) were used in this experiment. Their fur was carefully removed using scissors. Different formulations of aqueous and emulsion gels were then applied to the mice's skin using cotton swabs. Photographs were taken at two hours interval for a total of 24 hours [15].

RESULTS AND DISCUSSION:

TABLE 2: PHYSICAL CHARACTERIZATION OF FORMULATIONS

Formulation	Spreadibility (cm^2) PP SD		%Drug Content	pH	Viscosity (N·s m–2)	%Moisture Content	%Moisture Uptake
F1	5.6	9.5	90.02	5.5	80.1	12	10

F2	4	8	90.05	5.8	81	13	11.7
F3	6	10	93	6	83	11	9.6
F4	3.48	7.5	91	6.2	86	11.6	9

Spread Ability: Good spread ability ensures the product is evenly applied, improving patient compliance and drug absorption. The spread ability test was conducted using two different methods: the parallel plate method and the slip-and-drag method. In both methods, it was concluded that higher concentrations of HPMC and CMC in aqueous gel provide better results than in emulgel.

Drug Content: The drug content is typically expressed as a percentage of the labeled amount, and should fall within an acceptable range (e.g., 90-110%) to ensure consistency and efficacy. This test is crucial for evaluating the uniform distribution and stability of the drug within the formulation, ensuring therapeutic effectiveness. The drug content of all formulations was presented in Table 2 and it confirmed that the emulgel performs better than the aqueous gel.

Viscosity: It also plays a crucial role in the stability of the emulsion or gel, preventing phase separation or settling of active ingredients. The ideal viscosity should be high enough to maintain stability but low enough to allow smooth application on the skin or other surfaces. Viscosity was measured using a Brookfield viscometer at various RPMs, and it was concluded that the emulgel was more viscous than the aqueous gel due to the higher concentrations of HPMC and CMC.

pH: The pH of an aqueous or emulgel formulation is measured to ensure its compatibility with the skin or intended application site.

The ideal pH range for topical formulations is usually between 5 and 7, matching the skin's natural acidity to avoid irritation or disruption of the skin barrier. The pH of the emulgel was 6.2, while the pH of the aqueous gel was found to be 5.8.

Moisture Content: Maintaining appropriate moisture content is essential to prevent microbial growth and ensure the formulation retains its intended consistency. The percentage of moisture content for all formulations, as shown in **Table 2** and confirms that the aqueous gel has higher moisture content.

Moisture Uptake: Excessive moisture uptake can affect the consistency, spread ability, and stability of the formulation, potentially leading to phase separation, microbial growth, or reduced efficacy. The percentage of moisture uptake for all formulations indicated that the maximum moisture content in the aqueous gel compared to the emulgel.

FTIR: The FTIR analysis of the pure drug was conducted to examine its functional groups. The characteristic peaks and chemical groups present in the IR spectrum are shown in **Fig. 2.** Peaks observe at different wavelengths include O-H at 3741 cm^{-1}, =O at 3033.46 cm^{-1}, and N-H at 2932 cm^{-1}. The major peaks correspond to the functional groups, confirming the sample as PH.

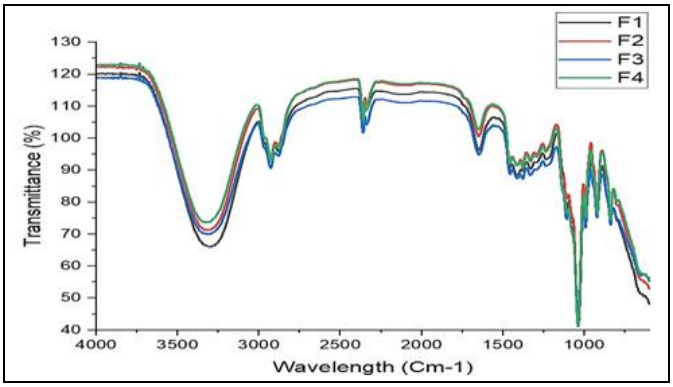

FIG. 2: FTIR STUDY OF THE FORMULATIONS

***In-vitro* Release Study:** The maximum percentage of drug release for the aqueous gel was achieved in 3 hours, while the emulgel showed drug release over 6 hours. This indicates that the emulgel exhibits a sustained release effect compared to the aqueous gel.

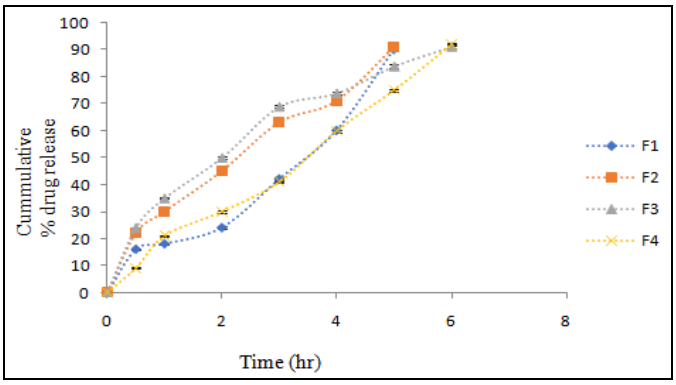

FIG. 3: *IN-VITRO* RELEASE STUDY

***Ex-vivo* Permeation Study:** An *ex-vivo* study of an aqueous or emulgel formulation involves testing drug permeation or absorption using biological tissues, typically skin or mucosa excised from animals or humans, under controlled conditions. It helps evaluate drug release, permeation, and potential irritation, ensuring the formulation is effective and safe for human use before clinical trials. The maximum percentage of drug release for the aqueous gel was achieved in 4 hours, while the emulgel extended up to 6 hours. This indicates that the emulgel demonstrated sustained release pattern.

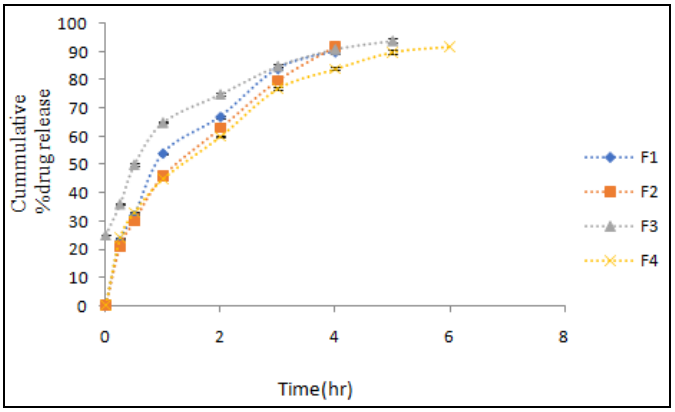

FIG. 4: *EX-VIVO* PERMEATION STUDY

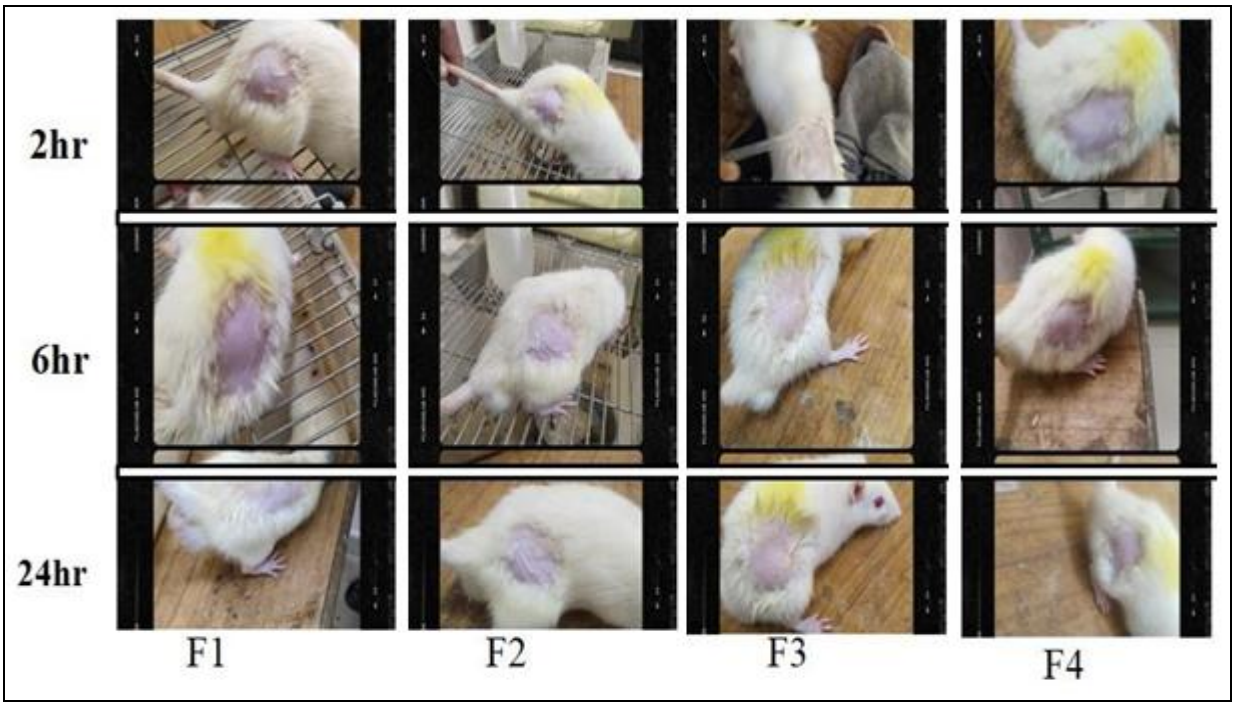

FIG. 5: SKIN IRRITATION STUDY

Skin Irritation Study: The results help determine the product's safety and tolerability. Ideally, no significant irritation should occur, indicating the formulation is safe for topical use. Mice were used as the model animals, and their fur was trimmed with scissors. Photographs were taken at intervals from 2 hours up to 24 hours after application of gel.

CONCLUSION: The current research aimed to prepare a topical gel formulation for treatment of infantile hemangioma. The *in-vitro* results revealed the prepared gel is stable and could be effective against infantile haemangioma.

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CONFLICTS OF INTEREST: Nil

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