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Quality by design (Qbd) assisted formulation and development of nano-sponges gel containing hydroquinone and salicylic acid for topical delivery

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Abstract
The integration of Quality by Design (QbD) principles in the formulation and development of topical delivery systems represents a significant advancement in pharmaceutical sciences, particularly for enhancing the efficacy and safety of active ingredients. This study applies Quality by Design (QbD) principles to develop a nanosponges gel system incorporating Hydroquinone and Salicylic Acid for skin lightening and acne treatment. Nanosponges enhance drug stability, control release, and improve skin permeation. Using Design of Experiments (DoE), key formulation parameters such as polymer concentration, surfactant type, and drug load were optimized. The gel was tested for particle size, zeta potential, drug entrapment, and release profiles, with stability and efficacy assessed in real-world conditions. The QbD approach successfully produced a stable, efficient formulation, demonstrating its value in advancing topical drug development.

Keywords: Nanosponge, QbD, hydroquinone, salicylic acid, gel

Introduction

Quality by Design in formulation and development

In the area of pharmaceutical quality improvement, USFDA has recognized the need of stricter controls over manufacturing processes for consistent product quality and better regulatory decision making. An effective tool designed to achieve these objectives is Quality by Design (QbD). QbD is a systematic approach to formulation development so as to achieve robust process and consistent end product quality (Food, 2004) [1]. QbD was first described by famous quality professional Joseph M. Juran (Joseph *et al.,* 1998) [2]. Juran thought that quality could be planned, so that maximum quality crises and difficulties related to quality would reduce. His concept called "designed in" is used in QbD for optimization of process/product. According to ICH Q8 guideline, QbD is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (ICH Q8, 2009). As per the guidelines, a systematic approach to development should include a combination of prior knowledge, design of experiments (DOE), quality risk assessment and knowledge management (ICH Q10) all over the product lifecycle. The aim of implementation of QbD is to obtain more understanding of input parameters and formulation process to avoid future risk and get a product with predetermined quality. QbD is a method of choice in formulation development to get robust and quality product followed by continuous improvement. Ideally, developing a comprehensive template for designing controlled release formulations should help in solving the robustness issues generally related to controlled release formulations. QbD principles can be the possible answer to this constraint. QbD is widely used tool in formulation and development. It is particularly helpful in designing robust processes with well understood operational limits and their significance. Implementation of QbD is a complex and challenging work in pharmaceutical industry. Scientists have used QbD tools in development of various formulations such as tablet (Charoo *et al.,* 2012) [4], emulsion, nanosuspension, liposomes, pellet preparations, gastroretentive tablets, (Badawi *et al.,* 2014) [19] etc., and processes such as melt extrusion

(Verma *et al*., 2009) [5], direct compression, spay drying (Xu *et al.*, 2012) [6] etc., with the aim of robust design. QbD has been made mandatory for product development and filing with USFDA since January 2013. However, QbD principles are largely misunderstood (Kan *et al.*, 2014) [7].

Nanosponge

The development of a wide range of nanotechnology has begun to change the basis of disease diagnosis, treatment and prevention. Various nano-devices had a significant impact on medical technology, greatly improving the efficacy of many existing drugs and enabling the construction of brand-new treatment methods. Nanosponge is a new type of material with a cavity of a few nanometers in size, in which various substances can be encapsulated (Pandey *et al.*, 2019) [8]. These particles can carry lipophilic and hydrophilic substances and increase the solubility of poorly water-soluble molecules (Panda *et al.,* 2015) [9]. Nanosponge is a virus sized, naturally degradable scaffold like structure. The long polymer strands are mixed in solution with small molecules called cross-linking, which have affinity for certain parts of polymer (Kapileshwari *et al.,* 2020) [10].

Drug Release Mechanism of Nanosponges

Sponge atoms have an open arrangement and active materials can freely enter and exit the particles and enter the carrier until equilibrium is reached. In the case of topical administration, once the finished product is applied to the target tissue, the active substance already in the carrier will be absorbed into it, depleting the carrier that will become unsaturated, thus disturbing the balance. This will allow the active substance to flow from the sponge particles into the carrier and from it to the target tissue, until the carrier dries or is absorbed. Even after that, the sponge particles remaining on the surface of the tissue will continue to gradually release the active substance to the tissue, providing a prolonged release over time (Kapileshwari *et al.,* 2020) [10].

Material and Methods

Initially carbopol-934 was immersed in 50 mL of warm water (A) for 2 hr and was homogeneously dispersed using magnetic stirrer at 600 rpm. In separate container carboxymethyl cellulose and methyl paraben was added into 50 ml warm water (B) and stirred continuously to make stiff gel. Both the mixtures A and B were mixed with the continuous stirring. Then tri-ethanol amine (Drop wise) was added to neutralize the pH and nanosponges of optimized formulation were incorporated into the dispersion to obtained Gel. At this stage, permeation enhancer (Propylene glycol) was added. The final dispersion was agitated until smooth gel was formed without lumps (Abbas *et al*., 2019 and Silpa *et al*., 2021) [11, 12].

Composition of gel formulation (Table-1)

Table 1: Shows Composition of gel formulation

S. No	Excipients	Quantity (gm)
1.	Carbopol 934	1.00 gm
2.	Carboxymethyl cellulose	1.00 gm
3.	Propylene glycol	0.5 ml
4.	Methyl paraben	0.2 ml
5.	Nanosponges	1.0 gm
6.	Tri-ethanolamine	q.s
7.	Water	100 ml

Evaluation parameters of nanosponge

Zeta potential

The zeta potential was measured for the determination of the movement velocity of the particles in an electric field and the particle charge. In the present work, the nanosponges was diluted 10 times with distilled water and analyzed by Zetasizer Malvern instruments. All samples were sonicated for 5-10 minutes before zeta potential measurements (Kumar *et al*., 2018 and Penjuri *et al.*, 2016) [13, 14].

Particle size

The size of nanosponges was measured using Malvern Zeta sizer (Malvern Instruments). The dispersions were diluted with Millipore filtered water to an appropriate scattering intensity at 25 °C and sample was placed in disposable sizing cuvette. The size data is documented in Table 1 **(**Sharma and Pathak, 2011) [15].

Entrapment efficiency

% Entrapment efficiency was determined by indirect estimation. Drug -loaded nanosponges were centrifuged at 15,000 rpm for 30 min using REMI Ultra Centrifuge. The entrapped drug was determined in the supernatant solution using UV spectrophotometer. The peak area was determined and amount of free drug is determined by extrapolating the calibration curve. And drug entrapment calculated by using below equation (Swetha *et al.*, 2011, Solunke *et al*., 2019) [16, 17]. The entrapment efficiency data is documented in Table 1.

Entrapment efficiency % = Total drug conc. - Supernatant drug conc. / total drug conc.*100

Scanning Electron Microscopic (SEM)

The electron beam from a scanning electron microscope was used to attain the morphological features of the optimized Hydroquinone and salicylic acid loaded nanosponges were coated with a thin layer (2-20 nm) of metal(s) such as gold, palladium, or platinum using a sputter coater under vaccum. The pre-treated specimen was then bombarded with an electron beam and the interaction resulted in the formation of secondary electrons called auger electrons. From this interaction between the electron beam and the specimen's atoms, only the electrons scattered at 90° were selected and further processed based on Rutherford and Kramer's Law for acquiring the images of surface topography (Anwer *et al.*, 2019) [18].

Result and Discussion

Particle Size: The average particle size of the prepared drug loaded Nanosponges was measured using Malvern zeta sizer. Particle size analysis showed that the average particle size of drug loaded Nanosponges formulation was found to be 492.8 nm (Figure-1).

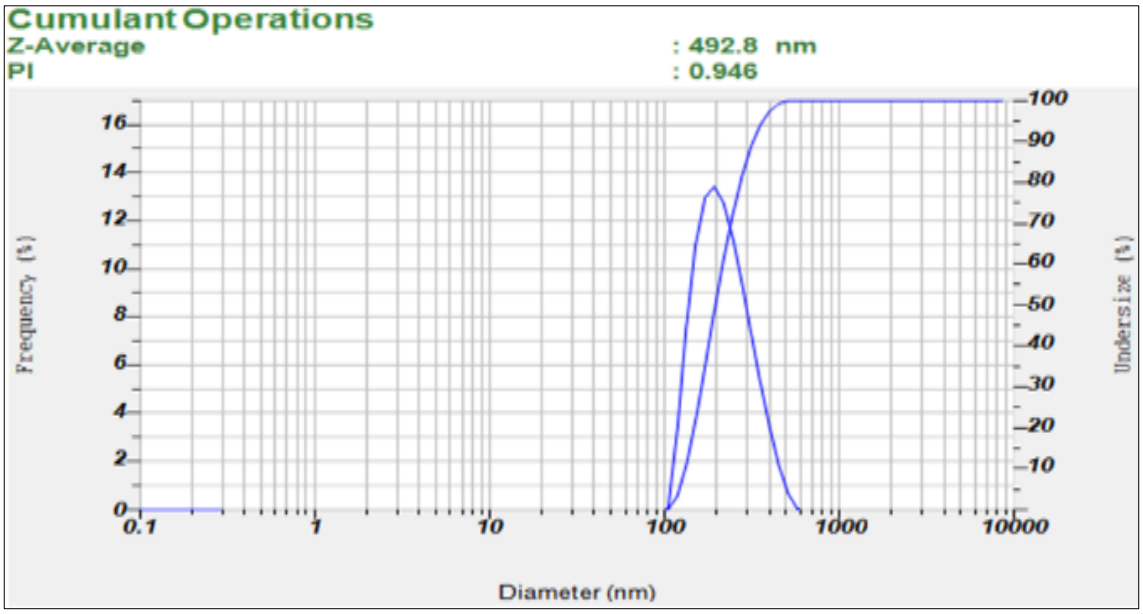

Fig 1: Shows Particle size of Nanosponges

Zeta potential: Zeta potential of Nanosponges formulation was found to be range - 54.4 Mv mV with peak area of 100% intensity. These values indicate that the formulated Nanosponges are stable (Figure-2).

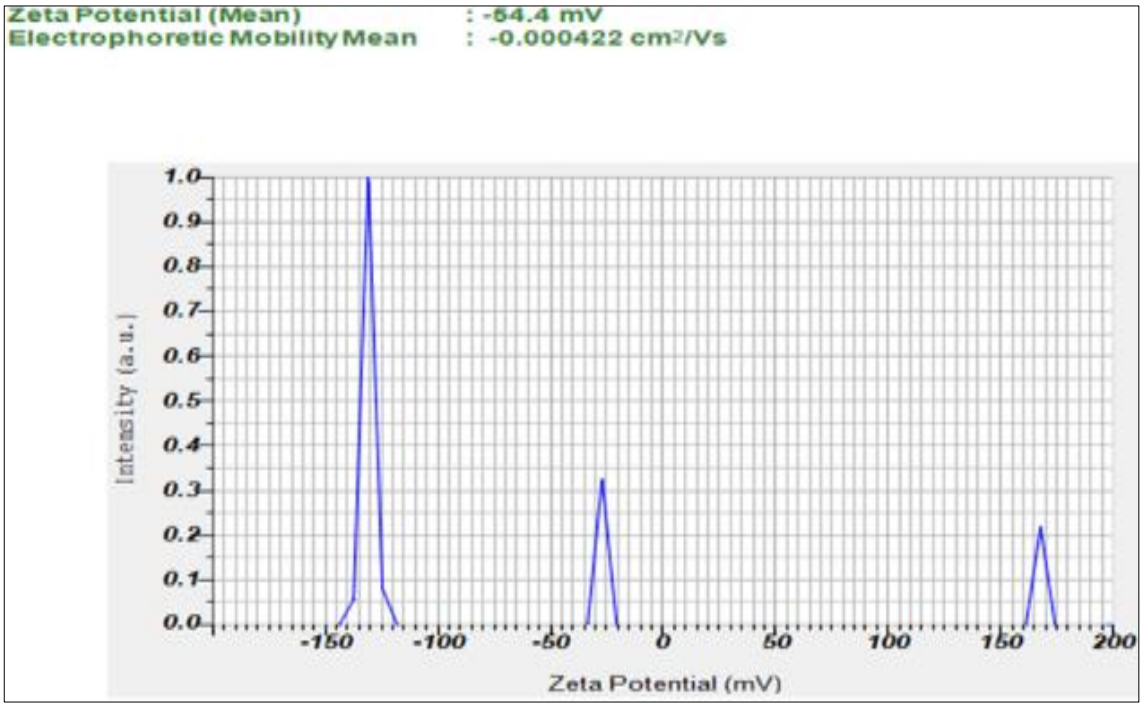

Fig 2: Shows Zeta potential of Nanosponges

Entrapment efficacy: The prepared Optimized nanosponges possess high drug entrapment efficiency and found to be in the range of 95.3% (Table-2).

Table 2: Shows Entrapment efficacy of Predicted Value and Actual Value.

S. No.	Formulations	Entrapment efficacy (Predicted value)	Entrapment efficacy (Actual value)
1.	Nanosponges	96.8%	95.3%

Scanning electron microscope (SEM): Scanning electron micrograph of the prepared Nanosponges at 27.99 kx magnification showed that the Nanosponges were porous with a smooth surface morphology and spherical shape. The spongy and porous nature of Nanosponges was clearly observed in the SEM images (Figure-3).

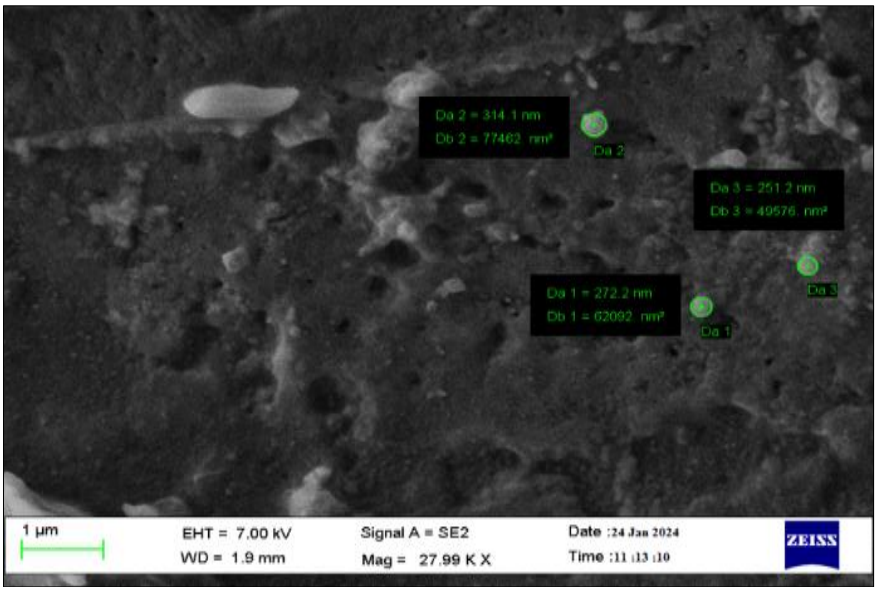

Fig 3: Shows Nanosponges observed by Scanning electron microscope

5. *In-vitro* drug release (Table-3)

Table 3: Depicts Release kinetics study of optimized formulation

Time (Hr)	cumulative % s drug released	% drug remaining	Square root time	log Cumu % drug remaining	Log time	Log cumulative %drug released
0	0	100	0.000	2.000	0.000	0.000
2	21.18	78.82	1.414	1.897	0.301	1.326
4	36.09	63.91	2.000	1.806	0.602	1.557
6	43.63	56.37	2.449	1.751	0.778	1.640
8	57.6	42.4	2.828	1.627	0.903	1.760
10	66.13	33.87	3.162	1.530	1.000	1.820
12	77.56	22.44	3.464	1.351	1.079	1.890
14	82.45	17.55	3.742	1.244	1.146	1.916
16	95.01	4.99	4.000	0.698	1.204	1.978

6. Correlation value Table-4

Table 4: Shows Correlation value (R^2 value)

Formulation	Model	Kinetic parameter values
Gel	Zero Order	$R^2 = 0.979$
	First Order	$R^2 = 0.886$
	Higuchi	$R^2 = 0.971$
	Korsmeyerpeppas	$R^2 = 0.820$

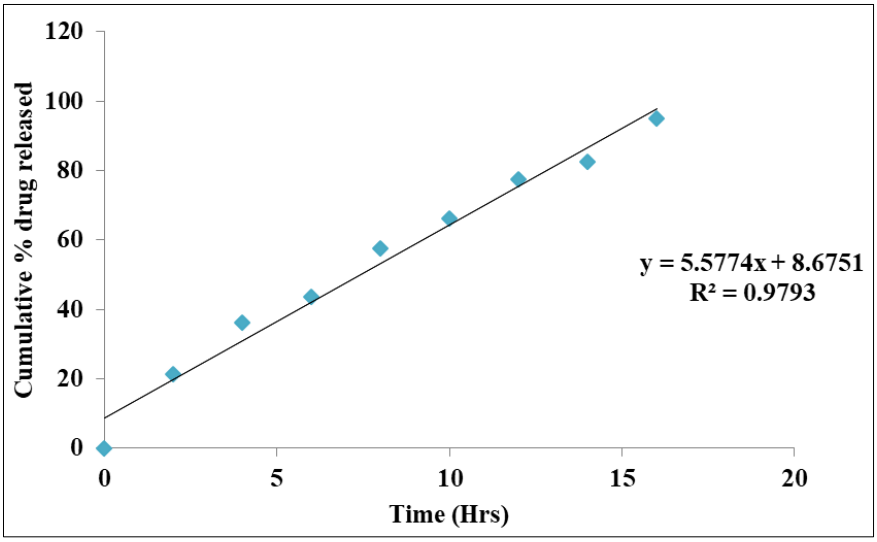

Fig 4: Zero order kinetic model

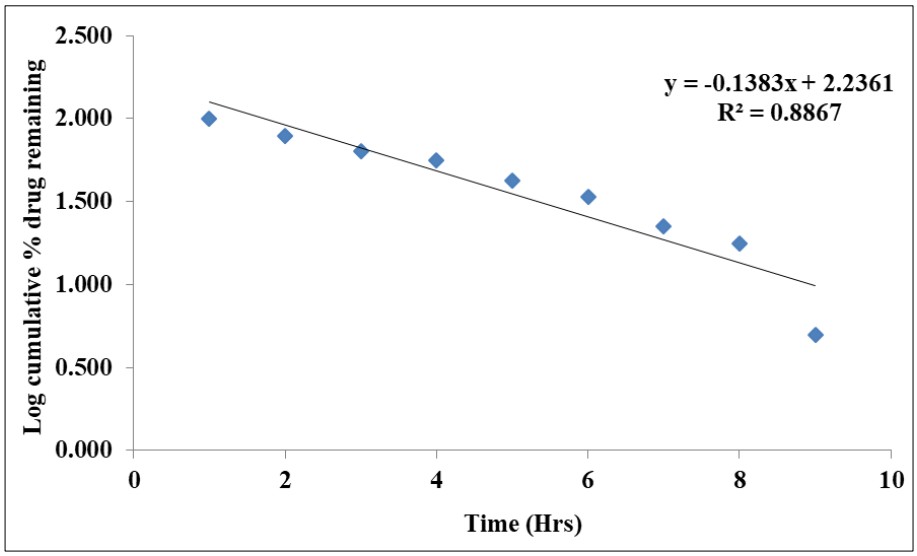

Fig 5: First Order Kinetic Model

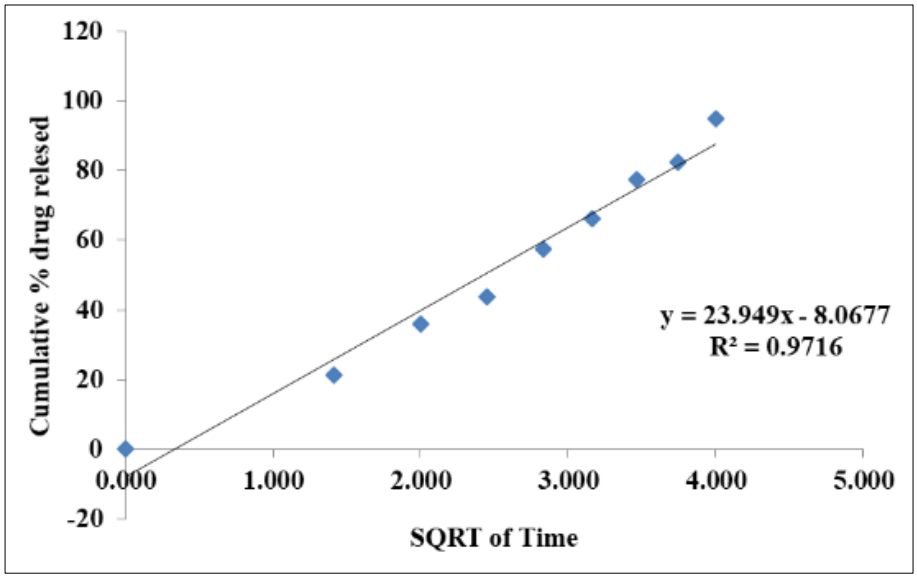

Fig 6: Higuchi model

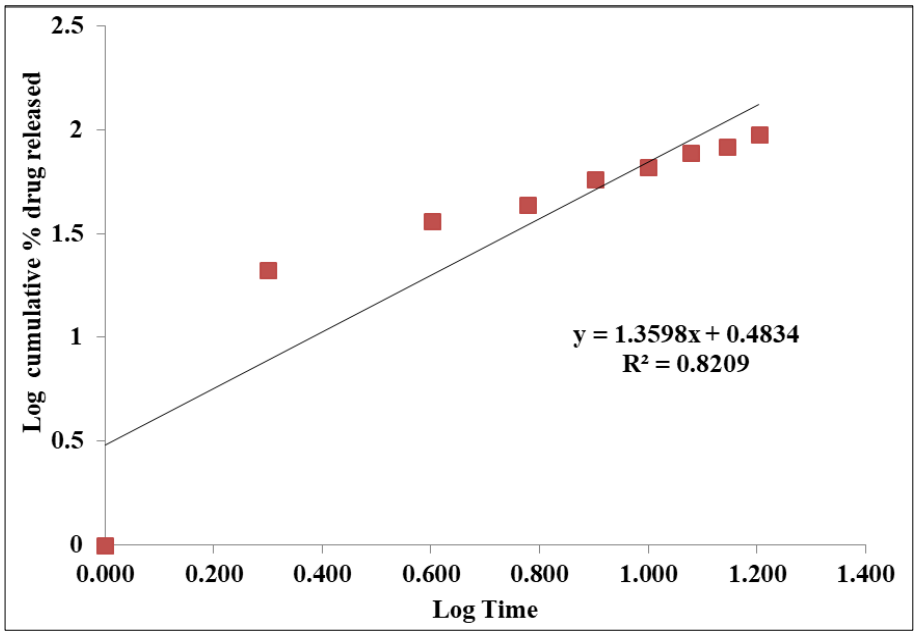

Fig 7: Korsmeyer peppas

Conclusion

This study successfully demonstrated the application of Quality by Design (QbD) principles in the formulation and development of a nanosponge-based gel containing Hydroquinone and Salicylic Acid for topical delivery. The systematic QbD approach allowed for the identification of critical material attributes (CMAs) and critical process parameters (CPPs), optimizing the formulation to achieve desired quality attributes.

The nanosponge gel exhibited improved stability, controlled drug release, and enhanced permeation, which are critical for effective topical treatment of hyperpigmentation and acne. The encapsulation of Hydroquinone and Salicylic Acid in nanosponges significantly mitigated their degradation and potential side effects, offering a more sustained and localized therapeutic effect.

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