Available online on 15.08.2019 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

DEVLOPMENT AND INVITRO EVALUATION OF NANOSUSPENSION GEL OF BENZOYL PEROXIDE

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A B S T R A C T

Novel drug delivery systems are designed with an intend to deliver drugs to the specific site at a rate and extent directed by the needs of the body and it directs an active entity to specific site of action during the period of treatment. Acne vulgaris is a common skin disease, affecting about 70-80% of adolescents and young adults. It is a multifactorial disease of the pilosebaceous unit. it has been developed as possible carriers to deliver antifungal drugs to the target site and to enhance an epidermal permeation across the skin.this article we present benzoyl peroxide can increase solubility and permeability of topical used.when benzoyl peroxide is very widely used in the mild to moderate acne vulgaris and rosacea.

KEYWORDS-Benzoyl peroxide, Surfactant, Drug release kinetic, Polymer, Nanosuspension gel

A R T I C L E I N F O: Received 18 April 2019; Review Completed 03 July 2019; Accepted 18 July 2019; Available online 15 August 2019

Cite this article as:

Ancheria R K *, Jain S, Kumar D, Soni S L, Sharma M, Devlopment and Invitro Evaluation of Nanosuspension Gel of Benzoyl Peroxide, Asian Journal of Pharmaceutical Research and Development. 2019; 7(4):49-55.

DOI: http://dx.doi.org/10.22270/ajprd.v7i4.515

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INTRODUCTION

Semi-solids establish a significant proportion of pharmaceutical dosage forms. They serve as transporters for drugs that are topically delivered by system of the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and external ear lining. Acne vulgaris is a common skin disease, affecting about 70-80% of adolescents and young adults.

It is a multi factorial disease of the pilosebaceous unit. The influence of androgens at the onset of adolescence leads to an enlargement of the sebaceous gland and a rise in sebum production[1].

Topical retinoid has been used in acne therapy since 1962. The first one was tretinoin, which remains in use today.

Novel drug delivery systems are designed with an intend to deliver drugs to the specific site at a rate and extent directed by the needs of the body and it directs an active entity to specific site of action during the period of treatment. It has been developed as possible carriers to deliver antifungal drugs to the target site and to enhance an epidermal permeation across the skin[2].

Gels

Gel is a colloidal system that is mainly 99%(w/v)liquid, which is restrained by the surfacetension, a gelation agent isused to form the consistency of the gel. Gel scan be used for the topical delivery through skin,rectal,vaginal and ophthalmic routes[1,2].

Nanosuspension

Nanosuspension is submicron colloidal dispersions of nanosized drug particles stabilized by surfactants. Nanosuspension consists of the poorly water-soluble drug without any matrix material suspended in dispersion. These can be used to enhance the solubility of drugs that are poorly soluble in water as well as lipid media. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster.

Advantages of Nanosuspension

- Enhance the solubility and bioavailability of drugs
- Suitable for hydrophilic drugs
- Higher drug loading can be achieved
- Dose reduction is possible
- Enhance the physical and chemical stability of

drugs
- Provides a passive drug targeting

Objective
- Quick onset of action
- Fast absorption of drug
- To improve bioavailability
- Providing ease of use for consumers

METHODOLOGY

Preformulation studies

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of Preformulation study is to investigate critical physiochemical factors which assure identity, purity and product performance and quality. These are various method used in Preformulation study Melting point determination, Development of calibrations curves of Benzoyl peroxide, Determination of absorbance maxima(λ_{max}), Partition coefficient, Solubility of drug, Drug and excipients compatibility studies[3].

Preparation of Nanosuspension

Nanosuspension was prepared by media milling technique, glass beads were used as milling media. In 20 ml glass vial, weighed quantities of glass beads were taken and 3 ml distilled water was added in this vial, surfactant and drug were incorporated and combination was carried out on magnetic stirrer for particular period of time. Batch volume, vessel size, magnetic bead size and stirring speed were kept constant[4].

RESULT AND DISCUSSION-

Melting point determination[5,6]-

Table 1: Melting Point of Benzoyl Peroxide

Observed melting point	Reported melting point
104.33°C±0.577°C	**105 °C**

Value is expressed as mean ± SD; n = 3

Discussion: The melting point of drug was found to be range104°C ± 0.75°C; hence drug sample was free from any type of impurities.

Partition coefficient of Benzoyl peroxide-

Table 2: Partition coefficient of Benzoyl peroxide

Observed log P	Reported log P	Inference
3.59±0.732	3.42	Reveals the lipophilic nature of drug

Value is expressed as mean ± SD; n = 3

Discussion: The partition coefficient of ***Benzoyl peroxide*** in n- Octanol: Water was found to be 3.59±0.732; this indicates that the drug is lipophilic in nature[7].

Solubility studies

Table 3: Solubility profile of Benzoyl peroxide

Solvent	Solubility (mg/ml)	Inference
pH 7.4	1.27±1.095	slightly soluble
Ethanol	35.232±0.429	Soluble
Distilled water	1.273±0.0143	slightly soluble
Diethyl ether	67.82±0.286	Soluble
DMSO	394.45±2.86	freely soluble
Chloroform	14.88±0.0429	sparingly soluble
Methanol	43.43±0.248	Soluble
DCM	67.57±0.286	Soluble
Acetone	47.14±0.248	Soluble

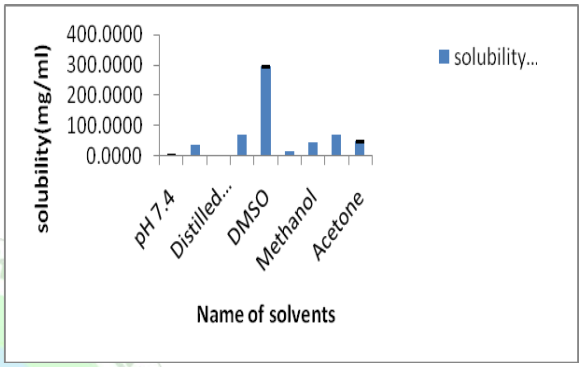

Figure 1: Solubility of Benzoyl peroxide in organic solvents

Drug and excipients compatibility studies

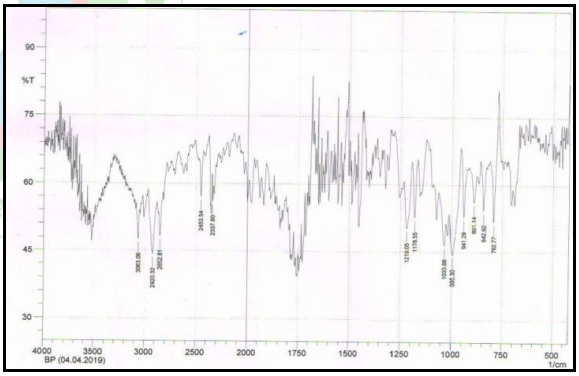

Figure 2: FT-IR spectrum of Benzoyl peroxide

Table 4: FT-IR interpretation data of Benzoyl peroxide

Functional group	Observed peak (cm^{-1})	Reference Peak (cm^{-1})
Aromatics (C-H)	792.77, 842.92, 891.14	900–675
Alkenes (=C–H bend)	941.29, 995.3	1000–650
aliphatic amines (C–N stretch)	1033.88, 1178.55, 1219.05	1250–1020
Aromatics(C-H)	3063.06	3100–3000

Discussion: The principal IR absorption peaks of Benzoyl peroxide at792.77, 842.92, 891.14cm^{-1} (C-H stretching) Aromatic, 941.29, 995.3cm^{-1} ((=C–H bend stretching) Alkenes, 1033.88, 1178.55, 1219.05cm^{-1} (C–N stretch)aliphatic amines , 3063.06 cm-1 (C-H) Aromatics

were all observed in the spectra of Benzoyl peroxide. These observed principal peaks. This observation confirmed the purity and authenticity of the Benzoyl peroxide[8,9].

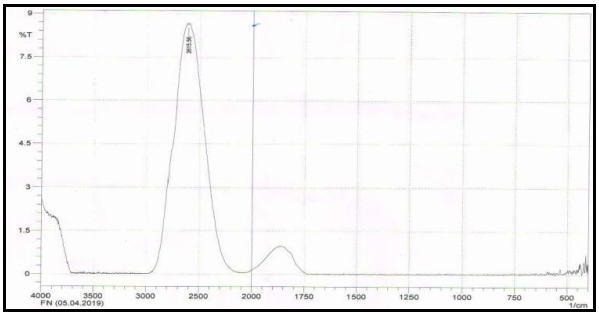

Figure 3: FT-IR spectrum of Physical Mixture (Benzoyl peroxide and Sodium dodecyl sulphate)

Table 5: Interpretation of FTIR of Physical Mixture

Functional group	Observed peak (cm^{-1})	Reference Peak (cm^{-1})
aliphatic amines (C–N stretch)	1076.32, 1251.84	1033.88, 1178.55, 1219.05
Aromatics (C–C stretch)	1450.52	1500–1400
Carboxylic acids (C=O stretch)	1693.56	1760–1690
Alkenes (–C=C– stretch)	1645.33	1680–1640
Carboxylic acids (C=O stretch)	1755.28, 1782.29	1760–1690
Aromatics (C-H)	3063.06	3063.06

Discussion: FTIR of physical mixture studies were carried out the eliminate the possibility of interaction between drug and excipients used analytical method of drug estimation .All the spectrum peaks revealed that corresponding peaks of drugs are present in the above spectra along with excipients peaks. Hence no interaction was observed in this mixture[10,11].

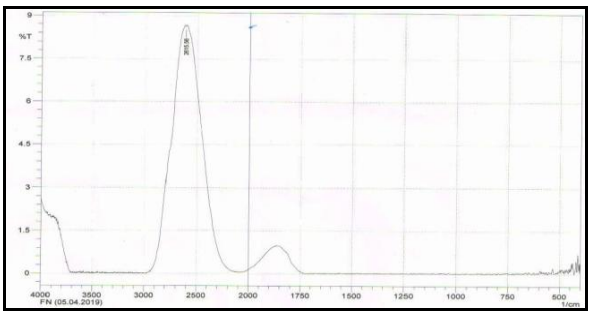

Figure 4: FT-IR spectrum of formulation

Table 6: Interpretation of FTIR of formulation

Functional group	Observed peak (cm^{-1})	Reference Peak (cm^{-1})
Carboxylic acids (O–H stretch)	2615.56	3300–2500

Discussion: FTIR of physical mixture studies were carried out the eliminate the possibility of interaction between in formulation. The spectrum peaks revealed that corresponding peaks of drugs are present in the above spectra along with excipients peaks. Hence, in the formulation we found that drug was entrapped[12,13].

OPTIMIZATION OF FORMULATION PARAMETERS

Table 7: Different compositions of benzoyl peroxide loaded Nanosuspension

Formulation code	Stabilizer	Time (hr)	Solubility(mg/ml)
F-1	Poloxamer 407	4	0.1464±0.000248
F-2	Poloxamer 407	8	15.467±0.2865
F-3	Poloxamer 188	4	11.166±0.2481
F-4	Poloxamer 188	8	2.4813±0.0429
F-5	Sodium alginate	4	0.0959±0.00286
F-6	Sodium alginate	8	18.196±0.28652
F-7	Polyvinyl alcohol	4	3.755±0.01432
F-8	Polyvinyl alcohol	8	4.604±0.929
F-9	SDS	4	22.084±0.85957
F-10	**SDS**	**8**	**35.235±0.42978**

Discussion: From the above data, it was found that the solubility increases was significant till 8hr to obtain desired (maximum) solubility in appropriate concentration of SDS stabilizer. Therefore, the final formulation of nanosuspension was optimized F-10 formulation. Above the study we observed amount of stabilizer increases, decreases the solubility of formulation, that's why we optimized the minimum concentration of stabilizer,therefore, considered for further studies[14].

Table 8: Optimization of concentration of drug

Formulation Code	Drug Concentration (%w/v)	Solubility(mg/ml)
D1	1	12.15±0.859
D2	**2.5**	**29.44±1.00**

Discussion: The optimized concentration of drug, it was found **29.44±1.00 mg/ml** maximum solubility in 2.5 % of drug concentration, and theses above the observation, we finalized the 2.5 % of drug concentration[15].

Table 9: Optimization of concentration of drug (beads)

Formulation Code	Concentration of beads (%w/v)	Solubility (mg/ml)
B1	80	14.64±0.859
B2	**100**	**32.83±0.286**
B3	120	22±1.00

Discussion: The optimization of bead concentration depend on the attrition, and above the data, it was found **32.83±0.286mg/ml** maximum attrition in **B2** formulation containing 100% concentration of beads[16,17,18].

Table 10: Final Optimization of all Formulation Parameters

Sr .No	Optimized formulation of Benzoyl peroxide Nanosuspension	
1	Type of surfactant	SDS
2	Ratio of beads	0.2-0.4mm
3	Concentration of drug	2.5% w/v
4	Concentration of beads	100% w/v
5	Concentration of SDS	0.2% w/v
6	Stirring time	8 hours

Characterization of Nanousupension

Optical microscopy

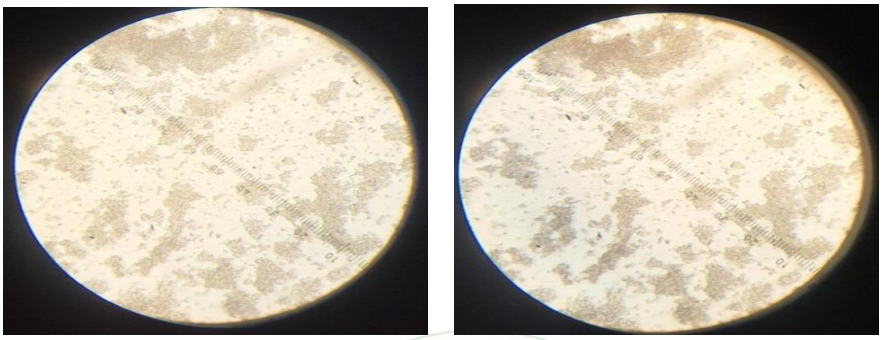

Figure 5: Optical microscopy of benzoyl peroxide loaded nanosuspensi

Particle Size -

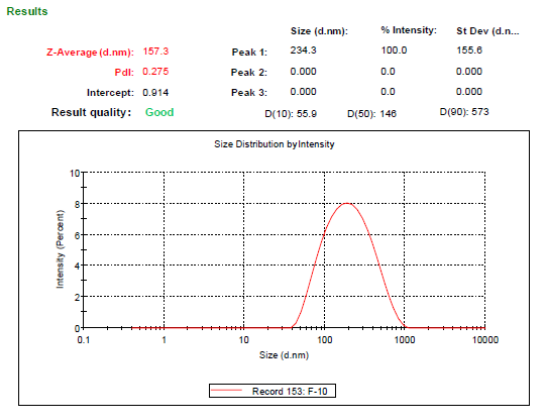

Figure 6: Particle size of benzoyl peroxide Loaded Nanosuspension

Zeta Potential-

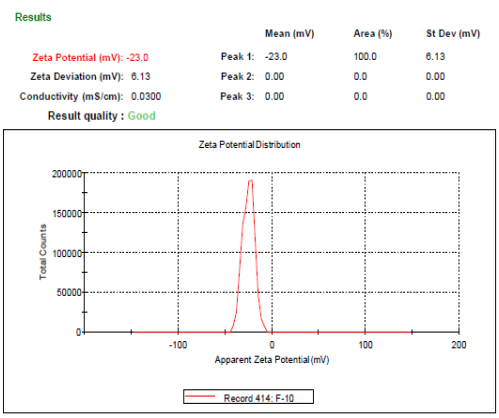

Figure 7: zeta potential of benzoyl peroxide

Discussion: The zeta potential of F-10. Formulation is -23.0± 4.75mV.From the results of zeta potential, it was found that formulation of Nanosuspension have a stable cationic and anionic concentration, thus it is actual for transdermal applications[19,20].

EVALUATION OF BENZOYL PEROXIDE LOADED NANOSUSPENSION GEL[21,22,23]

Appearance of Gel-

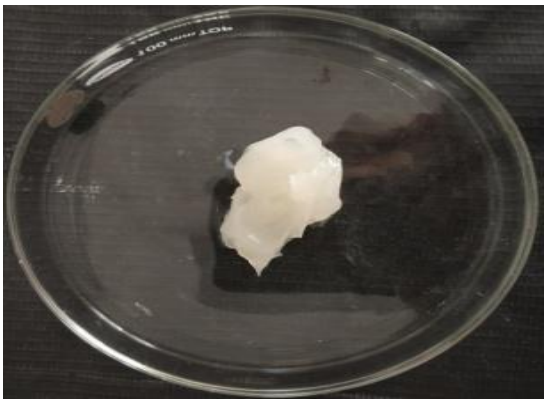

Figure 6: Appearance of gel

Table 8: Drug content of Benzoyl peroxide loaded Nanosuspensions gel-

S. No	Formulation code	% Drug content
1	F-1	85.06±0.1801
2	**F-2**	**96.61±0.36026**
3	F-3	89.55±3.0049
4	F-4	88.74±0.514

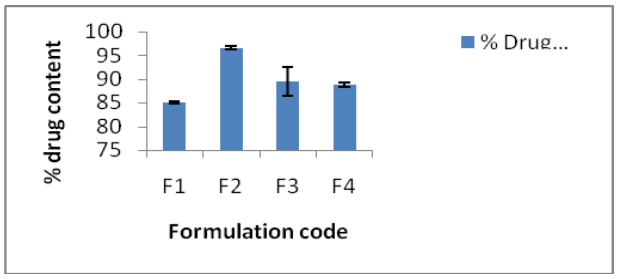

Figure 9: Drug content of Benzoyl peroxide loaded Nanosuspension gel

Discussion: The % Drug content of benzoyl peroxide loaded Nanosuspension gel was found to 96.61±0.36026% and,85.06±0.1801,respectively. The % Drug contentof all formulations was found to be satisfactory, so we further proceed with further more formulations, they shows good % Drug content. Hence, the method adopted for Nanosuspension formulations was found to be suitable[24,25].

In vitro Permeation study-

Table 12: % Drug Release of Nanosuspension gel formulation

Time (min)	% Drug Release F1	% Drug Release F2	% Drug Release F3	% Drug Release F4
1	3.57±0.023	3.57±0.023	3.57±0.0230	3.41±0.023
2	5.04±0.046	5.04±0.046	5.04±0.0461	4.89±0.0461
3	5.88±0.384	7.88±0.384	5.88±0.3846	5.88±0.384
4	7.29±0.065	8.29±0.065	7.29±0.0657	7.28±0.061
5	8.82±0.046	10.82±0.046	8.82±0.0461	8.80±0.030
6	10.51±0.046	19.51±0.046	10.51±0.0461	10.51±0.046
7	14.74±0.023	33.74±0.023	14.74±0.461	14.74±0.023
8	33.89±0.46	45.89±0.461	31.81±0.461	22.89±5.69
10	44.21±0.46	61.21±0.461	43.66±0.461	37.21±0.461
12	48.26±0.46	67.36±0.461	47.17±1.396	45.26±0.461
22	52.30±0.17	78.4±0.174	49.21±0.174	49.28±0.461
24	53.28±0.31	80.38±0.314	50.60±0.314	50.19±0.314

Discussion: It was found that in vitro skin permeation release of **F2** Formulation was best explained by the plot showed the highest linearity as compare to remaining formulations. The F2 formulation showed sustained release mechanism[26].

Based on in vitro permeation study results mentioned in table 7.20, optimized benzoyl peroxide nanosuspension gel showed around 80.38% drug release in 24 hr, whereas % release percentage from remaining benzoyl peroxide nanosuspension gel formulations were around 53.28%,50.60%, and 50.19%, respectively in 24hr.

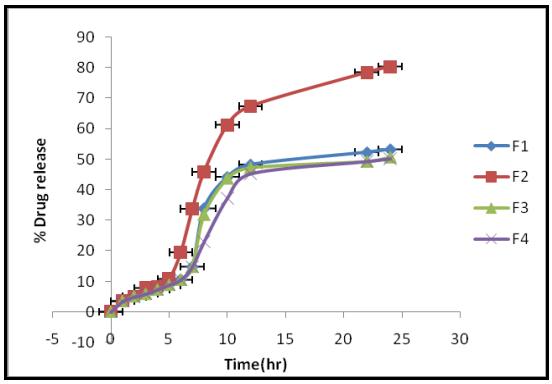

Figure 10: Spreadablity of Benzoyl peroxide loaded Nanosuspension gel formulation

Drug release Kinetic study [26, 27]

Zero Order Release

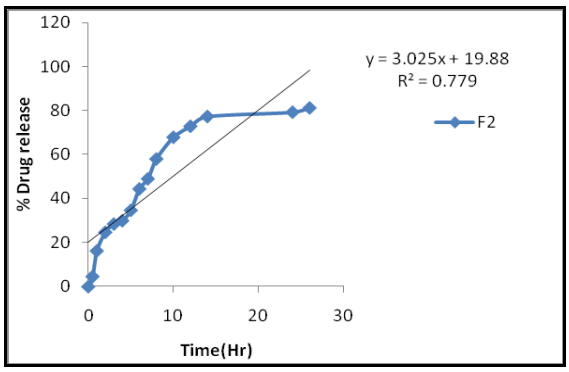

Figure 11: Zero order Drug Release of Formulation F2

First Order Release

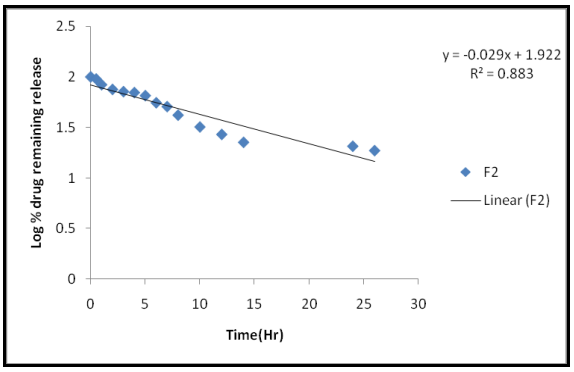

Figure 12: First orders Drug Release of Formulation F2

Higuchi Model Release

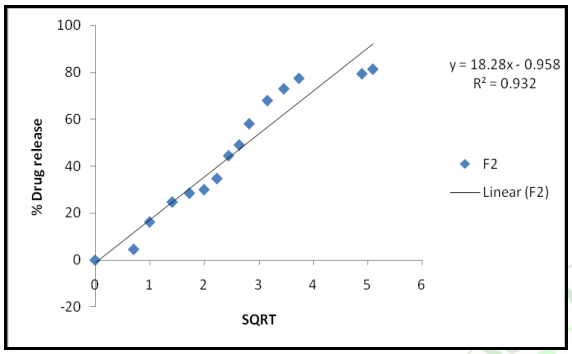

Figure 13: Higuchi model Drug Release of Formulation F2

Korsmeyer-Peppas model Release

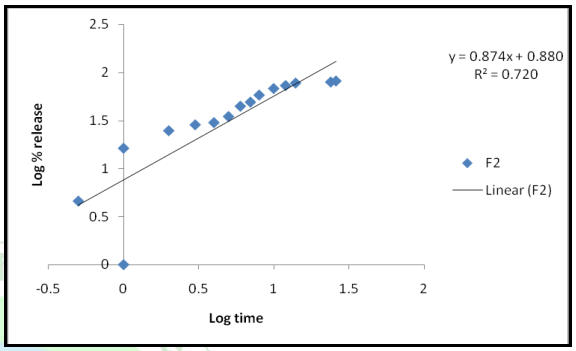

Figure 14: Korsmeyer-Peppas model Drug Release of Formulation F2

Table 13: Kinetic equation parameter of F2 Formulation

Formulation Name	Zero order		First order		Higuchi		Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
	0.779	3.02	0.883	-0.0293	0.932	18.28	0.7208	0.8744

Discussion: The *in vitro* drug release of Nanosuspension gel formulation F2 was best explained by, as Higuchi kinetics, the plots showed the highest linearity (R^2=0.932), followed by First order (R^2=0.883), and zero order (R^2=0.779), Korsmeyer-Peppas(R^2=0.7208), and suggesting that the diffusion plays an important role in the sustained release.

The data obtained for in vitro release shown in **13** were fitted into equation for the zero order, first order and higuchi and Korsmeyerpeppas release models. The interpretation of data was based on the value of the resulting regression coefficients.

The zero order rates described the system where the drug release independent of its concentration showed the percent drug release Vs time for zero order kinetics. The higuchi order rate described the release from systems where the release of drugs from a matrix as a square root of a time- dependent process based on Fickian diffusion[28,29].

The calculated regression coefficients for zero order, first order and higuchi models and Korsmeyer were shown in **Table 13**. It was found that in vitro drug release of F2 Formulation was best explained by higuchi model as the plot showed the highest linearity. The value of R^2 found to be highest for the higuchi model[30].

CONCLUSION:

The SEM micrographs revealed that F2 nanosuspension gel were formed with uniform nanosuspension particles. The nanosuspension gel had passed the formulation of gel with different carbopol concentration varies, and finalized on basis of drug content, viscosity, spreadibility and % drug release were found 86.61±0.36026, 131000±0.157735027, 3.83±0.01 and 80.38±0.314. It was found that the in vitro drug release of F2 was best explained by Higuichi as the plot showed the highest linearity. The value of R2 found to be 0.932 highest for the higuichi order.

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