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ERYTHROMYCIN GEL - A TOPICAL ANTI-ACNE PREPARATION

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ABSTRACT

Carbopol^{R} gel bases containing Erythromycin (2%w/w) were formulated and screened for its anti-acne activity. Both in-vitro and in-vivo studies were carried out on laboratory models, animals and human volunteers. Drug release was evaluated using cellophane membrane. Primary skin irritation study was performed on albino rabbits using Draize patch technique. Reduction in the number of acne and its basal diameter was observed in human volunteers.

INTRODUCTION

Acne vulgaris is a highly variable disease attracting a crisp social rebuttal. Various anti-acne preparations are available, each having a different physiological effect on the prevailing condition.
Erythromycin, a macrolide antibiotic is reported to inhibit the growth of Propionibacterium acnes or Corynebacterium acnes - the major cause leading to the surgence of facial eruptions in the form of acne[1].
Acne can however also occur due to hormonal imbalance, excess sebum production or due to inflammatory reactions. Erythromycin is specifically used to treat acne of bacterial origin[2]. The present research work

TABLE-1

Formulations

Ingredients	Formulations, %w/w		
	I	II	III
Erythromycin base I.P.	2.00	2.00	2.00
Propylene glycol	40.00	40.00	40.00
Methanol	8.00	8.00	8.00
Menthol	0.04	0.04	0.04
Methyl paraben	0.18	0.18	0.18
Prpopyl paraben	0.02	0.02	0.02
Sodium metabisulphite	0.10	0.10	0.10
Disodium edetate	0.10	0.10	0.10
Carbopol 934/ 940/ 941 (I) (II) (III)	1.00	1.00	1.00
Triethanolamine	qs	qs	qs
Lavender	qs	qs	qs
Purified water qs to make	100.00	100.00	100.00

was directed to the formulation of a gel containing Erythromycin (2%w/w) and then evaluate its anti-acne activity.

EXPERIMENTAL

Materials: Erythromycin base (Rhone and Poulenc(I) Ltd), Carbopols^{R} (Goodrich, USA), Propylene glycol, methanol, menthol, triethanolamine, disodium edetate, sodium metabisulphite and parabens.

Preparation of Gel: A clear dispersion of Carbopol 940 (1%w/w) was prepared in water using moderate agitation. Intermittent sprinkling of Carbopol prevents lump formation resulting in a clear homogenous dispersion. Erythromycin was dissolved in propylene glycol and methanol. Various ingredients viz. parabens, sodium metabisulphite & disodium edetate were dissolved in water and added to the drug solvent system. Triethanolamine was used to neutralise and volume made using water. Gels thus prepared were degassed by centrifuging at 2000 rpm to remove entrapped air(Table-1).

In-vitro Studies

i. Diffusion through Agar Gels[3]: Agar cup plate method was used. A 1 in 10 dilution of a 24 hr old culture of S.aureus was used. Sterile nutrient agar 25ml was used and the cup diameter was 6.5mm. Weighed amount of gel was placed in the cup. Zone diameter was measured after 24 hrs on incubation at 37°C.

ii. Diffusion through Cellophane Membrane[4]: Cellophane membrane was used as a rate limiting barrier for the in-vitro release studies. Weighed amount of the formulation was placed on the cellophane membrane which was attached to a two-port cylinder. This was then suspended into a "Dissolution Rate Test Equipment U.S.P. XIX" such that the surface just touches the dissolution medium. Receptor medium was phosphate buffer pH 8.0 which was stirred at 100 rpm using a basket, and maintained at 37°C. Aliquots were withdrawn at regular intervals and analysed on Beckman DB spectrophotometer at λ_{max} = 488nm.

In-vivo Studies

I. Primary Skin Irritation Study: Primary irritation to the skin was measured by a Draize patch test[6] on the abraded and intact skin on the dorsal side of albino rabbits, clipped free of hair from the experimental region. A minimum of 4 rabbits were used. Test sample (0.5 gm of gel) was spread on a surgical gauze and placed in position using a cotton cloth. After 24 hrs the patches were removed and the results evaluated. Scoring was repeated after 72 hrs. Equal number of exposures were made on abraded skin (Fig.1)

II. Selection Criteria for Acne Clinical Study:

a. A well balanced male/female population was considered with subjects between 15-28 years.

b. The minimum and maximum number of lesions were counted before recruitment.

Number of areas where test sample was applied = 2
Number of areas where negative control applied =2
Number of areas where dry surgical gauze was placed = 2

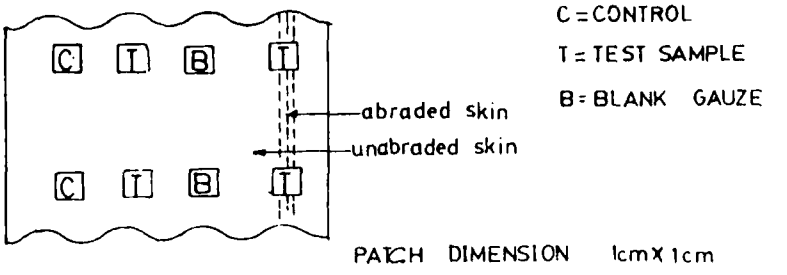

Fig.1

Diagram showing the division of skin area

c. Subjects previously treated with antibiotics within the last 4 to 8 weeks were not recruited.

d. Subjects who had received hormones were not enrolled since these drugs affect the rate of sebum production.

e. Females on contraceptive treatment were excluded since it can affect the acne condition.

III. Acne Clinical Study[7]

a. Half Face Study: This involved counting the number of acne on one side of the face and applying the formulation twice daily for three weeks.

b. Full Face Study:

The number of acne on the whole of the facial area was noted and the gel applied twice daily for 1 week.

RESULTS AND DISCUSSIONS

A number of solvents were used to solubilise Erythromycin. Methanol was used as it gives a better cooling effect and is cheaper. II and III were clear gels, while I was opaque. Low concentrations of Carbopol i.e. 0.5% & 0.75% resulted in gels of low

TABLE-2

Drug release with and without Cellophane Membrane

Time Mins.	% Drug Release Cellophane Membrane	Without Cellophane Membrane
15	16.23	20.12
30	28.35	29.91
45	32.16	38.04
60	40.11	49.96
75	34.21	57.75
90	50.08	70.26
105	62.21	90.19
120	68.58	98.73

TABLE-3

Primary Skin Irritation Evaluation (R = Rabbit)

Patch Type	R-1	R-2	R-3	R-4	Average Score
Control (negative)	0	0	0	0	0
Test (unabraded)	0	0	0	0	0
Test (abraded)	0	0	0	1	0.25
Formalin	-	-	4	-	4

consistency. III required a higher concentration of Carbopol to give a consistency at par with II, hence II was opted For further Studies.

Diffusion through Cellophane Membrane: Table-2 depicts that at the end of 2 hrs the drug release was 68.58%

Primary Skin Irritation Study: Formalin (0.8%v/v) was used as a standard irritant and was scored as 4 (Table-3).

No reaction :0
Very slight erythema or edema :1
Well defined erythema/ edema :2
Moderate to severe erythema/ edema :3
Beet red erythema/ escher formation :4

Acne Clinical Study:

I. Diametrical Reduction of a Selected Acne:

The basal diameter was measured using Vernier Callipers. The diameter of the acne before, during and at the end of the treatment was monitored (Table-4).

TABLE-4

Diametrical Reduction of a Selected Acne

Sub.	Acne appearence	D-1	D-3	D-5	D-7	After 1 week
AA	Red	2.86	2.82	2.80	2.76	Scaly scar
BB	Red + Pus	2.02	2.02	2.02	1.82	Scar
CC	Red + Pus	3.20	3.18	3.18	3.12	Scar
DD	Red	3.80	3.76	3.66	3.52	Blind scar
EE	Red	3.24	3.28	3.24	3.20	Scar
FF	Red	3.76	d i s c o n t i n u e d			
GG	Red	2.86	2.92	2.82	2.50	Scar
HH	Red	4.42	4.44	4.30	4.20	Scaly scar
II	Red + Pus	3.32	3.26	3.24	3.16	Blind scar

TABLE-5

Lesion count of Seven Volunteers

Sub.	No. of lesions on : 1st day	8th day	Sub.	No. of lesions on : 1st day	8th day
I	29	8++	V	28	6++
II	32	6++	VI	19	3++
III	18	2++	VII	20	2++
IV	26	4++			

TABLE-6

Lesion Count of 20 Volunteers for 21 Days

Sub.	No. of lesions, days 1	7	14	21	Sub.	No. of lesions, days 1	7	14	21
A	9	++	*	*	K	18	3++	++	+
B	14	++	++	+	L	20	++	+	+
C	12	+	*	*	M	29	8++	++	+
D	19	++	++	+	N	15	++	++	+
E	6	++	++	++	O	13	++	++	+
F	8	++	+	+	P	6	++	+	*
G	9	++	++	+	Q	11	++	++	+
H	15	++	+	*	R	15	++	+	+
I	26	6++	++	++	S	9	++	++	+
J	13	++	++	+	T	10	++	++	*

Subject FF was previously on systemic antibiotic treatment, hence her evaluation was discontinued. The appearence of acne before and after treatment was also noted. In all, 7 volunteers were screened in this study. Throughout the clinical study the statistical interpretation was done by t-test for significance. Latin square method was followed during the evaluation.

II. Half Face Study:

Nine volunteers were chosen, of which two were rejected during the study due to non co-operation. Observations were scored on the basis of the following symbolic notations (Table-5):

++ 100% scars left
+ 75% - 90% scars left
* 50% - 75% scars left

Numericals before symbols indicate no. of scars left.

III. Full Face Study:

20 volunteers were selected (Table-6) on the basis of the clinical requirements enlisted

Recurrence in two volunteers E and I was noted after 5 weeks with 4 and 2 eruptions respectively.

CONCLUSIONS

In-vivo studies conducted on human volunteers and animals clearly demonstrate the efficiency of Carbopol^{R} based Erythromycin gel formulation in reducing the number of acne. The drug release through this gel system is countenanced by in-vitro diffusion studies. It is recommended to apply the gel twice daily for a minimum period of two weeks for a maximum effect.

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REFERENCES

1. Kucers A., and Bennet N. Mck., The Use of Antibiotics, 4th ed., William Heinemann Medical Books, London, p853 (1988)

2. Eady E.A., Holland K.T., Cunliffe W.J. et al. (1982). The Use of Antibiotics in Acne Therapy, J.Antimicrob. Chemother.; 18:89

3. Stoughton R.B., Arch. Dermatol.; 118, 476, (1982)

4. Sanghavi N.M., Puri R.D., Kamath P.R., Indian Drugs, 26 (4), 167 (1989).
5. Kligman A.M. and Kwong T., Br. J. Dermatol.; 100, 699-702, (1979).
6. Draize J.H., et al., J. Pharmacol. Expt. Ther.; 82, 377 (1944).
7. Nacht. S., Cosm. Toil.; 101, 52 (1986).