DEVLOPMENT AND INVITRO EVALUATION OF NANOSUSPENSION GEL OF BENZOYL PEROXIDE

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ABSTRACT

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

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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.

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.

Gels

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

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($\lambda_{max}$), Partition coefficient, Solubility of drug, Drug and excipients compatibility studies.

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.

RESULT AND DISCUSSION-

Melting point determination

| Solvent   | Observed melting point | Reported melting point |
|-----------|------------------------|------------------------|
| pH 7.4    | 104.33±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-

| 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.

Discussion: FTIR of physical mixture studies were carried out to 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.

Table 5: Interpretation of FTIR of Physical Mixture

| Functional group                  | Observed peak (cm⁻¹) | Reference Peak (cm⁻¹) |
|-----------------------------------|----------------------|-----------------------|
| aliphatic amines                  | 1076.32, 1251.84     | 1033.88, 1178.55, 1219.05 |
| Aromatics                         | 1450.52              | 1500–1400             |
| Carboxylic acids                  | 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               |

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 to 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.

Table 7: Different compositions of benzoyl peroxide loaded Nanosuspension

| Formulation code | Stabilizer     | Time (hr) | Solubility (mg/ml) |
|------------------|----------------|-----------|--------------------|
| F-1              | Poloxamer 407  | 4         | 0.146±0.000248      |
| F-2              | Poloxamer 407  | 8         | 15.46±0.2865        |
| F-3              | Poloxamer 188  | 4         | 11.166±0.2481       |
| F-4              | Poloxamer 188  | 8         | 2.481±0.0429        |
| F-5              | Sodium alginate| 4         | 0.095±0.00286       |
| F-6              | Sodium alginate| 8         | 18.196±0.28652      |
| F-7              | Polyvinyl alcohol| 4    | 3.75±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.

Table 8: Optimization of concentration of drug

| Formulation Code | Drug Concentration (% w/w) | 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 these above the observation, we finalized the 2.5 % of drug concentration.
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                             | 224±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 beads16,17,18.

Characterization of Nanouspension

Optical microscopy

Table 10: Final Optimization of all Formulation Parameters

| Sr .No | Optimized formulation of Benzoyl peroxide Nanosuspension |
|--------|----------------------------------------------------------|
| 1      | Type of surfactant                                       |
| 2      | Ratio of beads                                           |
| 3      | Concentration of drug                                    |
| 4      | Concentration of beads                                   |
| 5      | Concentration of SDS                                     |
| 6      | Stirring time                                            |

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 applications19,20.

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

Appearance of Gel:

Figure 5: Optical microscopy of benzoyl peroxide loaded nanosuspension

Figure 6: Particle size of benzoyl peroxide

Figure 7: Zeta potential of benzoyl peroxide

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±0.0049    |
| 4     | F-4              | 88.74±0.514     |

Discussion: The % Drug content of benzyol peroxide loaded Nanosuspension gel was found to 96.61±0.36026% and 85.06±0.1801, respectively. The % Drug content of 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.

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±0.461      | 45.89±0.461      | 31.81±0.461      | 22.89±5.69       |
| 9          | 44.21±0.46       | 61.21±0.461      | 43.66±0.461      | 37.21±0.461      |
| 10         | 48.26±0.461      | 67.36±0.461      | 47.17±1.396      | 45.26±0.461      |
| 12         | 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.

Based on in vitro permeation study results mentioned in table 7.20, optimized benzyol peroxide nanosuspension gel showed around 80.38% drug release in 24 hr, whereas % release percentage from remaining benzyol peroxide nanosuspension gel formulations were around 53.28%,50.60%, and 50.19%, respectively in 24hr.
Drug release Kinetic study 26, 27

Zero Order Release

![Zero Order Release Graph](image1)

First Order Release

![First Order Release Graph](image2)

Higuchi Model Release

![Higuchi Model Release Graph](image3)

Korsmeyer-Peppas model Release

![Korsmeyer-Peppas Model Release Graph](image4)

**Figure 11:** Zero order Drug Release of Formulation F2

**Figure 12:** First order Drug Release of Formulation F2

**Figure 13:** Higuchi model Drug Release of Formulation F2

**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 |
|------------------|------------|-------------|---------|--------|
|                  | R² | kₐ | R² | kₐ | R² | kₐ |
| F2               | 0.779 | 3.02 | 0.883 | -0.0293 | 0.932 | 18.28 |
| Linear (F2)      | 0.874 | 0.7208 | 0.874 | 0.7208 | 0.874 |

**Discussion:** The in vitro drug release of Nanosuspension gel formulation F2 was best explained by, as Higuchi kinetics, the plots showed the highest linearity (R²=0.932), followed by First order (R²=0.883), and zero order (R²=0.779). Korsmeyer-Peppas(R²=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 Korsmeyer-peppas 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 R² 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 higuchi order.

**REFERENCE**

1. Atar M, Kausar A, Reheman A. Preparation of new formulation of anti-acne creams and their efficacy. Afr J Pharm Pharmacol. 2010; 4(6):298-303.

2. Rehman Zulfakar MH. Recent advances ingel technologies for topical and transdermal drug delivery. Drug Development and Industrial Pharmacy. 2014; 40(4):433–40.

3. Verma S, Burgess D. Solid Nanosuspensions: the emerging technology and pharmaceutical applications as nanomedicine, in: A.K. Kulshreshtha, O.N. Singh, G.M. Wall (Eds.), Pharmaceutical Suspensions: From Formulation Development to Manufacturing, Springer, New York. 2010; 285–318.
4. Kessiglou F, Panmai S, Wu Y. Nanosizing—oral formulation development and biopharmaceutical evaluation, Adv. Drug Delivery Rev. 2007; (59):631–644.

5. Nurkeeva, Zauresh S, Khutoryanskiy, Vitaliy V; Mun, Grigoryi A; Sherbakova, Marina V; Ivashchenko, Anatoly I; Atikhozhina, Nazira A. "Polycomplexes of poly (acrylic acid) with streptomycin sulfate and their antibacterial activity", European Journal of Pharmaceutics and Biopharmaceutics. 2004;57(2):245–9.

6. Giulia Bonaccucina, Sante Martelli, Giovanni F. Palmieri, “Rheological, mucoadhesive and release properties of Carbopol gels in hydrophilic cosolvents”International Journal of Pharmaceutics. 2004; 282: 115–130.

7. Ashford RD. Ashford’s Dictionary of Industrial Chemicals. London, England: Wavelength Publications Ltd. 1994; 119.

8. Nehal Daebis, Ossama Y Abdallah, Magda El-Massik, and Handym Abdellkader, Formulation and Characterization of Itraconazole Oral Nanosuspension: Methyl Cellulose as Promising Stabilizer, Elyns Journal of Pharmaceutical Research. 2015; 1:1-8.

9. Ankush Gupta, Sima Singh, Niranjan G Kotla, Thomas J Webster, Formulation and evaluation of a topical niosomal gel containing a combination of benzoyl peroxide and tretinoin for antiacne activity. International Journal of Nanomedicine. 2013;10.

10. Roya Yadollahi, KrasimirVasilev, Clive A. Prestidge, and SpomenkaSimovic, Polymeric Nanosuspensions for Enhanced Dissolution of Water Insoluble Drugs” Hindawi Publishing Corporation Journal of Nanomaterials. 2013;10

11. Keck CM, Muller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenization. Eur J Pharm Biopharm. 2006; (62):3-16.

12. Schwartz JS, Weissapir MR, Friedman DI. Enhanced Transdermal Delivery of Diazopen by Submicron Emulsion Creams. Pharm. Res. 1995; 12(5):687–692.

13. Couarraze G, Grossiord JL. Initiation a laRheologie; Lavoisier Delivery of Diazepan by Submicron Emulsion Creams. Pharm. Res. 2000; 178(1):137–141.

14. Sanchez J, Myers TN, Peroxides and Peroxide Compounds, Organic Peroxides. Kirk-OthmerEncyclopedia of Chemical Technology. New York, NY: John Wiley & Sons. Online Posting Date. 2000.

15. Bojar RA, Cunliffe WJ, Holland KT. The short-term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflora. Br J Dermatol. 1995; 132(2):204-8.

16. Yeung D, Nacht S, Bucks D, Maibach HI. Benzoyl peroxide: percutaneous penetration and metabolic disposition. II. Effect of concentration. J Am Acad Dermatol. 1983; 9(6):920-4.

17. Nacht S, Yeung D, Beasley JN Jr, Anjo MD, Maibach HI: Benzoyl peroxide: percutaneous penetration and metabolic disposition. J Am Acad Dermatol. 1981; 4(1):31-7.

18. Swauger JE, Dolan PM, Zweier JL, Kuppersamy P, Kensler TW: Role of the benzoyloxyl radical in DNA damage mediated by benzoyl peroxide. Chem Res Toxicol. 1991;4(2):223-8.

19. Hegemann L, Toso SM, Kitay K, Webster GF: Anti-inflammatory actions of benzoyl peroxide: effects on the generation of reactive oxygen species by leucocytes and the activity of protein kinase C and calmodulin. Br J Dermatol. 1994; 130(5):569-75.

20. Grau M, Guasch J, Montero JL., Felipe A, Carrasco E, Julia S. Pharmacology of the potent new nonsteroidal anti-inflammatory agent aceclofenac. Arzneimittelforschung.1991; 41 (12):1265-76.

21. Arul B, Sathyamurthy D. Formulation and evaluation of ketorolac tromethamnune gels. The Eastern Pharmacist. 1998; 135-6.

22. Chowdary KPR, Kumar PA. Formulation and evaluation of topical drug delivery systems of ciprofloxacin. Ind J Pharm Sci. 1996; 58(2):47-50.

23. Sanghavi NM, Mahalaxmi D. Determination in vitro release of clobetasol propionate from topical bases. Indian Drugs. 1993; 30(8):364-70.

24. Islam MT, Rodriguez-Hornedo N, Ciotti S, Ackermann C. Rheological characterization of topical carboner gels neutralized to different pH. Pharm Res. 2004; 21:1192-1199.

25. Devi US, Ganesan M, Mohanta GP, Manavalan R. Design and evaluation of tetracycline hydrochloride gels. Indian Drugs. 2004; 41(8):364-70.

26. Nokhodchi A, Nazemiyeh H, Ghafourian T, Hassan Zadeh D, Valizadeh H, Bahary LAS. The effect of glycerichin on the release rate and skin permeation of diclofenac sodium from topical formulations. IL Farmaco. 2002; 57:883-8.

27. Tas C, Ozkan Y, Savaser S, Baykara T. In vitro release studies of chlorpheniramine maleate from gels prepared by different cellulose derivatives. IL Farmaco. 2003; 58:605-11.

28. Grau M, Kayser O, Muller RH. Nanosuspensions of poorly soluble Drugs reproducibility of small-scale production. Int J Pharm. 2000; 196:155-160.