



## Formulation and evaluation of topical azelaic acid gel

Jaideep Bajaj<sup>1</sup> and Dinesh Sharma\*<sup>2</sup>

<sup>1</sup>Department of Pharmacology, Khalsa College of Pharmacy, Amritsar, Pinjab

<sup>2</sup>Sun Pharmaceutical Industries Ltd., Gurgaon, Haryana

---

### ABSTRACT

Azelaic acid, anti-acne drug has been selected having very low solubility and permeability. The poor water solubility and permeability of azelaic acid results in difficulties in the formulation of this substance for topical application. Topical formulations of azelaic acid are available in the concentration ranging from 10-20 % w/v. Marketed azelaic acid gel (15% w/v) improves some of the less satisfactory properties of cream formulations, such as their high lipid and emulsifier content, inherent instability, sticky feel, and whitening effect, a nominally lower strength in comparison to marketed cream (20% w/v). The most frequent treatment-related cutaneous adverse events that occurs during administration of azelaic acid gel include burning/ stinging/tingling and pruritus. Gels are considered to be the most suitable delivery vehicle for topical formulation. Use of chemical penetration is one of the approaches to reduce the systemic adverse effects of topically applied drugs to enhance their permeability so as to reduce the topically applied dose. Hence, our present work attempted to increase its permeability and reducing side effects by using two different types of penetration enhancer i.e. from natural source i.e. piperine and that of synthetic i.e. DMSO and their combination.

---

### INTRODUCTION

Acne vulgaris is a chronic inflammatory dermatitis disorder of the pilosebaceous follicle and characterized by open comedones (black heads), or closed comedones (white heads). It is also characterized by inflammatory lesions which includes papules, pustules, or nodules [1]. Comedones are the clinical lesion that results from follicular plugging. It is a disorder of sebaceous follicles which are special pilosebaceous units located on the face, chest and back in the body [2]. *Propionibacterium acnes* and *Staphylococcus epidermidis* have been recognized as pus-forming bacteria triggering inflammation in acne [3].

Despite acne being an almost universal condition in younger people and affects almost 80% of young adult adolescents. Acne is more common among girls, in the age group of 12 years or younger and among boys in the age group of 15 years or older [4].

#### What causes acne? [5-9]:

- Acne occurs at the earlier age with more severe condition having family history. The percentage of occurrence is almost 80% in first-degree relatives. In this, innate inclination for follicular epidermal hyper proliferation with subsequent plugging of the follicle are involved
- There is an accumulation of dead skin cells that block or cover pores
- Additional aggravating factors include excess sebum, the presence and activity of *Propionibacterium acnes*
- Inflammation

- e) Cornification of the pilosebaceous duct  
 f) Abnormal epithelial desquamation and follicular obstruction caused due to increased androgen production. It leads to the complication of primary precursor lesion in acne—the microcomedone.

The topical treatment of acne includes topical retinoids, benzoyl peroxide (BPO), azelaic acid, erythromycin, clindamycin, and combination therapies [10-16].

From the decades, it has been reported in the literature that topical treatment of acne is more effective as compared to systemic therapy. It is because of its occurrence in the pilosebaceous unit of the skin. In this study, azelaic acid is selected as a model drug. It is a naturally occurring aliphatic dicarboxylic acid found in whole grain cereals and animal products. It possesses various biological activities with topical application. It has demonstrated efficacy in the treatment of acne vulgaris, rosacea, and various hyperpigmentary disorders. Due to its poor water solubility it results in difficulties in the preparation of topical formulation. The present investigation aims to reduce the concentration of the active drug concentration of azelaic acid by maintaining the therapeutic efficacy by using different types of penetration enhancers. In this study, hydrogel based polymer is used for preparation of formulation i.e. carbopol. Due to its high stability, good bio-compatibility and less toxicity it is used. In this study, two penetration enhancers were used dimethylsulphoxide (DMSO) and piperine.

## EXPERIMENTAL SECTION

### Chemicals

Azelaic acid is purchased from Himedia Laboratories Ltd, Mumbai. Benzoic acid (Molychem, Mumbai), piperine (Yucca enterprises, Mumbai), Triethanolamine (Molychem, Mumbai), Carbopol – 934 LR (Sd Fine – Chem Ltd, Mumbai), DMSO (Molychem, Mumbai) and Glycerine (Loba chemicals laboratories, Mumbai).

### Preparation of topical azelaic acid gel

**Table 1** illustrates the formulae used to prepare the azelaic acid based gel formulation. The formulations were prepared by method reported by Santoyo et al., [17]. In this preparational method, carbopol powder (1 g) was slowly added into water (100 ml) under constant stirring condition. 10 gm of this prepared solution was taken and azelaic acid (20%) was added to it. Both were allowed to swell for two hours, to obtain a homogeneous mixture. Then, it was stirred for 60 minutes at 1000 rpm, followed by addition of 0.5 ml of triethanolamine drop wise to adjust the pH. To this mixture benzoic acid and glycerine were added. During mixing DMSO and piperine were added in the formulation as penetration enhancers. Mixing was continued until transparent gel appeared.

**Table 1: Different gel formulation compositions (All weights are in g) for 20% w/w azelaic acid**

Formulation code	Azelaic acid	Carbopol mixture	Benzoic acid	Piperine	Triethanolamine	Glycerine	Dimethyl sulphoxide
FG	2.4	10.0	0.05	-	0.4	2.0	-
FGP <sub>L</sub>	2.4	10.0	0.05	0.24	0.4	2.0	-
FGP <sub>M</sub>	2.4	10.0	0.05	0.46	0.4	2.0	-
FGP <sub>H</sub>	2.4	10.0	0.05	0.65	0.4	2.0	-
FGD <sub>L</sub>	2.4	10.0	0.05	-	0.4	2.0	0.06
FGD <sub>M</sub>	2.4	10.0	0.05	-	0.4	2.0	1.2
F GD <sub>H</sub>	2.4	10.0	0.05	-	0.4	2.0	2.4
FGDP	2.4	10.0	0.05	0.65	0.4	2.0	2.4

### EVALUATION OF GEL

The gel was evaluated for pH, drug contents, viscosity, spreadability and *in-vitro* permeation study.

#### Determination of pH

Accurately weighed 5±0.01 g of the gel was dispersed in 45 ml of water and the pH of suspension was determined at 27°C using the pH meter [18].

#### Drug content uniformity

The formulation equivalent to 50 mg of drug was taken and dissolved in small quantity of ethanol. Then the formulation was warmed on the water bath so that the drug present in the formulation was completely dissolved. Then the solution was filtered through Whatman filter paper into 50 ml volumetric flask. The volume was made up to the mark to give concentration of 1000 mcg/ml. From this different concentration of solution was taken in 10 ml

volumetric flask and volume was made upto 10 ml with ethanol and absorbance was measured by UV spectrophotometer at 210 nm against blank [18].

#### Viscosity

The viscosity of formulated gel was measured by Brook field Viscometer (LV DV-III ultra programmable Rheometer) using spindle CP-52 at varying speed and shear rates. The measurements were made over the range of speed setting from 0.10, 0.20, 0.30, 0.40 and 0.50 rpm with 60 sec between two successive speeds as equilibration with shear rate ranging from 0.20 sec<sup>-1</sup> to 1.0 sec<sup>-1</sup>. Viscosity determinations were performed at room temperature. The viscosity data was plotted for Rheogram-Viscosity in cps v/s shear rate in sec<sup>-1</sup>.

#### Spreadability

Spreadability is a term expressed to denote the extent of area to which the topical application spreads on application to skin on the affected parts. The therapeutic efficiency of the formulation also depends upon its spreading value. Hence, determination of spreadability is very important in evaluating topical application characteristics. For the determination of spreadability, excess of sample (3 g) was applied in between two glass slides and was compressed to uniform thickness by placing 1000 gm weight for 5 minute. Thereafter weight (50 gm) was added to the pan and the top plate was subjected to pull with the help of string attached to the hook. The time in which the upper glass slide moves the lower plate to cover a distance of 10 cm is noted. A shorter interval indicates better spread ability [18]. The spreadability (S) was calculated using the formula:

$$S = \frac{M \times L}{T}$$

Where, S - Spreadability

M - Weight tied to upper glass slid

L - Length moved on glass slide

T - Time taken

#### In-vitro drug release study

In-vitro permeation studies were performed using vertical diffusion Franz cells with an effective diffusion area of 2.54 cm<sup>2</sup>. The cellophane membrane was mounted on the receptor compartment with upwards into the donor compartment. The donor compartment was filled with weighed amount 200 mg of formulated gel of different compositions. Receptor compartment was filled with Ethanol: Phosphate buffer (pH 7.4) (3:7 v/v) at 37°C and stirred by a magnetic bar at 600 rpm. At appropriate time interval 3 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh receptor solution up to 24 hr. The samples were analyzed by UV Spectrophotometer at 210 nm.

## RESULTS AND DISCUSSION

#### Determination of pH

pH of the prepared gel was found to be 5.7±0.23.

#### Drug content uniformity

The percentage drug content of prepared gel formulation was found to be 96.20±0.73%.

#### Viscosity

The mean average viscosity was found to be 8231.23±22.13 cps.

#### Spreadability

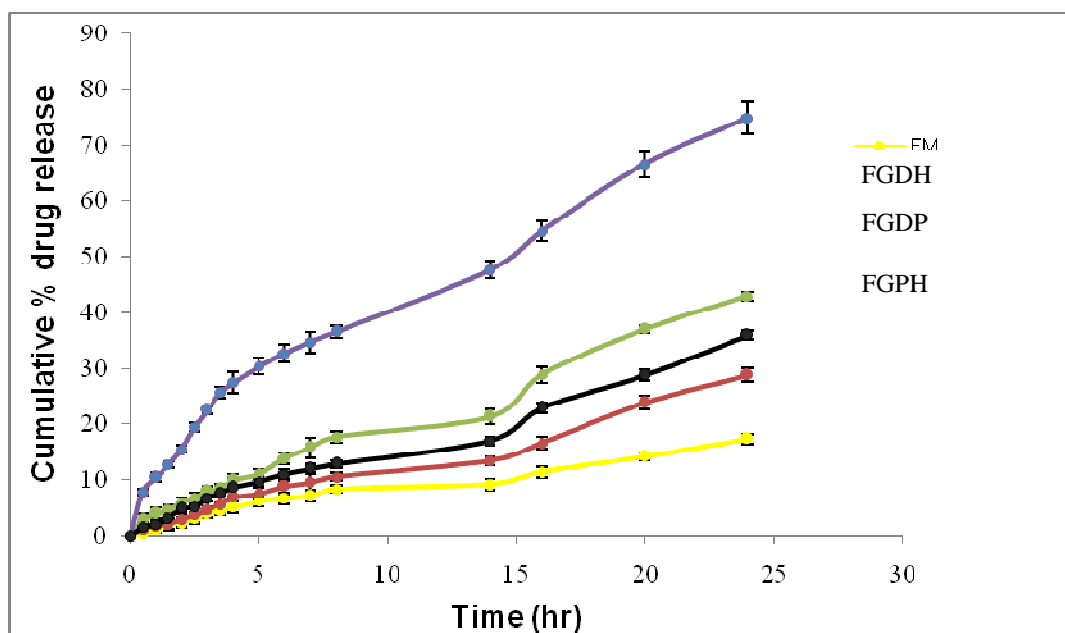
The spreadability was found to be 5.02±0.21 g-cm/sec.

#### In-vitro drug release study

Results of in-vitro drug released from different formulations are shown in **Table 2** and graphically shown in **Figure 1**.

Table 2: *In-vitro* drug release from marketed cream and formulated gels

Time (hr)	Cumulative % drug release				
	FM	FG	FGP <sub>H</sub>	FGD <sub>H</sub>	FGDP
0.5	0.56±0.8	1.15±0.5	1.56±0.7	2.87±0.8	7.89±0.9
1	1.22±0.6	1.82±0.7	2.13±0.7	3.97±0.8	10.46±0.9
1.5	1.99±0.7	2.11±0.5	3.15±0.8	4.68±0.9	12.78±0.7
±2	2.34±0.8	2.99±0.6	4.88±0.9	5.9±1.3	15.45±0.8
2.5	3.22±0.9	3.79±0.6	5.22±1.3	6.77±1.4	19.47±0.9
3	3.99±0.7	4.7±0.6	6.72±1.4	7.98±1.5	22.47±0.7
3.5	4.51±0.8	5.67±1.1	7.52±1.5	8.45±1.6	25.69±0.8
4	5.11±0.9	6.87±1.9	8.66±1.6	9.99±1.7	27.47±0.9
5	6.19±0.8	7.59±1.4	9.66±0.8	11.15±0.9	30.37±0.8
6	6.76±0.9	8.87±1.5	10.99±0.9	13.89±1.3	32.68±0.9
7	7.11±0.9	9.59±1.8	11.99±0.7	15.77±1.4	34.68±1.7
8	8.33±0.7	10.58±1.1	12.87±0.6	17.66±0.6	36.58±0.9
14	9.21±0.9	13.48±1.6	16.99±0.7	21.34±0.7	47.68±1.3
16	11.43±0.9	16.59±1.7	22.97±0.8	28.89±1.1	54.54±1.4
20	14.22±0.6	23.86±2.3	28.76±0.9	36.98±1.2	66.57±0.6
24	17.33±0.8	28.77±2.8	35.9±0.7	42.89±1.2	74.88±0.7

Figure 1: *In-vitro* drug release from marketed cream and formulated gels

### CONCLUSION

Two penetration enhancers were investigated along with their combination i.e. DMSO & piperine for enhancement of penetration of azelaic acid. Increase in amount of DMSO & piperine lead to increase in release of azelaic acid. Highest release was found when combination of DMSO & piperine was used i.e. the combination resulted in a synergistic enhancement of azelaic acid release from formulation. Prepared gel was characterized for pH determination, % drug content, viscosity and spreadability. pH of prepared gel was found to be close to skin pH i.e. 5.8. The average viscosity was found to be 8231.23±22.13 cps.

The influence of DMSO and piperine on the *in-vitro* penetration of azelaic acid through a synthetic membrane from carbopol gels was investigated using Franz-type diffusion cell. It was apparent that the incorporation of penetration enhancer in gels formulations lead to increase release profiles compared to its simple gel and marketed cream. Highest release was found when combination of DMSO & piperine was used i.e. the combination resulted in a synergistic enhancement of Azelaic acid release from formulation.

## REFERENCES

- [1] SVBershad, Mt Sinai *J Med.*, **2001**, 68(4&5), 279-285.
- [2] Brown SK, Shalita AR, *Lancet*, **1998**, 351, 1871–1876.
- [3] Kumar GS, Jayaveera KN, Kumar A, Umachigi P, Vrushabendra BMS, Kumar DVK, *Trop J Pharm Res.*, **2007**, 6(2), 717–723.
- [4] Krautheim A, Gollnick HPM, 2004. *Cli Dermatol.*, **2004**, 22,398-407.
- [5] Bhate K, Williams HC. *Brit J Dermatol.*, **2013**, 168 (3), **474–485**.
- [6] Thiboutot D, Gollnick H, Bettoli V, Dreno B, Kang S, Leyden JJ, *J Am Acad Dermatol.*,**2009**, 60 (5),1-50.
- [7] Haider A, Shaw JC, *JAMA*, **2004**, 292(6), 726-35.
- [8] Abad-Casintahan F, Chow SK, Goh CL, Kubba R, Miyachi Y, Noppakun N, *J Dermatol.*, **2011**, 38 (11)1041-8.
- [9] Williams HC, Dellavalle RP, Garner S, *Lancet*, **2012**, 379 (9813), 361-72.
- [10] Zaenglein AL, *Semin Cutan Med Surg.*, **2008**, 27 [3], 177–182.
- [11] Gollnick HP, Krautheim A, *Dermatology*, **2003**, 206 [1], 29–36.
- [12] Tucker R, Walton S, *Pharm J.*, **2007**, 279, 48–53.
- [13] Spellman MC, Pincus SH, *Clin Ther.*, **1998**, 20 [4], 711–721.
- [14] Unkles SE, Gemmell CG, *Antimicrob Agents Chemother.*, **1982**, 21[1], 39–43.
- [15] Toyoda M, Morohashi M, *Dermatolog.*,**1998**, 196 [1], 30–134.
- [16] Mills OH, Klingman AM, *Acta Derm Venereol.*, 197, 58 [6], 555–557.
- [17] Santoyo S, Arellano A, Ygartua P, Martin C, *Int J Pharm*, **1995**, 117 [2], 219-224.
- [18] Kane R, Naik S, Bumrela S, Kuchekar B, *J Pharm Res*, **2009**, 2[8], 1359-1364.