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Research Article

Formulation and Evaluation of Niosomal Gel for Treatment of Acne

Pallavi Goyal*, Ashish Jain, Steffi Thomas, Akhlesh Kumar Singhai

School of Pharmacy, LNCT University, Bhopal, M.P., India

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*Address for Correspondence:

Pallavi Goyal, School of Pharmacy, LNCT University, Bhopal, M.P., India

Abstract

A skin disease, like acne, is very common and normally happens to everyone at least once in their lifetime. The structure of the stratum corneum is often compared with a brick wall, with corneocytes surrounded by the mortar of the intercellular lipid lamellae. *Acne vulgaris* is a chronic inflammatory dermatosis which is notable for open and/or closed comedones (blackheads and whiteheads), and inflammatory lesions including papules, pustules, or nodules. It is a disorder of sebaceous follicles which are special pilosebaceous units located on the face, chest, and back. Skin is one of the most readily available organs on human body for topical management and is the major route of topical drug delivery system. Topical drug administration is a localized drug delivery system everywhere in the body during ophthalmic, vaginal, rectal and skin as topical routes. SA niosomes gel delivery system (SANG1 to SANG5) as a dispersed system, which consists of small droplets and well distributed in to immiscible vehicle. Niosome salicylic acid was prepared by Reverse phase evaporation method using cholesterol and span 80 and tween 20. Niosome were evaluated for vesicle shape, size determination, Entrapment efficiency and in-vitro drug release study. The result concluded that **SANG5** was best formulation with Carbopol 940 (2g), PVP, nutmeg oil base. The drug release profile and release kinetics are two important characteristics of the dosage forms, which play an important role for describing dissolution profile of dosage form.

Keywords: Topical drug delivery, *Acne vulgaris*, Niosomes, Gel, Carbopol 940, nutmeg oil

INTRODUCTION:

Acne is considered as one of the most widespread skin diseases. When extreme disfiguration occurs, it results in the development of severe consequences among the young people and may result in depression and suicide. *Acne vulgaris* is the second uppermost reason of suicide among skin diseases and occurs in both male and female; there is no preference among them, but the course is more severe in males [1]. Testosterone is the main androgen responsible for acne. One of its derivative dihydrotestosterone formed in the body by the action of enzyme 5-ά-reductase (type-1). Type-1 of 5- reductase is the foremost isotype found in human skin, specifically in SG rich area. As sebum content rises in acne patients due to rise androgen level and also regulated by them [2]. In most of the patients of seborrhea, despite normal levels of androgens sebum production is high because of increased sensitivity of sebocytes toward androgen (it may be the cause) Hence, seborrhea and acne can occur both at normal as well as higher levels of androgens. It was hypothesized by Weeks et al. that free fatty acid formed by action of lipase enzyme of P. acnes on the triglycerides of sebocytes is highly inflammatory and chemotactic. They also showed that inhibition of lipase cause the reduction in the free fatty acid amount in the skin, but it does not suppress the acne because of the formation of pro-inflammatory fraction of lipid by the other mechanisms than the bacterial lipase and are responsible for inflammation in acne [3]. It is known that during the formation of acne infundibulum changes occurs but the mechanism behind the changes yet clearly not known. One of the hypotheses said that local follicular insufficiency of linoleic acid effects and androgens which cause apparent early cornification of keratinocytes [4]. Hence, scientific data mainly concentrated toward *P. acnes*. *P. acnes* is a Gram positive having characters such as non-motility and pleomorphism. They are rod-shaped cells which cause the fermentation of sugars so as to yield propionic acid as one of their metabolic end products [5]. The various factors mentioned in the etiology contribute to the pathogenesis of acne in the following way. Seborrhea increase androgen concentration due to genetic factors as well as because of attainment of puberty all ultimately leads to the increased sebum production. On puberty, body's androgen production increases. In the sebocyte, androgens are synthesized as well as reuptake. Retention-proliferation hyperkeratosis first form microcomedone, which further grow and convert into comedone and this comedone further develop and form acne [6]. The main goal of treatment of acne is to stop scarring and minimize the duration of disease. It also focused to decrease the psychological stress that affects at least half of sufferers. So, clinical trial evidence of effectiveness of medicament plays important role in the management of acne. The main adverse effects associated with benzoyl peroxide are transient irritation of skin, occasional allergic contact dermatitis and bleaching of clothes. In long-term or in conjunction with oral antibiotics they can be used in the cure of moderate type of A. vulgaris [7]. Topical preparations of clindamycin and erythromycin are similar in terms of efficiency. These topical preparations are suitable for greasy skins because of their alcoholic base. Clindamycin in a lotion base is less irritating to dry or scaly skin and is preferred by women. Topical tetracycline is less effective and leaves a residue that may fluoresce under ultraviolet light. The development of antibiotic resistance in P. acnes limits the use of these topical antibiotics now [8]. Salicylic acid is an acid used to treat acne, psoriasis, calluses, corns, keratosis pilaris, and

warts. A compound obtained from the bark of the white willow and wintergreen leaves, and also prepared synthetically. It has bacteriostatic, fungicidal, and keratolytic actions. Its salts, the salicylates, are used as analgesics. Salicylic acid directly irreversibly inhibits COX-1 and COX-2 to decrease conversion of arachidonic acid to precursors of prostaglandins and thromboxanes.

The objective of proposed work is to develop niosomal drug delivery system exhibit reduced toxicities and retain enhanced efficacy compared with free complements. Salicylic acid-loaded niosome formulation can avoid systemic uptake of the drug. Niosomal gel exhibit reduced toxicities and retain enhanced efficacy compared with free complements. Niosomes gels are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose, increased stability and reduced side effects.

MATERIAL AND METHODS:

Preparation and characterization of niosomes: Niosomes with drug in different combinations prepared by the high speed homogenization method. The various formulations were prepared using drug 100 mg with varying amount of gelling agent and penetration enhancers. The composition of the formulation was prepared with nutmeg oil as a carrier, surfactant Tween 20, span 80 and glycerin in purified water by high speed homogenization. Accurately weighted quantities of surfactants and cholesterol were taken to give the desired ratio and were dissolving in 50 ml of ethanol in a round bottom flask. Then, accurately weighted amount of drug was added to the solvent (ethanol). The solvent was evaporated in a rotary flash evaporator at temperature of 60°C at 120 rpm until the smooth, dry lipid film was hydrated with 20 ml of PBS 7.0 was added and shaking on the water bath. The prepared niosome suspension was kept at 2 to 8°c temperature for 24 hrs [9] (Table 1).

Table 1: A variety of composition of different niosomes formulations

S. No.	Formulation code	Surfactant	Weight taken (gm)			Surfactant: cholesterol ratio
			Salicylic acid	Surfactant	Cholesterol	
1	SAN1	Span 80	1	10	2	05:01
2	SAN2		1	20	2	10:01
3	SAN3		1	30	2	15:01
4	SAN4	Tween 20	1	10	2	05:01
5	SAN5		1	20	2	10:01
6	SAN6		1	30	2	15:01

Preparation of niosomes gel: The gel base was prepared by dispersing Carbopol 940 in distilled water with constant stirring at a moderate speed using mechanical shaker, then the pH was adjusted to 6–6.5. The oil phase of the emulsion was prepared by dissolving span 20 in nutmeg oil. The aqueous phase was prepared by dissolving tween 20 / span 80 in distilled water and required weighed quantity of drug was dissolved in ethanol. Now all prepared both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70–80°C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature [10-11]. The obtained emulsion was mixed with the gel base in 1:1 ratio with gentle stirring to obtain the niosomalgel (Table 2).

Table 2: A variety of composition of different niosomalgel formulations

S. No.	Ingredient	SANG1	SANG2	SANG3	SANG4	SANG5
1	Salicyllic acid niosomes (mg)	Equivalent to 100 mg				
2	Carbopol 934 (g)	0.5	1	1.5	2	2.5
3	Nutmeg oil (ml)	7.5	7.5	7.5	7.5	7.5
4	Polyvinyl pyrrolidone (mg)	50	50	50	50	50
5	Water (ml)	q.s	q.s	q.s	q.s	q.s

Characterization of niosomes gel:

Physical examination: The prepared salicylic acid niosomes gel formulations were inspected visually for their color, appearance and consistency. The prepared salicylic acid niosomalgel formulations were inspected visually for their feeling after application on skin, color intensity, pH determination, consistency and extrudability determination. The gels were tested for homogeneity by visual inspection prior to the gels being filled into containers. They were also tested for their appearance and presence of any aggregates.

Globule size and polydispersity index (PDI): GS and PDI were determination by mean droplet size and polydispersity index of the emulsions was determined by zetasizer by sending samples of formulation to centre.

Viscosity determination: The viscosity of the formulated batches was determined by using a brook field viscometer. The assembly was connected to a thermostatically controlled circulating water bath maintained at 25°C. The sufficient quantity of gel base was filled in wide mouth jar separately and it should sufficiently allow dipping the spindle. Spindle was allowed to move freely into the emulgel and

the reading was noted with RPM of the spindle was adjusted to 2.5 RPM. The viscosities of the formulations were recorded.

Spreadability: Spreadability was determined by principle involved in this spreadability method is 'slip' and 'drag'. Thus, a ground glass slide is fixed onto the wooden block, while another upper glass slide having the same dimensions as that of the fixed ground slide is provided with a hook and placed on the ground slide. 2 g of emulgel were placed in between the glass slides and a weight of 1 kg was applied on the upper slide for 5 min to form a uniform film of the formulation between the slides. Excess of the formulation was scrapped off from the edges. The top plate was then subjected to a fixed weight of 100 g with the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7 cm was noted. A shorter interval indicates better spreadability. Spreading coefficient is determined by using the formula.

$S + m * l / t$

where, S = Spreadability, m = Weight tied to upper slide, l = Length of glass slides,

t = Time taken to separate the slides completely from each other.

Drug content determination: One gram each of emulgel was taken and dissolved in methanol and sonicated for 1 h respectively. The resulting solutions were filtered with 0.45 µm filter to obtain clear solutions. The drug content was analyzed using a UV spectrophotometer method at 297 nm.

In-vitro permeation studies: In-vitro permeation studies of the developed gels were carried out using Franz-diffusion cell. The dialysis membrane (Himedia, thickness 0.025 mm) was cut into equal pieces (6 cm×2.5 cm) and soaked into distilled water for 12 h before use. The drug release studies of the salicylic acid niosomalgel was carried out in 10 ml of phosphate buffer pH 6.8 saline maintained at 37±2°C with a magnetic stirrer with constant heating equipment. A sample of 2 ml of salicylic acid niosomes gel was placed in receptor compartment. Aliquot samples of 1 ml were withdrawn at the regular interval and replaced with same volume of fresh buffer. The aliquots were diluted with fresh media, if necessary. Amount of drug diffused through the membrane was measured by using U.V. spectrophotometer at the wavelength 297 nm against phosphate buffer.

RESULT AND DISCUSSION:

Niosome of salicylic acid as model drug prepared by high speed homogenization method using cholesterol and tewwn 80 and span 80 as surfactant. Niosomes were mixed with gel base and coverted to niosomal gel. The various formulations of salicylic acid containing carbopol 934 as gelling agent with nutmeg oil as vehicle. The various formulations were evaluated for globule size and polydispersity index (pdi) etc (Figure 1). The mean vesicular diameter of the optimized formulation was evaluated by using Malvern instrument. The mean vesicular diameter of the optimized formulation SANG5 containing the 10:1 ratio of Cholesterol: surfactant (tween 80) concentration was showing the minimum mean vesicular diameter of 124.11 nm and PDI was 0.211. The formulation SANG5 was prepared niosomalgel with Carbopol 940 (2.5g), PVP, Nutmeg oil base.

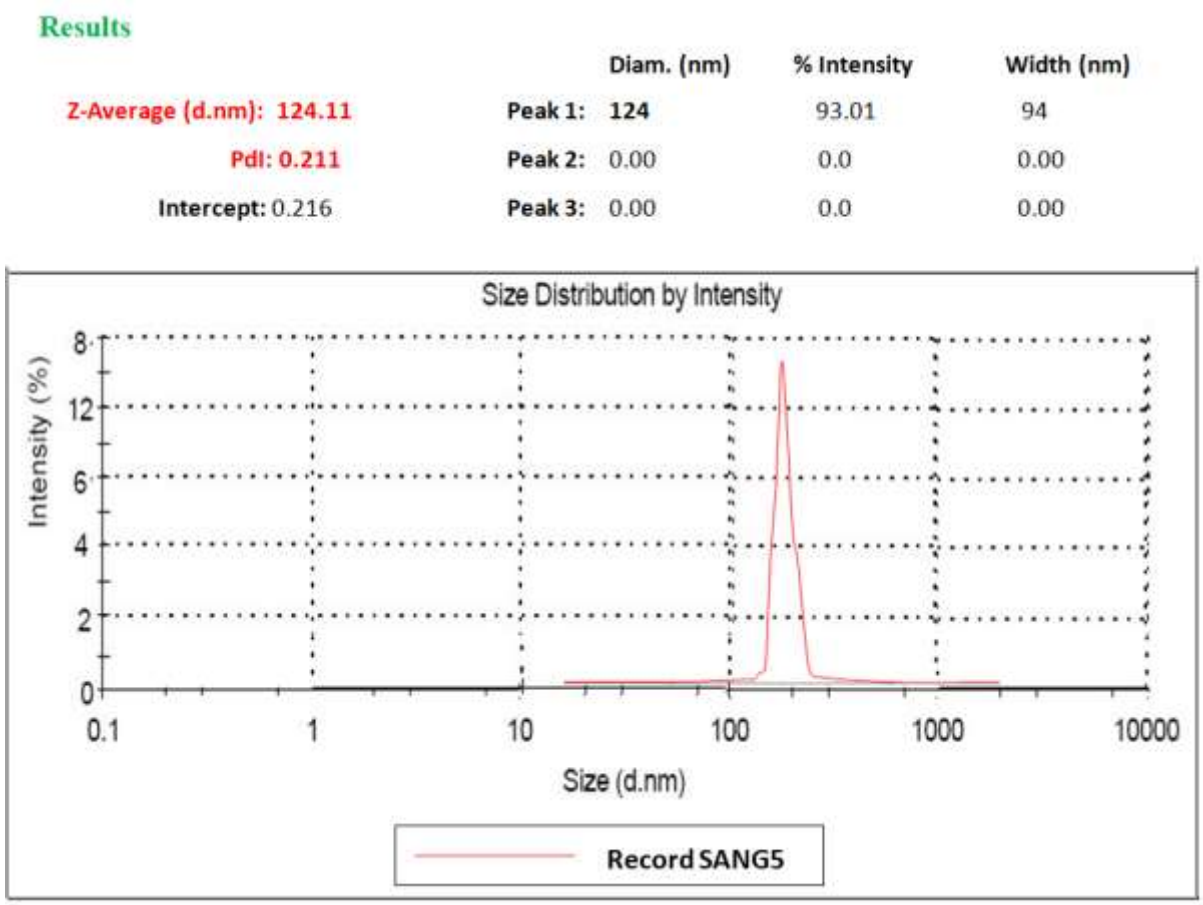

Figure 1: Determination of Globule (Particle) size and Polydispersity index (PDI) of formulations (SANG5)

The prepared niosomalgel formulations were examined visually for their feeling after application on skin, color intensity, pH determination, consistency and extrudability determination. The niosomes gels were tested for homogeneity by visual inspection prior to the gels being filled into containers. The Formulation SANG5 was best formulations among all the prepared formulations. The consistency of SANG5 was excellent (Table 3).

Table 3: Physical characterization of niosomes gel

S. No.	Parameters	Formulations				
		SANG1	SANG2	SANG3	SANG4	SANG5
1	Feel of application on Skin	Smooth	Smooth	Smooth	Smooth	Smooth
2	Consistency	Poor	Good	Good	Uniform	Excellent uniform
3	Extrudability	Good	Good	Excellent	Good	Excellent
4	Globule (Particle) size (nm)	141.11	137.14	127.17	119.21	124.11
5	Polydispersity index (PDI)	0.241	0.243	0.232	0.222	0.211
6	Viscosity (cps)	1534	1423	1379	1345	1335
7	pH	6.22	7.21	7.13	7.11	7.01
8	Spreadability (g.cm/sec)	8.1	10.43	11.02	11.54	12.98
9	Drug Content (%)	98.31	98.11	98.19	98.12	99.32

The drug release profile and release kinetics are two important characteristics of the dosage forms, which play an important role for describing dissolution profile of dosage form. The dissolution data was obtained after in-vitro release performance, fitted to mathematical different models. The result of release data were shown in Figure 2 - 3.

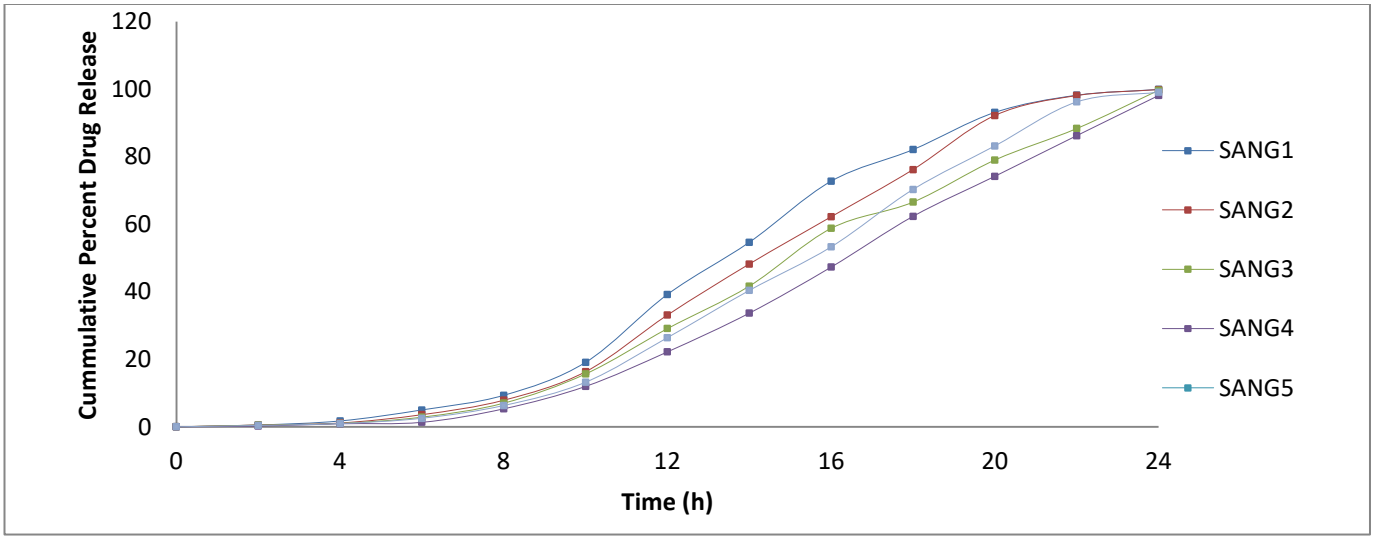

Figure 2: Zero-order plots for SA niosomalgel delivery system (SANG1 to SANG5)

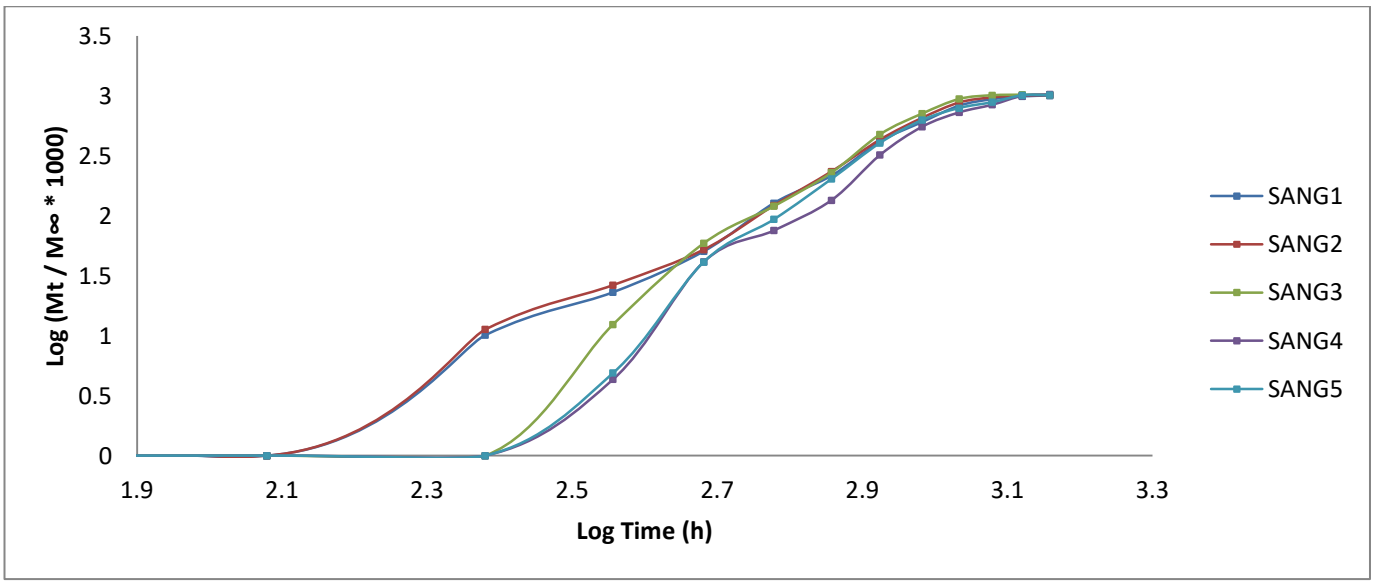

Figure 3: Korsmeyer's-Peppas plot for SA niosomalgel delivery system (SANG1 to SANG5)

The release data were computed in graph and release kinetic values were optimized. The formulations SANG1 to SANG5 showed the values of n> 0.5, followed Fickinan diffusion and supercase II transport mechanism. The value of t50% of SANG5 is more than 15 h. it will show better controlled release mechanism of prepared drug delivery system.

CONCLUSION:

Acne is considered as one of the most widespread skin diseases. The main goal of treatment of acne is to stop scarring and minimize the duration of disease. The topical preparation usage is the main way to treat it, and preparations that can be used for the treatment of mild acne. Niosomes are multilamellar vesicles that efficiently deliver active substance into skin systemic circulation or skin layers. They are used in topical drug delivery system to enhance the skin permeation of active substance. So, the prime objective of this study was to develop a niosomal gel of salisyllic acid to increase its skin permeation. The present investigation developed salicylic acid niosomes gel delivery system drug with better-permeable, controlled and localized delivery via topical route. The results of various permeation studies showed high permeation of salicyllic acid when gel was applied to skin and previous studies of niosomes, can be concluded that niosomes enhanced the permeation of salicyllic acid through the skin

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