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INFLUENCE OF ETHANOL, ISOPROPYL MYRISTATE & PROPYLENE GLYCOL ON IN VITRO PERMEATION OF DIMENHYDRINATE FROM TRANSDERMAL GEL

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Abstract
Carbopol 934P, the gelling agent utilized in the investigation and assessment, exhibits good consistency and tolerable flow behavior. The best result was obtained from the organoleptic, physicochemical determination. Formulations F14–F18 displayed varying release patterns during in vitro evaluation, however formulation F15 demonstrated the most consistent and optimal outcomes. The acquired data demonstrated that a combination of 2% ethanol, 1.75% isopropyl myristate, and 74.5% propylene glycol as a concentration is promising to boost dimenhydrinate permeability from transdermal gel. Using the Carbopol 934P gelling agent, the other outcomes, such as the organoleptic and flow properties, were successfully and effectively attained. Conclusion: Compared to other combinations of permeation enhancing agents, the use of ethanol as a permeation enhancer in combination with isopropyl myristate and propylene glycol is superior. Additionally, carbopol is a promising gelling agent that can be used to make gel dosage forms.

Key words: carbopol 934P, consistency, gel, in vitro, permeation enhancer, permeation.

Introduction
Dimenhydrinate also known as (B-dimethyl amino ethyl benzo hydrol ether 8-chloro theophyllinate) is a drug that is recommended to avoid motion sickness-related nausea, vomiting, and dizziness[3] Dimenhydrinate is a white, crystalline solid in powdered form and has pKa of 8.87 with a 0.1 mg/mL water solubility The goal of the current work is to enhance the therapeutic efficacy of dimenhydrinate and reducing the related disadvantages of traditional administration techniques by concentrating on transdermal formulations. To enhance the permeability of pharmaceutical agents through the skin in the case when they are poorly absorbed orally, the use of permeation enhancer is required much attention. The most widely used gelling agent is Carbopol, also known as poly (acrylic acid) polymer. Carbopol has a wide variety of applications including enhancement of rheological parameters of semisolids, cosmetics, and pharmaceutical emulsions. The therapeutic efficacy of the drug is ultimately enhanced by gel systems containing compatible and best

permeation enhancer because the drug permeates quickly and effectively after the gel dosage form is applied topically [1]. Ethanol, propylene glycol, and isopropyl myristate were previously used very effectively as penetration enhancers; they facilitate drug permeation by first increasing the solubility of compound due to formation of eutectic mixture with drug and secondly by modifying the stratum corneum properties [2]. It has also great implementation in other dosage forms also as used in sustained release tablets to maintain the release of drugs from dosage forms as well as used best viscosity imparting agent to form microgel networked structure in hydrophilic solutions [3]. In this research work is mainly related to prepare a gel by using carbopol 934P with good rheological behavior and have a good permeation of drug through it by using ethanol in combination with other penetration enhancing agents. It works well with other dosage forms as well. For example, it is the best viscosity imparting agent when forming a microgel networked structure in hydrophilic fluids, and it is also utilized in sustained release tablets to maintain the release of pharmaceutical active ingredient from dosage forms [3]. The primary goal of this research project is to use carbopol 934P to build a gel with good rheological behavior and good drug penetration through it utilizing ethanol in conjunction with other penetration-enhancing agents.

MATERIALS & METHODS

Dimenhydrinate sourced from (wonder pharmaceuticals, china), water, IPA (Isopropyl Alcohol) from Avon commercial, Ethanol provided by J K Enterprises Chemical, Carbopol 934P by Ami Polymer Pvt. Ltd.India, Diethanolamine from Avinya Chemicals Private Limited, Propylene glycol by J K Enterprises Chemical, Isopropyl Myristate from Fengchen group Co., Ltd china, and Butyl Hydroxytoluene by Sisco Research laboritories Pvt Ltd.

Gel Preparation method

Precise measurements of Propylene Glycol, Carbopol 934P, and Purified Water were made in order to formulate Dimenhydrinate gel. These materials were then put into a homogenizer vessel and heated to a maximum temperature of 104°C. Simultaneously, Dimenhydrinate, , isopropyl alcohol, and ethanol were weighed and combined in a separate container until Dimenhydrinate achieved complete dissolution.A small volume of isopropyl alcohol (2ml) was heated to a maximum temperature of 55°C in a separate vessel. Within this warmed isopropyl alcohol, the necessary quantity of Butyl Hydroxytoluene was measured, weighed, and added, dissolving under the agitation of a magnetic stirrer. This resulting mixture was then introduced into the container containing the Carbopol compound. The API mixture from the second container was subsequently blended with the contents of the first container. Following thorough mixing, additional purified water was introduced to achieve the desired gel weight, and the entire mixture underwent meticulous blending. To prevent air entrapment, the gel underwent sonication for 3 minutes to eliminate any trapped air bubbles. Table 1 shows composition of all formulations.

Physical properties of gel formulations

A produced gel formulation's elegance and aesthetic appearance are largely dependent on its physical attributes, which include color, odor, consistency, and uniformity as observed visually. [4].

Consistency and homogeneity

To determine the consistency of the gel a cone with a fixed rod attached was dropped into the center of a clear container holding a gel sample at a distance of 10 cm, covering the distance in 10 seconds. The cone's journey distance was observed and recorded. [5].

pH

Certain medications' solubility is entirely reliant on pH, which can eventually impact absorption and therapeutic efficacy. A China-made digital pH meter was used to measure the pH of all prepared gel formulations. A diluted sample of 1 g of gel was added to 100 mL of pure water, and the

measurement was obtained after two hours. All of the results were recorded for all prepared gel formulations.

Sr	Materials	F15 %	F16 %	F 17 %	F18 %	F19 %	F20 %	F21 %
1.	Dimenhydrinate	2	2	2	2	2	2	2
2.	Isopropyl alcohol	-	2	2	2	-	-	-
3.	Propylene glycol	74.5	80	74.5	74.5	69	75	81
4.	Ethanol	2	1	1	1	2	2	2
5.	Isopropyl myristate	1.75	1	1.5	1.75	1	1.75	1
6.	Carbopol 934p	1.5	2.5	1.75	0.5	1	1.75	2
7.	Diethanolamine	1.50	1.50	1.50	1.50	1.50	1.50	1.50
08.	Butylhydroxytoluene	1	1	1	1	1	1	1
09.	Distlled water	15.75	9	14.75	15.75	22.5	15	9.5
Total		100	100	100	100	100	100	100

Table 1. Gel formulations containing all ingredients in %

Extrudability, viscosity and spreadability

In order to conduct the extrudability test, a collapsible tube containing a gel sample was set under a known weight. After 10 seconds, the distance that the expelled gel traveled after a known weight was placed was recorded. The extrudability of the gel [6] sample was then determined using the formula E = W/A, where W stands for weight in grams and A for area in cm2. The main factor influencing the flow behavior and gel expelling from the container is rheological assessment The adherence of semisolid dosage forms to the skin is predicted by rheological investigations as well. This determination distinguishes between thin and viscous semisolids, and the difference in viscosities has many impacts on the skin, including residence time and discomfort level. The viscometer, a Visco QCTM 100 from (Anton Paar, Austria), had spindle L 4 as part of its working specifications. At room temperature, or between 20 and 25 °C, the rotational speed was 6 rpm was calculated from the three readings that were obtained [7]. A glass slide was fixed to a wooden piece in order to test the spreadability of all manufactured gel compositions. A pre-measured sample weighing two grams was then placed on the slide One kg weight was then placed on the upper slide for around four to five minutes, after which a second slide with the same size was placed on the first slide. The area (7.5 cm) traveled by the upper slide with a string of wire attached and 80g of weight was recorded in s [8].

Irritation test on skin

To check the irritation effect on gel preparations a rabbit was used. The rabbit skin was properly shaved, and then a sample of gel was applied. The skin was examined for any changes in color and morphology after 24 hours had passed [9].

Assay of Dimenhydrinate/drug content

Pharmaceutical active ingredient undergoes analysis of assay in order to verify the pure API's percentage purity. In this study, an excess of diminhydrinate was combined with 5 mL of phosphate buffer at pH 5.8 and 7.4 in two different beakers, and the mixture was mixed for approximately 96 hrs at 37± 1°C using a thermo-regulator stirrer. Subsequently, the two aforementioned mixtures were centrifuged for 10 minutes at 13,000 rpm. From the filtered supernatant, appropriate dilutions were made. Using a spectrophotometer set to measure absorbance at 278 nm, the amount of drug in each solvent system was determined [10]

In vitro permeation study

It is possible to anticipate the drug's penetration through the stratum corneum and its various layers using ex vivo (animal skin) and in vitro (artificial membranes, such as silicone membranes). Franz diffusion cells, which were purchased locally from a lab-sonic equipment supplier in Lahore, Pakistan, were used for the in vitro evaluation. The dimenhydrinate permeability was characterized using an artificial silicone membrane. The obtained Franz diffusion cell had a double jacketed receptor compartment with a 12 mL capacity and a 1 mL donor compartment with a 1.76 cm2 area. The receptor solution was created by mixing ethanol and phosphate buffer pH 7.4 in various ratios of 60:40 v/v. A corresponding gel sample containing approximately 20 mg dimenhydrinate was placed in the donor compartment, and during evaluation, the sample was removed after 30 minutes, 60 minutes, and then every hour up to five hours. A silicone membrane was carefully tightened between the donor and receptor compartments. A total volume of 12 mL was used in the receptor compartment. An equivalent volume of freshly prepared solution was added to the receptor chamber after each sample was removed in order to maintain the sink conditions throughout the test. Every sample's drug concentration was measured using a UV-visible spectrophotometer set to 278 nm λmax [10] at a designated time.

Statistical analysis

The collected data from drug permeation trials will be statistically processed using the Tukey HSDa,b test and the ANOVA test.

RESULTS AND DISCUSSION

If a drug molecule produces, un-wanted and dangerous effects in the shape of side effect fol- lowed by oral administration, then topical route is to be preferred especially as compare to the oral rout for the drug used to treat the symptoms like nausea vomiting related to motion sickness.

Physical properties of gel formulations

It is vital to conduct an organoleptic or physical assessment of gel preparations to ensure that their aesthetic qualities meet acceptable standards. The created gel compositions were all transparent and white in color, as indicated by the results, confirming the specified criteria.

Consistency and homogeneity

Every gel formulation exhibited good consistency and no lumps were visible. When applied to skin, there was no grittier feeling, confirming homogeneity. The results for homogeneity and consistency are shown in Table 2.

pH

pH has a significant impact on the drug's solubility, which influences how well it permeates the skin's various membranes, as well as on the prevention of pH-related skin irritation, which in turn impacts the patient's comfort. The data obtained indicated that the pH range for all prepared gels was 5.80 to 6.20, as presented in Table 2. These results showed that there would be no adverse effects or irritation when applying the produced gels to the skin's surface. [12].

Extrudability, viscosity and spreadability

The degree to which the gel preparation is driven out of the collapsible tube upon shearing is known as extrudability. The experiment to be carried out to see if the gel can be extruded is called an extrudability test. Table 3 contain extrudability results for each gel formulation showed that carbopol, the gelling agent used, produced the best consistency and gelling, making the gel easy to extrude. [13]. Good flow properties are crucial for prepared gel formulations that are intended for topical treatment. A gel preparation with good flow properties will readily emerge from the collapsible tube, make application on the skin simple, and facilitate easy spreading throughout the skin. The observed results are listed in Table 3, and the viscosity data for the optimal gel preparation F15 was 113 x 103 CPs [14].

Irritation test on skin

Rabbits were used to test how irritated animal skin was by gel preparation. The results obtained for the freshly manufactured and formulated gel's irritating effect showed that no erythema or edema had been seen. In order to validate the outcomes, discomfort was also noticed ten days later, ensuring the gel's safety. [15]

Formulation	Organoleptic Observation				pH (mean)
	Color	Physical appearance	Homogeneity	Feel on application	
F15	white	Transparent	Homogenous	smooth	6.15
F16	white	Transparent	Homogenous	smooth	6.10
F17	white	Transparent	Homogenous	smooth	5.90
F18	white	Transparent	Homogenous	smooth	6.20
F19	white	Transparent	Homogenous	smooth	5.90
F20	white	Transparent	Homogenous	smooth	6.10
F21	white	Transparent	Homogenous	smooth	5.80

Table 2. Physical (organoleptic) properties results with pH

Formulation	Viscosity (x103 CPs)	Extrudability (g/cm^2)	Spreadability (G/cm/sec)	Assay Content
F15	113	12.95	15.30	102.2
F16	111	13.66	15.56	98
F17	121	12.40	16.00	101.05
F18	111	12.22	17.10	99.5
F19	120	14.22	18.80	99.4
F20	116	14.75	18.25	99
F21	9,000	12.20	20.33	98

Table 3. Results of extrudability, viscosity, spreadability and assay content.

Assay for drug content

A technique or process called assay content is employed to look into the availability and consistency of a medication in a certain dosage form. Dimenhydrinate's drug content results in all formulations fell between 98% and 102.2% which is within the EUROPEAN PHARMACOPOEIA 6.5 (90-110%) range. This suggests that the medication was dispersed evenly across all formulations. Table 3 contains a tabulation of all test content data.

In vitro permeation study

After a dosage form is applied transdermally, there are a number of techniques (both in vitro and ex vivo) that can be used to calculate the percentage of the medication that crosses the various skin membranes. Artificial (silicone membrane for in vitro characterization) and excised rabbit skin for ex vivo characterization are two examples of membranes that are used. The receptor solution was chosen using the procedure outlined in earlier research [17]. The results of using a combination of several penetration enhancers are addressed here.

Effect of Ethanl, isopropyl myristate and propylene glycol on permeation

The gel formulations F15-F21 comprises of various concentrations of excipients like ethanol (1%and 2%, respectively), isopropyl myristate (1%, 1.5%, and 2%, respectively) and propylene glycol (1%, 1.5%, and 1.75% respectively) was used. The maximum amount of dimenhydrinate permeated in F15 was 93.54% in 300 min, in F16 was 70.28% F17 75.34, F18 59.35%, F19 70.36%, F20 75.26, in 300 min, and the maximum amount permeated in F21 gel formulation was 74.30% in 300 min, as showed in Table 4. The permeability effect Ethanol, isopropyl myristate and propylene glycol predicted promising permeation of the dimenhydrinate. While results of permeated amount of active pharmaceutical ingredient from optimized formulation F15 was maximum 93.54%.

Formulation	%age release					
	30 minutes	60 minutes	120 minutes	180 minutes	240 minutes	300 minutes
F15	14.86	22.41	40.76	61.27	79.54	93.54
F16	03.54	14.48	20.60	35.93	40.16	70.28
F17	07.93	12.17	37.52	45.08	53.29	75.34
F18	05.95	17.39	22.19	35.70	41.21	59.35
F19	03.63	14.50	20.70	35.98	40.18	70.36
F20	07.87	12.12	37.42	44.98	53.19	75.26
F21	7.84	12.10	37.16	44.70	52.98	74.30

Table 4. Permeation of Isotretinoin in % gel at different time intervals.

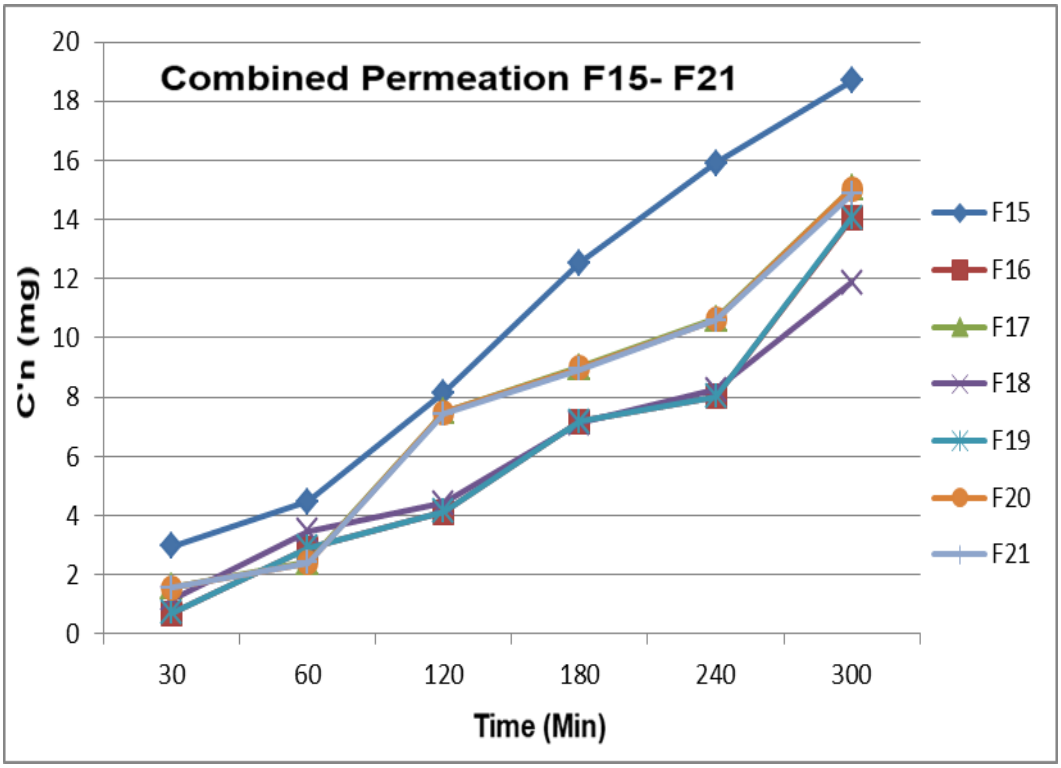

Figure 1. Combined permeation graph of all formulations (F15-F21).

Calculations of permeation parameters

Table 5 showed the details about the values of drug permeated

Time (Min)	Abs	Cn (mg)	Cn (ug)	Vt (ml)	Vs (ml)	Vt-Vs	C'n (ug)	Q (ug/cm2)
0	0	0	0	12	0.15	11.85	0	0
30	0.127	2.96384	2963.827	12	0.15	11.85	2963.827	1677.321
60	0.218	5.08752	5087.516	12	0.15	11.85	5151.912	2915.627
120	0.349	8.14468	8144.692	12	0.15	11.85	8352.192	4726.764
180	0.525	12.2520	12252.04	12	0.15	11.85	12723.22	7200.468
240	0.682	15.916	15915.98	12	0.15	11.85	16737.28	9472.15
300	0.802	18.716	18716.45	12	0.15	11.85	19931.40	11279.80
J (ug/cm2/h)							30.12752	

Table 5. Permeation parameters of optimized transdermal Gel F15. Abs.: drug absorbance at a λmax, Conc. (mg): drug absorbed amount (in mg), Conc. (µg): drug absorbed (in µg), Total Vol (mL): complete volume in mL of receptor solution in Franz diffusion cell. Sample Vol (mL): volume of each sample withdrawn, Q (µg/cm2): drug cumulative amount through 1 cm2 of silicone membrane, and J: flux is an amount of the drug permeated pin g/cm2/h.

Formulation	Steady state flux (J) J (ug/cm^2/h)	C'n (ug)	Q (ug/cm^2)
F15	30.12	19931	11279
F16	35.57	14985	8480
F17	21.10	16029	9071
F18	39.68	12649	7158
F19	35.99	15386	8520
F20	20.66	15949	8666
F21	20.20	14745	8542s

Table 6. In vitro permeation coefficient of gel formulations F15-F21

Flux and permeation of all formulations

Permeation of gel formulations drug concentration in the donor compartment; results are recorded in Table 6.

Statistical analysis

Null hypothesis: Ho mean values of all the formulation are same. Alternative hypothesis: Ha mean values all the formulation are not same. Tests of between-subjects effects are given in Table 7. The test statistic of formulation F > = F0.05 (5, 25) = 2.62. P < = P (0.05) now we reject the null hypotheses in favour of alternative hypotheses, it means that all the formulation different to each other in drug releasing.

The test statistic of time interval F > = F0.05 (5, 25) = 2.62. We have enough evidence to reject the null hypotheses because the mean values of drug releasing with time-intervals are different to each other (Table 8, Fig. 2).

Time (Min)	Abs	Cn (mg)	Cn (ug)	Vt (ml)	Vs (ml)	Vt-Vs	C'n (ug)	Q (ug/cm2)
0	0	0	0	12	0.15	11.85	0	0
30	0.127	2.96384	2963.827	12	0.15	11.85	2963.827	1677.321
60	0.218	5.08752	5087.516	12	0.15	11.85	5151.912	2915.627
120	0.349	8.14468	8144.692	12	0.15	11.85	8352.192	4726.764
180	0.525	12.2520	12252.04	12	0.15	11.85	12723.22	7200.468
240	0.682	15.916	15915.98	12	0.15	11.85	16737.28	9472.15
300	0.802	18.716	18716.45	12	0.15	11.85	19931.40	11279.80
J (ug/cm2/h)							30.12752	

Table 5. Permeation parameters of optimized transdermal Gel F18. Abs.: drug absorbance at a λmax, Conc. (mg): drug absorbed amount (in mg), Conc. (µg): drug absorbed (in µg), Total Vol (mL): complete volume in mL of receptor solution in Franz diffusion cell. Sample Vol (mL): volume of each sample withdrawn, Q (µg/cm2): drug cumulative amount through 1 cm2 of silicone membrane, and J: flux is an amount of the drug permeated pin g/cm2/h.

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	19109.972[a]	10	19610.997	48.117	.000
Intercept	41532.340	1	41532.340	1102.537	.000
Formulation	2652.435	5	562.489	14.285	.000
Time_Interval	15747.527	5	3169.505	81.949	.000
Error	966.812	25	38.676		
Total	61218.134	36			

Table 7. Tests of between-subjects effects (ANOVA)

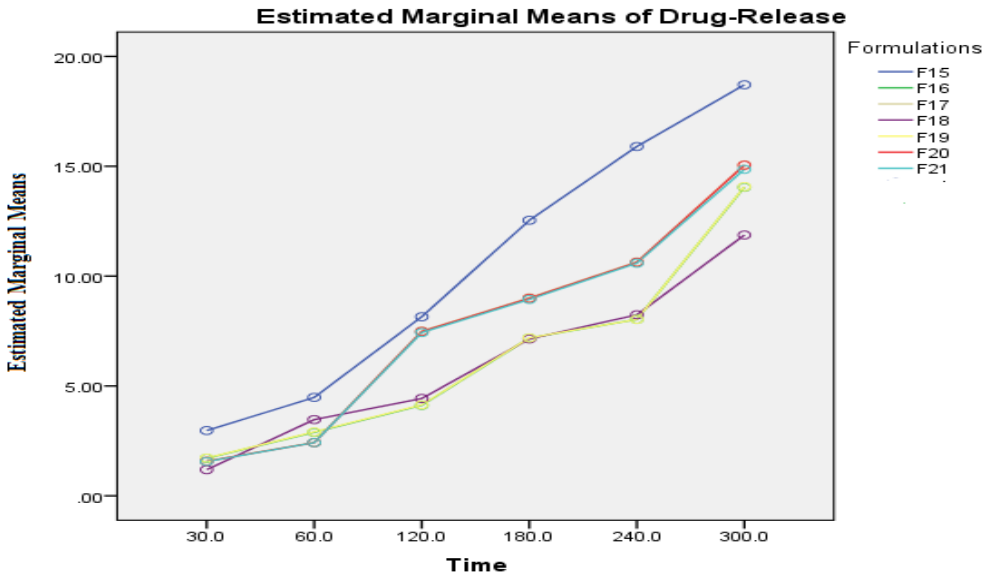

Figure 2. Estimated marginal means of drug releasing (F15-F21)

Formulation	N	Subset			
		1	2	3	4
F15	7	1.7243			
F16	7	3.0029			
F18	7		6.1786		
F19	7		8.7129	8.7129	
F20	7			10.2957	
F21	7				14.8100
Sig.		.775	.122	.586	1.000

Table 8. Homogeneous subsets drug releasing (Tukey HSDa,b) (F15-F21). Means for groups in homogeneous subsets are displayed. Based on observed means. The error term is Mean Square (Error) = 24.659. [a] Uses Harmonic Mean Sample Size = 7.000. b Alpha = .05.

CONCLUSION

In the current research work the number of prepared gel formulations was seven having code numbers F15 to F21. A result of all formulated gel preparations was good regarding different physical evaluations and assay content. The optimized gel was F15 because it showed best in vitro permeation as compare to all other gel preparations through artificial silicone membrane.

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