

SELF-ASSEMBLED NANO STRUCTURES (SANS) CARRIER FOR TOPICAL DELIVERY OF BENZOYL PEROXIDE**B. K. Dubey*, Deepak Kumar Basedia, Brijesh Kunvar Mishra****Technocrates Institute of Technology, Pharmacy, Hatai Kheda Road, opp. Hataikheda Dam
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ABSTRACT

The present study focuses on the development and evaluation of a novel self-assembled nano structures carrier drug delivery system, for the topical delivery of benzoyl peroxide (BPO). SANS carriers were prepared using hydroxyapatite (HA) as the ceramic core and coated with different carbohydrate polymers trehalose, dextran, and sucrose to assess their impact on physicochemical characteristics and drug release behavior. Six formulations (F1–F6) were developed, among which F5 (1% dextran-coated) demonstrated the most favorable properties, including a vesicle size of 120.32 nm, a surface charge of -36.85 mV, and the highest entrapment efficiency of 74.45%. In-vitro release studies showed that F5 exhibited a sustained release profile with approximately 89.98% cumulative release over 12 hours, following Higuchi ($R^2 = 0.991$) and Korsmeyer–Peppas ($R^2 = 0.990$) kinetics, indicating diffusion-controlled drug release. TEM analysis confirmed the spherical morphology and nanoscale structure of the SANS carriers. Furthermore, stability studies revealed that refrigeration maintained better vesicle integrity and entrapment compared to room temperature storage. These results suggest that SANS carriers are a promising carrier system for the effective, stable, and sustained topical delivery of benzoyl peroxide, with potential applications in dermatological therapies, particularly for acne treatment.

Keywords: SANS carriers, benzoyl Peroxide, topical drug delivery, entrapment efficiency; *in-vitro* release, nanocarriers, stability study, acne treatment.

INTRODUCTION

The increasing prevalence of skin conditions such as acne vulgaris, eczema, and psoriasis has driven significant advancements in the development of effective topical drug delivery systems. Among these, benzoyl peroxide (BPO) is a commonly used therapeutic agent, especially for treating acne due to its antibacterial and comedolytic properties¹. However, despite its widespread use, BPO's stability, skin irritation potential, and poor solubility often limit its effectiveness in topical formulations. Therefore, developing novel delivery systems that can overcome these challenges while enhancing drug

penetration, bioavailability, and controlled release is crucial. One promising approach is the use of SANS carriers, a self-assembled nanocarrier system that offers significant advantages in drug delivery, especially for hydrophilic and hydrophobic agents like BPO.

The nanostructures composed of a ceramic core, often made of materials such as hydroxyapatite (HA) or calcium phosphate, coated with a carbohydrate layer (e.g., trehalose, sucrose, or dextran). This unique structure provides a platform for high drug loading, biocompatibility, and stability, making SANS carriers an ideal candidate for delivering drugs like BPO to the skin. The ceramic core provides mechanical stability and biocompatibility, while the carbohydrate coating ensures better stability, preventing drug degradation, and promoting controlled release. These properties are particularly significant when designing systems for sensitive molecules such as Benzoyl Peroxide, which can degrade under environmental conditions such as UV light and heat ².

The key advantage of using SANS carriers for the topical delivery of BPO lies in their ability to overcome skin barrier challenges. The skin is a formidable barrier to the penetration of active pharmaceutical ingredients (APIs), particularly hydrophobic molecules. SANS carriers, due to their nano-size and surface properties, can effectively penetrate the stratum corneum and deliver BPO deeper into the skin layers where it exerts its therapeutic effect. Additionally, the hydrophilic carbohydrate layer can further enhance drug solubility and extend drug residence time at the application site, improving therapeutic outcomes while minimizing side effects such as irritation ³.

Moreover, SANS carriers offer the potential for sustained drug release, which is particularly beneficial in acne treatment, where prolonged therapeutic activity is often required. The ceramic core of SANS carriers, combined with the polymer coating, can act as a reservoir that slowly releases BPO, ensuring continuous therapeutic effects over extended periods, reducing the need for frequent reapplications ³.

This research on SANS carriers as nanocarriers for Benzoyl Peroxide delivery is significant not only for improving the pharmacokinetics of BPO but also for advancing the field of nanomedicine in dermatology. With a focus on enhanced stability, improved skin penetration, and controlled release, SANS carriers can revolutionize the way topical treatments for acne and other skin disorders are formulated, providing a non-invasive, targeted, and more effective alternative to conventional treatments.

Material and Methods

Preparation of self-assembled nano structures (SANS)

SANS carriers were prepared through a three-step self-assembly process involving synthesis of a hydroxyapatite (HA) core, carbohydrate coating, and drug adsorption ⁴. The HA core was synthesized via wet chemical precipitation using calcium nitrate and ammonium phosphate at pH 9–10, followed by

drying at 80°C. The dried nanoparticles were coated with aqueous solutions of trehalose (F1–F3), dextran (F4–F5), or sucrose (F6) at varying concentrations (0.5–1.5%), stirred for several hours to facilitate surface adsorption.

Benzoyl Peroxide (20%) was dissolved in a suitable solvent with Tween 80 (1–3%) as a surfactant. The carbohydrate-coated HA particles were added and stirred for 4–6 hours for drug adsorption. Glutaraldehyde (1%) was used for cross-linking to stabilize the formulation.

Table 1: SANS carriers formulations with different carbohydrate coatings

Ingredient (%)	F1	F2	F3	F4	F5	F6
Benzoyl Peroxide	20	20	20	20	20	20
Tween 80	1	2	3	1	2	3
Glutaraldehyde	1	1	1	1	1	1
Polymer Used	Trehalose (0.5%)	Trehalose (1%)	Trehalose (1.5%)	Dextran (0.5%)	Dextran (1%)	Sucrose (1.5%)
Water (q.s.)	100	100	100	100	100	100

Characterization and evaluation of Benzoyl Peroxide loaded SANS carriers

Characterize the SANS carriers using various techniques, Surface charge and vesicle size, entrapment efficiency, transmission electron microscopy (TEM), and *in-vitro* diffusion study.

Surface charge and vesicle size

The vesicles size and size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (Malvern Zetamaster, ZEM 5002, Malvern, UK)⁵. Zeta potential measurement of the SANS carriers was based on the zeta potential that was calculated according to Helmholtz–Smoluchowsky from their electrophoretic mobility. For measurement of zeta potential, a Zetasizer was used with field strength of 20 V/cm on a large bore measures cell. Samples were diluted with 0.9 % NaCl adjusted to a conductivity of 50 IS/cm.

Entrapment efficiency

One milliliter of SANS carriers suspension was centrifuged at 15,000 rpm for 1 h to allow the separation the entrapped drug from the un-entrapped drug ⁶. After removal of the supernatant, the sediment was lysed using methanol and then analyzed spectrophotometrically at 245nm using a UV spectrophotometer (Labindia 3000+). The EE% of prepared SANS carriers was calculated applying the following equation:

$$\% \text{ Entrapment Efficiency} = \frac{\text{Theoretical drug content} - \text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Transmission electron microscopy

TEM was used to examine the morphology and internal structure of the prepared SANS carriers. A thin sample was mounted on a carbon-coated copper grid and stained with uranyl acetate to enhance contrast ⁷. After reaching optimal vacuum, the TEM instrument was calibrated, and the sample was loaded into the column. An electron beam was directed through the sample, and the transmitted electrons were captured to generate high-resolution images on a digital detector, revealing nanoscale structural details.

In vitro drug diffusion study

The dialysis diffusion approach was used to perform *in vitro* drug release of prepared SANS carriers utilizing the dissolution test apparatus ⁸. The dissolving media was phosphate buffer pH 7.4. The dialysis technique was carried out utilizing a cellulose acetate dialysis membrane with a molecular weight cutoff of 12,000–14,000 moles. This membrane ensures drug penetration while retaining SANS carriers vesicles. Before usage, the membrane was soaked in fake tears for 12 hours. A glass cylinder with a length of 8 cm and a diameter of 1 cm was filled with four ml of SANS carriers dispersion, and a dialysis membrane was threaded to the mouth of the cylinder. Each glass cylinder was attached to the shaft of the dissolution apparatus (USP Dissolution tester, Labindia DS 8000) and descended down into a 100 ml beaker containing 50 ml of as dissolution medium without touching the bottom surface of the beaker. The beaker was then placed into vessels of dissolution apparatus that contained about 100 ml of water to keep temperature at $34 \pm 0.5^\circ\text{C}$. The glass cylinders were adjusted to rotate at a constant speed of 20 rpm. One ml of dissolution medium was withdrawn at predetermined time intervals (0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 and 6 h).

To maintain a consistent volume, the samples were changed with new dissolving media. The concentrations of drugs in samples were measured spectrophotometrically at 245nm, the wavelength of the drug.

The release tests were done in triplicates, with the mean and standard deviation reported. At the end of each sampling period, samples are removed and replaced with equal quantities of fresh receptor fluid.

Mathematical models for in-vitro drug release

Quantitative analysis of *in-vitro* drug release can be modeled using several kinetic equations to understand release mechanisms:

Zero-Order Kinetics

Describes a constant drug release over time:

$$Q_t = Q_0 + K_0 t$$

Ideal for sustained-release systems where K_0 is the zero-order release constant.

First-Order Kinetics

Drug release depends on the remaining concentration:

$$\log Q_t = \log Q_0 - (K_1 t / 2.303)$$

Used for water-soluble drugs in porous matrices; K_1 is the first-order constant.

Higuchi Model

Describes release as a diffusion process from a matrix system.

$$Q = KH\sqrt{t}$$

Based on Fickian diffusion, where KH is the Higuchi constant.

Korsmeyer–Peppas Model

Used for polymeric systems to analyze release mechanism:

$$M_t/M_\infty = at^n$$

Where n indicates the mechanism (Fickian or non-Fickian). Extended forms account for lag time (**(l)**) and burst effect (**(b)**) when applicable.

RESULTS AND DISCUSSION

The present study was conducted to formulate and evaluate SANS carriers as a nanocarrier system for the topical delivery of Benzoyl Peroxide (BPO), a widely used antibacterial and keratolytic agent in acne treatment. The formulations (F1–F6) were developed using hydroxyapatite (HA) as the core material and different carbohydrate coatings trehalose, dextran, and sucrose, to analyze their influence on physicochemical properties, drug release behavior, and stability.

Vesicle size across the formulations ranged from 120.32 nm (F5) to 165.58 nm (F2), placing all in the optimal nanometer range for enhanced skin penetration. Notably, F5, which used 1% dextran, exhibited the smallest vesicle size, indicating a denser and more stable coating around the HA core, potentially facilitating deeper skin permeation.

All formulations showed a negative surface charge, ranging from -26.65 mV (F6) to -36.85 mV (F5). A higher absolute zeta potential ($ZP > 30$ mV), as seen in F1 and F5, generally indicates better colloidal stability due to electrostatic repulsion, helping prevent particle aggregation over time.

Entrapment efficiency varied from 68.85% (F1) to 74.45% (F5). The higher EE of F5 can be attributed to the optimal viscosity and binding properties of dextran, which may create a more compact matrix capable of effectively holding the drug. This further supports the selection of F5 as the optimized formulation for detailed in vitro and kinetic analysis.

TEM imaging of F5 revealed spherical, uniformly distributed nanoparticles, confirming successful self-assembly and nanoscale morphology. The dense and smooth surface is consistent with high entrapment efficiency and reduced burst release.

The in-vitro drug release profile of F5 demonstrated a sustained release pattern, reaching 89.98% cumulative release over 12 hours. The release data were fitted into various kinetic models, with Higuchi ($R^2 = 0.991$) and Korsmeyer–Peppas ($R^2 = 0.990$) showing the best correlation, indicating that drug release was primarily diffusion-controlled through the carbohydrate matrix.

The Peppas exponent (n) would help distinguish the mechanism further, but given the high fit with Higuchi, Fickian diffusion appears to be the dominant release mechanism, appropriate for topical systems aiming for prolonged skin exposure.

Stability testing of F5 over 3 months at 4°C and room temperature (25–28°C) demonstrated a notable increase in vesicle size and reduction in entrapment efficiency at higher temperatures, especially after the second month. This could be due to aggregation or degradation of the carbohydrate shell under elevated conditions. Additionally, turbidity observed in samples stored at room temperature further indicates structural instability, reinforcing the recommendation for refrigerated storage to maintain formulation integrity.

Table 2: Results of vesicle size and surface charge

S. No.	F. Code	Vesicle size (nm)	Surface Charge (mv)
1	F1	145.58	-36.65
2	F2	165.58	-32.25
3	F3	132.25	-32.25
4	F4	149.85	-29.98
5	F5	120.32	-36.85
6	F6	146.65	-26.65

Table 3: Results of Entrapment efficiency

S. No.	F. Code	Entrapment efficiency (%)
1	F1	68.85±0.65
2	F2	72.23±0.74
3	F3	70.12±0.85
4	F4	69.98±0.32
5	F5	74.45±0.45
6	F6	69.98±0.39

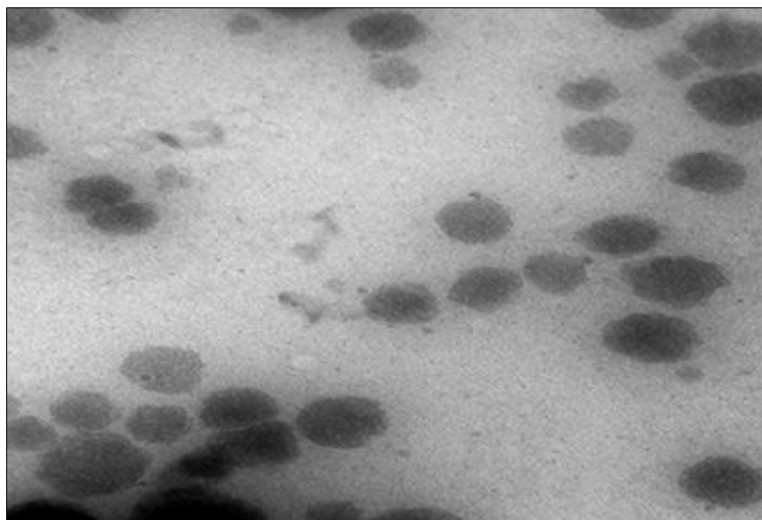
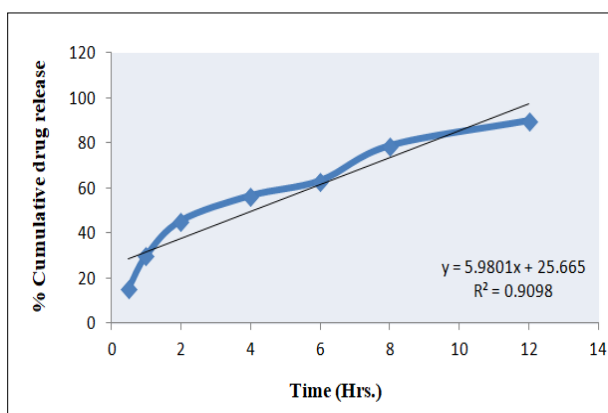


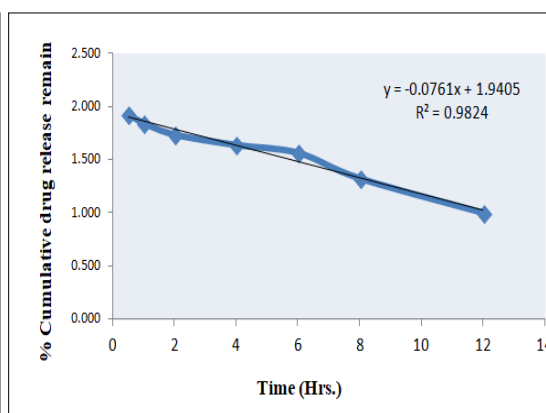
Figure 1: TEM image of optimized formulation F5

Table 4: *In vitro* drug release study of prepared SANS carriers F5

S. No.	Time (hr)	Root T	Log T	% Cumulative Drug Release	% Cumulative Drug Release Remain	Log % Cumulative Drug Remain to be Release	Log % Cumulative Drug Release
1	0.5	0.707	-0.301	15.65	84.35	1.926	1.926
2	1	1	0	29.98	70.02	1.845	1.845
3	2	1.414	0.301	45.56	54.44	1.736	1.736
4	4	2	0.602	56.65	43.35	1.637	1.637
5	6	2.449	0.778	63.32	36.68	1.564	1.564
6	8	2.828	0.903	78.85	21.15	1.325	1.325
7	12	3.464	1.079	89.98	10.02	1.001	1.001



(a)



(b)

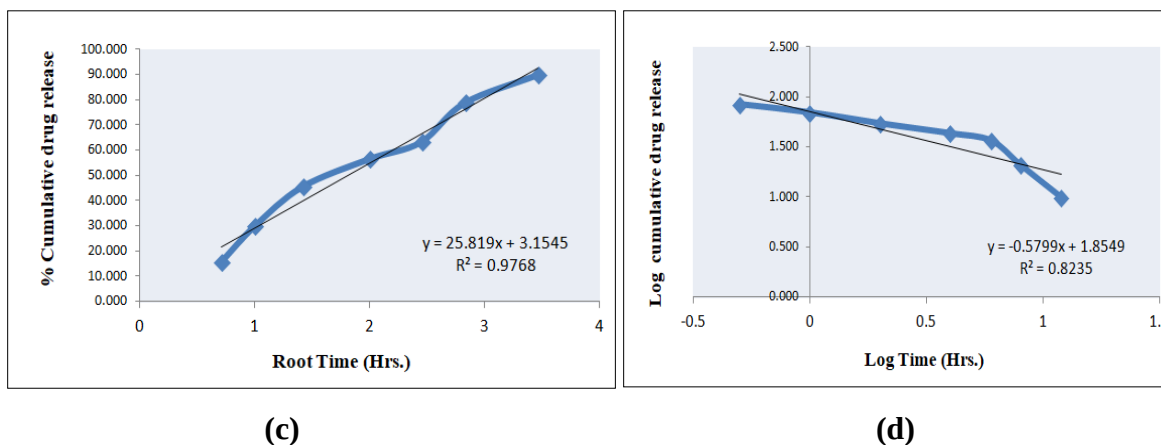


Figure 2: Release kinetics graphs of SANS carriers optimized formulation F5, a) Zero order, b) First order, c) Higuchi, d) Korsmeyer

Table 5: Release Kinetics of SANS carriers optimized formulation F5

Formulation	Zero order	First order	Higuchi	Korsmeyer
F5	0.941	0.892	0.991	0.990

Table 6: Stability Study of optimized formulation of SANS carriers formulation F5

Characteristic	Time (Month)					
	1 Month		2 Month		3 Month	
Temperature	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C	4.0 ±0. 2°C	25-28±2°C
Average vesicles size (nm)	122.32	125.45	125.65	136.69	129.98	150.32
% EE	73.32	69.98	71.12	68.85	70.32	62.32
Physical Appearance	Normal	Turbid	Normal	High turbid	Normal	High turbid

CONCLUSION

This study successfully demonstrated the potential of SANS carriers system for the topical delivery of benzoyl peroxide (BPO). Using hydroxyapatite as a ceramic core and various carbohydrate coatings, particularly dextran, the formulations achieved desirable physicochemical characteristics including optimal particle size, surface charge, and high entrapment efficiency. Among all, formulation F5 (1% dextran-coated SANS carriers) emerged as the most promising, exhibiting sustained drug release behavior that closely followed Higuchi and Korsmeyer–Peppas models, suggesting a diffusion-controlled mechanism. Furthermore, TEM analysis confirmed the nano-range and uniform morphology

of the particles, while stability studies emphasized the importance of low-temperature storage to maintain formulation integrity. These findings highlight SANs carriers as a viable and effective nanocarrier for enhancing the therapeutic performance, stability, and patient compliance of BPO in topical acne treatment. Future research can explore in-vivo efficacy, skin permeation studies, and clinical safety assessments to further validate the application of SANs carriers in dermatological formulations.

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