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DESIGN AND DEVELOPMENT OF PEEL-OFF MASK GEL FORMULATION OF TRETINOIN FOR ACNE VULGARIS

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1. INTRODUCTION

Acne disease affects oil glands of the skin. The small pores in skin connect to oil glands which makes an oily substance called as sebum. The pores connect to the glands by a canal called as follicle inside which the oil carries dead skin cells to the surface of the skin. When these follicles clogs up, a pimple start to grow, sometimes, the hair, sebum, and skin cells clump together into a plug. The growth of bacteria in the plug causes swelling.[1, 2]

Propionibacterium acnes (P. acnes) is the anaerobic bacterium that causes acne. Other causes are family/Genetic history, hormonal activity; such as menstrual cycles and puberty, skin irritation or scratching, stress, through increased output of hormones from the adrenal (stress) glands, hyperactive sebaceous glands, accumulation of dead skin cells that block or cover pores, hyperkeratinisation, oily skin or hair, some prescription medications, cosmetics that contain chemicals and vegetable oil, some nutritional deficiencies.[3]

The pathogenesis of acne is very complex, but four basic steps have been identified (Fig.1).

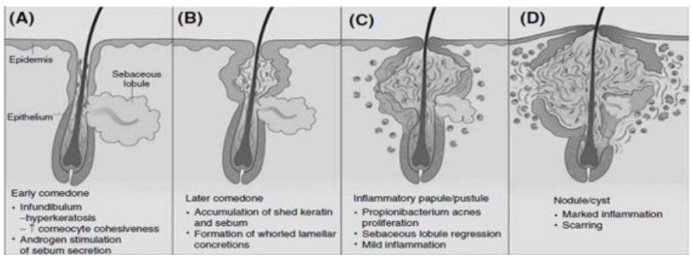

Fig. 1: Acne pathogenesis. The four key steps in acne pathogenesis, (A) Follicular epidermal hyperproliferation, (B) Excess sebum production, (C) Inflammation, and (D) The presence and activity of propionibacterium acnes.[4]

Retinoic acid derivatives like tretinoin, adapline etc. are mainly used for the treatment of acne vulgaris. Tretinoin is a photosensitive drug hence its formulations are used in night time. Several formulation like cream, gel, ointment, and lotions are available in market, by application of such formulations on acne of face, back and chest, it is difficult to expect their effects for a significant longer period of time, because they are easily removed by wetting, movement, and contacting. As a result conventional therapy of acne is normally having issues related with long treatment period and relapse of the disease. Therefore, the bioadhesive gels (peel-off mask gel formulations) that have good accessibility and retention on skin could be developed for localized treatment of acne vulgaris and it would be better and have low side effects. These new drug delivery systems use film forming polymers for drug delivery for longer period of time. It will also have the added advantage of cleansing the clogged pores of skin by removing the dirt and deposited sebum and microbes.[5-12]

In clinical drug therapies, topical application allows localized drug delivery to the site of interest, this enhances the therapeutic effect of the drug while minimizing systemic side effects.

Peel-off mask can be used as an alternative route of administration to accommodate patients who cannot tolerate oral antibiotics. The advantages of peel-off also include therapeutic benefits like reducing dosing schedule, convenience, and patient-friendliness. It is beneficial to remove blackheads, dead skin. It also helps to tone the skin and treat the wrinkles.[13-17]

2. MATERIALS AND METHOD

For the formulation of peel-off mask gel tretinoin (Procured form shalaks pharmaceutical, New Delhi) was used as active compound, Carbowax 1450 as solubilizer, ethanol as solvent, propylene glycol and glycerin as humectants, sodium metabisulfite as antioxidant, and benzyl alcohol as preservative (all the excipients used were of high quality or AR grade).

2.1 SELECTION OF POLYMER AND EXCIPIENTS

The selection of various formulation excipients for the development of peel-off mask gel formulation was done on the basis of following considerations which includes therapeutic efficiency, drug stability, toxicity, dispersibility, spreadability, etc.

2.1.1 Selection of Film Forming Polymer and its Concentration

Polyvinyl alcohol has excellent film forming, emulsifying, and adhesive property. It is odorlessn and nontoxic in nature. It has high tensile strength and flexibility which is required for a good film forming agent used in peel-off mask gel formulations.

The selection of appropriate polymer concentration that has good solubilizing capacity for tretinoin and spreadability for peel-off mask formulation was done. The gel strength of peeloff mask gel containing various polymer concentrations was measured through texture analyzer (TA.XT Plus®). The results of gel strength study are shown in (Table 1).

Table 1: Texture analysis of polymeric gel of polyvinyl alcohol

S.No	Polymer (w/v)	Firmness (g)	Cohesiveness (g.sec)	Consistency (g)	Index of viscosity (g.sec)
1	Polyvinyl alcohol 15%	16.167	158.054	-10.120	-54.683
2	Polyvinyl alcohol 20%	23.576	190.881	-14.346	-192.155
3	Polyvinyl alcohol 25%	64.167	548.0	-44.705	-466.358

2.1.2 Selection of Humectants

Humectants are used in topicaldosage forms to increase the solubility of the active ingredient, to enhance its skin penetration and its activity time. Humectants also enhance the hydration of skin. This can also use to prevent moisture loss and cracking of polyvinyl alcohol film. Glycerin and propylene glycol were selected as humectants for development of tretinoin pee-off mask gel formulation in the present studies.

2.1.3 Selection of Solvent

Solvent selection is the most important criteria in the formulation of peel-off gel as the film forming properties of the peel-off gel depends upon the rapidity of solvent evaporation from the surface of the skin. Various solvents having high volatility rate were studied in different concentrations for their film forming property. Different concentrations of acetone and ethanol containing peel-off gel were formulated and evaluated for film drying time and consistency.(Table 2)

Table 2: Effect of different solvents on peel-off gel formulation

S.No	Solvent	Concentration (% w/w)	Drying time (min.)	Consistency of gel
1	Acetone	20	3.42	Good
2	Ethanol	20	6.20	Excellent

2.1.4 Selection of Antioxidants and Preservatives

Tretinoin is a highly unstable drug. It gets easily oxidized in the presence of oxygen, so there is need of an effective antioxidant which protects it against oxidation. Sodium metabisulfite (0.02% w/w) was selected to retard oxidation of tretinoin and benzyl alcohol (0.02% w/w) was used as preservative for development of peel-off mask gel formulation.

2.2 PREPARATION OF PEEL-OFF MASK GEL FORMULATION

Polyvinyl alcohol (PVA) solution was prepared by dissolving PVA in water by heating at 85-90ºC on a water bath. The antioxidant (sodium metabisulfite) was added to PVA solution to prepare solution-A. Tretinioin and Carbowax 1450 were dissolved in ethanol and mixed with mixture of benzyl alcohol, glycerin, and propylene glycol and stirred to obtain a clear solution, i.e., solution-B. Solution-B was transferred to solution-A under constant stirring to obtain a homogeneous gel formulation. The gel was kept overnight under refrigerated condition to remove the entrapped air and stored in airtight and light resistant containers until used. (Table 3)

Table 3: Formulation design of peel-off mask gel formulation

S.No	Ingredient (%w/w)	Ingredient (% w/w)								
		Formulation code								
		Polyvinyl alcohol 15% (w/v)			Polyvinyl alcohol 20% (w/v)			Polyvinyl alcohol 25% (w/v)		
		TR1	TR2	TR3	TR4	TR5	TR6	TR7	TR8	TR9
1	Tretinoin	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
2	Polyvinyl alcohol	70	72	70	70	72	70	70	72	70
3	Carbowax 1450	2	2.5	2	2	2.5	2	2	2.5	2
4	Benzyl alcohol	0.2	0.2	-	0.2	0.2	-	0.2	0.2	-
5	Sodium metabisulfite	0.2	0.2	-	0.2	0.2	-	0.2	0.2	-
6	Glycerin	0.8	1.1	0.6	0.8	1.1	0.6	0.8	1.1	0.6
7	Propylene glycol	3	4	3	3	4	3	3	4	3
8	Ethanol	24	20	22	24	20	22	24	20	22
9	Tween 60	-	-	2	-	-	2	-	-	2
10	Methylparabane	-	-	0.2	-	-	0.2	-	-	0.2
11	Sodium thiosulfate	-	-	0.2	-	-	0.2	-	-	0.2

2.3 EVALUATION OF GEL

2.3.1 Physical Evaluation of Peel-Off Mask Gel

Color of peel-off mask gel was determined visually, by observing gel under a white background. The formulated gel was applied on the human skin and its spreadability and drying time were noted. The observations are recorded in table 4.

Table 4: Physical evaluation of peel-off mask gel formulations

S. No.	Formulation code	Color	Spreadability	Drying time (min.)
1	TR1	Yellow	++	12.10
2	TR2	Yellow	+++	9.47
3	TR3	Yellow	++	11.31
4	TR4	Yellow	++++	7.29
5	TR5	Yellow	++++	6.25
6	TR6	Yellow	+++	8.10
7	TR7	Yellow	++	10.30
8	TR8	Yellow	++	13.45
9	TR9	Yellow	++	13.10

+ + Good, + + + Very good, + + + + Excellent

2.3.2 Determination of Drug Content of Formulated Batches of Peel-Mask Gel Formulations

Approximately 200 mg of gel was taken in a petridish and 5 ml of 30% v/v methanolic phosphate buffer (pH 5.5) buffer was added to it. The gel was dissolved in it with a gentle shaking with glass rod. The resulting solution was transferred to 10 ml volumetric flask and sonicated for 15 minutes and then the volume was made upto the mark with 30% v/v methanolic phosphate buffer (pH 5.5). The solution so obtained was filtered using Whatman filter paper no. 41 and analyzed spectrophotometrically at 342 nm. The drug content was calculated using following formula:

$$\text{Drug content (\%)} \quad \frac{\text{Actual amount of drug determined in 200 mg gel}}{\text{Theoretical amount of drug present in 200 mg gel}} \times 100$$

The calculated results are summarized in table 5.

Table 5: Drug contents of peel-off mask gel formulations

S. No.	Formulation code	Drug content (%)
1	TR1	81.21
2	TR2	83.74
3	TR3	80.45
4	TR4	92.30
5	TR5	94.06
6	TR6	88.22
7	TR7	80.84
8	TR8	87.37
9	TR9	85.33

2.3.3 In-Vitro Drug Release Study of Peel-Off Mask Gel Formulations and Dry Film of Optimized Peel-Off Mask Gel Formulation

In-vitro drug release study of peel-off mask gel formulations was carried out using modified dissolution assembly. 30% v/v methanolic phosphate buffer (pH 5.5) was used as a drug release medium and temperature was maintained at 32±0.5oC. At different time intervals, 3 ml of drug release fluid was withdrawn and replaced with equal volume of fresh drug release medium and analyzed spectrophotometrically at 342 nm. (Fig. 2 and 3)

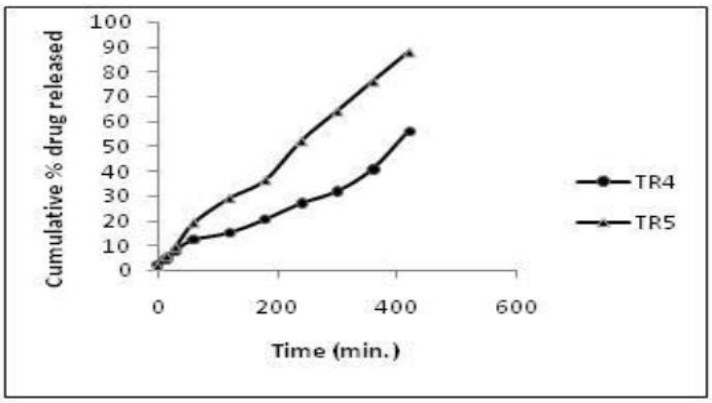

Fig. 2: In-vitro drug release profile of optimized peel-off mask gel formulations of tretinoin (formulation code TR4 & TR5)

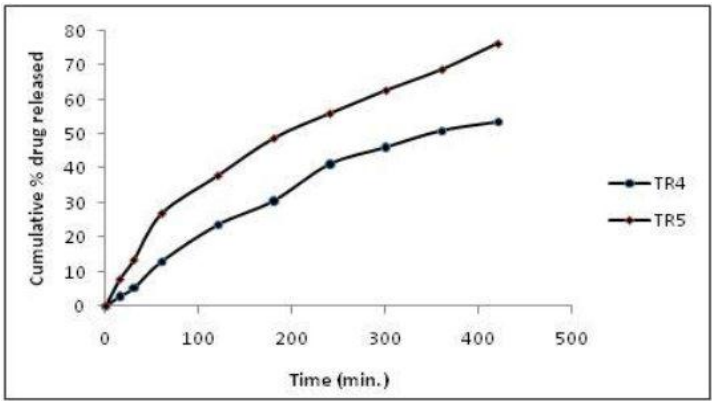

Fig. 3: In-vitro drug release profile of dry film prepared from optimized peel-off mask gel formulations of tretinoin (formulation code TR4 & TR5)

2.3.4 Evaluation of Gel Strength of Optimized Peel-Off Mask Gel Formulation

Gel strength of optimized peel-off mask gel formulations were determined using texture analyzer (TA.XT Plus). (Fig.4 and 5) (Table. 6)

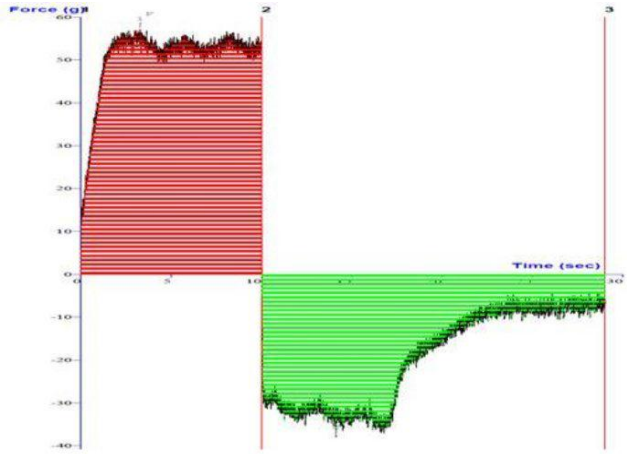

Fig. 4: Consistency graph of optimized peel-off mask gel formulation of tretinoin (formulation code TR5)

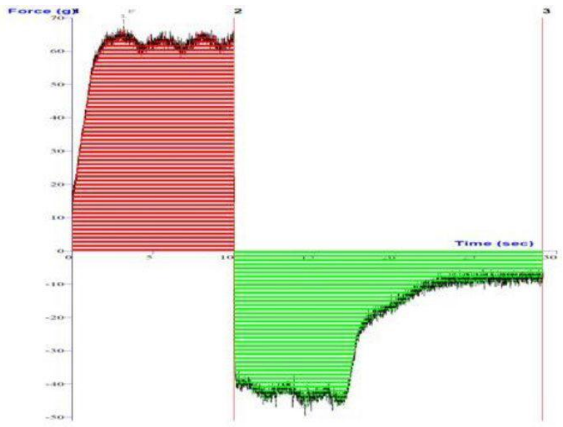

Fig. 5: Consistency graph of optimized peel-off mask gel formulation of tretinoin (formulation code TR4)

Table 6: Consistency study of optimized peel-off mask gel formulations of tretinoin (formulation code TR4 and TR5)

S. No	Formulation code	Mean max. +ve force 'firmness' (g)	Mean +ve area 'consistency' (g.sec)	Mean max. –ve force 'cohesiveness' (g)	Mean -ve area 'index of viscosity' (g.sec)
1	TR4	57.152	504.173	-38.027	-364.294
2	TR5	67.604	591.697	-49.480	-450.153

2.3.5 Evaluation of Spreadability of Optimized Peel-Off Mask Gel Formulation

Spreadability of optimized peel-off mask gel formulations were determined using texture analyzer (TA.XT Plus). (Fig.6 and 7) (Table 7)

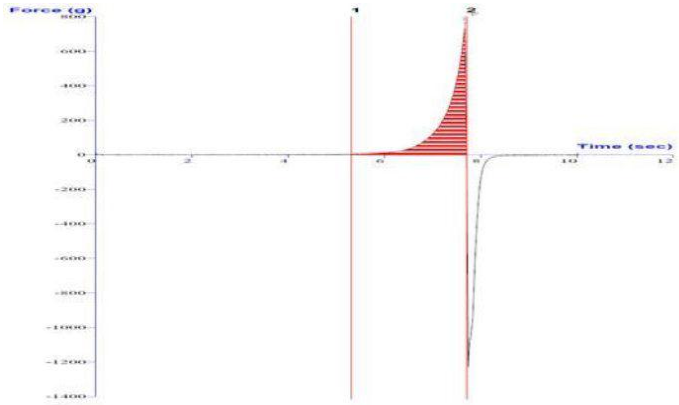

Fig. 6: Spreadability graph of optimized peel-off mask gel formulation of tretinoin (formulation code TR4)

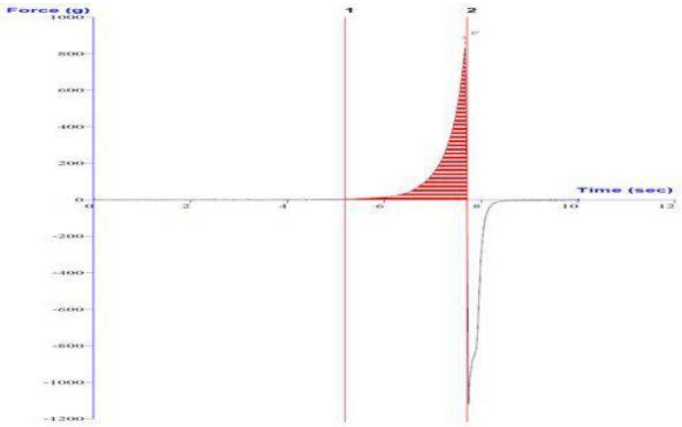

Fig. 7: Spreadability graph of optimized peel-off mask gel formulation of tretinoin (formulation code TR5)

Table 7: Spreadability study of optimized peel-off mask gel formulations of tretinoin (formulation code TR4 and TR5)

S. No.	Formulation code	Mean max. force *'firmness'* (g)	Mean area *'work of shear'* (g.sec)
1	TR4	734.522	276.821
2	TR5	833.37	324.230

2.3.6 Ex-Vivo Drug Permeation Study of Optimized Peel-Off Mask Gel Formulation Through Human Cadaver Skin

Study was carried out using human cadaver skin. The upper layer of human cadaver skin sample was excised and stored in phosphate buffer pH 5.5 until used. The separated skin was tied over the mouth of a glass test tube, and served as donor compartment. 30% v/v methanolic phosphate buffer (pH 5.5) was used as a drug release medium and temperature was maintained at 32±0.5oC. At different time intervals, 3 ml of drug release fluid was

withdrawn and replaced with equal volume of fresh drug release medium and analyzed spectrophotometrically at 342 nm. (Fig. 8)

2.3.7 Stability Study of Peel-Off Mask Gel Formulation

Study was performed by keeping the formulation at accelerated temperature 40oC and 2-8oC for one month. Drug content was determined initially and at a interval of the one week up to one month. (Table. 8)

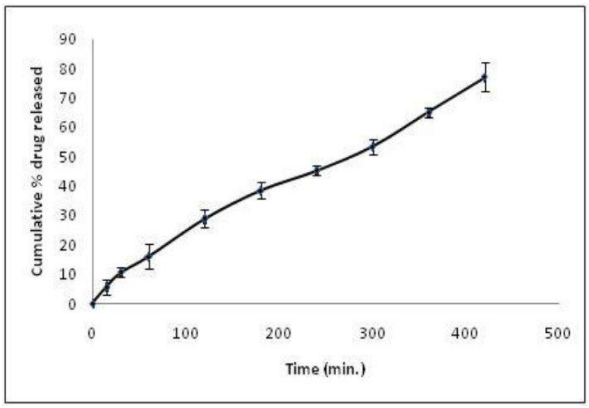

Fig. 8: Ex-vivo drug permeation profile of optimized peel-off mask gel formulation of tretinoin (formulation code TR5)

3. RESULT AND DISCUSSION

To optimize the peel-off mask gel formula the selected excipients were used in different concentration ratios. In-vitro drug release study was performed to know the effect of various ratio of excipients on the cumulative percentage drug release. The formulations were also evaluated for film drying time, and film property. The optimized formulations TR4 and TR5 were evaluated for gel strength, consistency and spreadability determination using texture analyzer (TA.XT Plus). It was observed that the optimized formulation TR5 has good gel strength, consistency and have superior spreadability as compared to formulation TR4. Thus, the peel-off gel formulation (formulation code TR5) was found to be the best among all the formulation batches designed. The selected optimized formulation TR5 was subjected to ex-vivo drug permeation through human cadaver skin. The result showed that the drug permeation was found to be consistent for 7 hr of study period. Based on the above findings, it can be said that a peel-off mask gel formulation of tretinoin can be developed. The peel-off mask gel formulation developed in the present study exhibited desirable film property and drug release attributes. The developed formulation can therefore be further taken for in-vivo and clinical studies for establishing its therapeutic and commercial applications.

4. CONCLUSION

The development of bioadhesive peel-off mask formulation of tretinoin was planned to overcome the drawbacks of poor contact time of conventional cream and gel formulations with skin after application. In present study it was planned to explore use of bioadhesive gels based peel-off mask system of tretinoin to facilitate its permeation through skin for longer period of time for effective treatment of acne vulgaris.

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