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Design, development and evaluation of solid dispersion incorporated transdermal gel of benzoyl peroxide

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Abstract
In recent years, the development of transdermal dosage form designed to have systemic effects has been attracting increasing attention, due to the several advantages that this administration route offers, such as a better control of blood levels, a reduced incidence of systemic toxicity, an absence of hepatic first-pass metabolism etc. Among the topical formulations, clear transparent gels have widely accepted in both cosmetics and pharmaceuticals. Gels have gained more and more importance because the gel-bases formulations are better percutaneously absorbed than creams and ointment bases. Most topical gels are prepared with organic polymers, such as carbomers, that impart an aesthetically pleasing, clear, sparkling appearance to the product, and are easily washed off the skin with water. In addition, many gels contain penetration enhancers, such as alcohol, in the formulation. Benzoyl Peroxide (BPO) is a first-line topical treatment in acne vulgaris. BPO is an old and established treatment agent with keratolytic and antibacterial action. The major drawback of BPO is its poor aqueous solubility. Solid dispersion is an effective technique which can easily enhance the dissolution rate of drugs. This technique involves one or more hydrophobic drugs in an inert hydrophilic carrier or hydrophilic matrix at solid state. Solid dispersion also helps to improve its skin irritation side effect. Solid dispersion of Benzoyl Peroxide using β-cyclodextrin, PEG 6000 as a carrier is prepared and evaluated for various parameters such as % practical yield, drug content, *In-vitro* diffusion study, measurement of pH, Viscosity study, Homogeneity.

Keywords: Benzoyl Peroxide (BPO), Acne vulgaris, Solid dispersion, Transdermal gel

Introduction
Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical drug delivery systems are capable of delivering drugs to the upper and deeper layer of skin and offer many advantages over oral dosage forms including by passing hepatic metabolism, avoiding gastric degradation and minimizing systemic side effects due to site specified drug delivery [1]. Among the topical formulations, clear transparent gels have widely accepted in both cosmetics and pharmaceuticals. Gels have gained more and more importance because the gel-bases formulations are better percutaneously absorbed than creams and ointment bases. Therefore, transdermal gel formulations of Benzoyl Peroxide were made with different polymers. Out of various semisolids dosage forms, the gels are becoming more popular due to ease of application and better percutaneous absorption then other semisolid preparations. Effectiveness of topical applications mainly depends upon its rate and extent of drug release from the base.

The percutaneous absorption of drugs involves two consecutive processes: the release of the drug from the topical formulation, and its absorption into the skin at the site of application. Increasing the release rate of the drug from the dosage form might therefore improve percutaneous absorption. The release rates of drugs from topical preparations depend directly on the physiochemical properties of the carrier and the drug employed [2]. Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting solvent method. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The solid dispersion, a first stated by Mayersohn and Gibaldi [3].

Solid dispersion can be prepared by fusion process, solvent process, melting solvent method, physical mixture, kneading method, supercritical fluid method. Solid dispersion is an effective technique which can easily enhance the dissolution rate of drugs [4]. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method. The technique has been used for a wide variety of poorly aqueous soluble drug. Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate [5].

Material and Methods

Formulation of solid dispersion prepared by kneading method

Inclusion complex by the kneading method was prepared by geometric mixing of the drug and polymer in molar ratio. Then the mixture was kneaded with 1ml of (the minimum amount of organic solvent possible) 1:1ml of Ethanol: Water to obtain a pasty mass, which is needed for a determined time and then dried in an oven 45 to 50 ˚C for 24 hours. The dried mass was pulverized and passed through sieve # 100 and stored in desiccators.

Table 1: Composition of Solid dispersion with different polymers

S. No.	Formulation code	Benzoyl Peroxide (mg)	β cyclodextrin (mg)	PEG 6000 (mg)
1	B1	20	100	-
2	B2	20	200	-
3	B3	20	300	-
4	B4	20	400	-
5	B5	20	500	-
6	P1	20	-	480
7	P2	20	-	960
8	P3	20	-	1440
9	P4	20	-	1920
10	P5	20	-	2400
11	F1	20	500	480
12	F2	20	500	960
13	F3	20	500	1440
14	F4	20	500	1920
15	F5	20	500	2400

Formulation of solid dispersion of optimized formulation

Inclusion complex by the kneading method was prepared by geometric mixing of the drug and polymer in molar ratio (40:1000:3840) then the mixture was kneaded with 1 ml of (the minimum amount of organic solvent possible) 1:1ml of ethanol: water to obtain a pasty mass, which is needed for a determined time and then dried in an oven 45 to 50˚C for 24 hrs. The dried mass was pulverized and passed through sieve # 100 and stored in desiccators.

Formulation of optimized solid dispersion incorporated transdermal gel of Benzoyl Peroxide

Carbopol 0.25%, 0.50%, 0.75%, 1% was added to purified water with stirring. Stirring of mixture was done for 40 min. Then sodium hydroxide dissolved in water was added to mixture and stirred for 10 min. Add 10% propylene glycol to all the above compositions of carbopol gel and 5% add DMSO in 0.75%, 0.1%. The mixtures were stirred for 30 minutes till elegant and smooth gel was obtained. Solid dispersion of Benzoyl Peroxide was dissolved in ethanol and added to above mixture and stirred for 15 minutes. Prepared gel was store in a suitable container.

Table 2: Composition of optimized solid dispersion (F4) incorporated transdermal gel

S. No.	Ingredients	G1	G2	G3	G4	G5	G6
1	Solid Dispersion of BPO (mg)	58.5	58.5	58.5	58.5	58.5	58.5
2	Carbopol (mg)	35 (0.25%)	105 (0.75%)	70 (0.50%)	140 (1%)	105 (0.75%)	140 (1%)
3	Propylene Glycol (ml)	1.4 (10%)	1.4 (10%)	1.4 (10%)	1.4 (10%)	1.4 (10%)	1.4 (10%)
4	DMSO (ml)	-	-	-	-	0.7 (5%)	0.7 (5%)
5	Water (ml)	14	14	14	14	14	14

Results and Discussion

Physical Characterization of Benzoyl Peroxide

The organoleptic studies of drug like general appearance like nature, color, odor etc. were performed by visual observations. Benzoyl Peroxide was observed as white, odorless, amorphous powder.

Identification of Benzoyl Peroxide

FT-IR Spectroscopy: The infrared spectrum of Benzoyl Peroxide (Figure-1) confirms the presence of the relevant functional groups (as the important peaks are listed in Table-3.

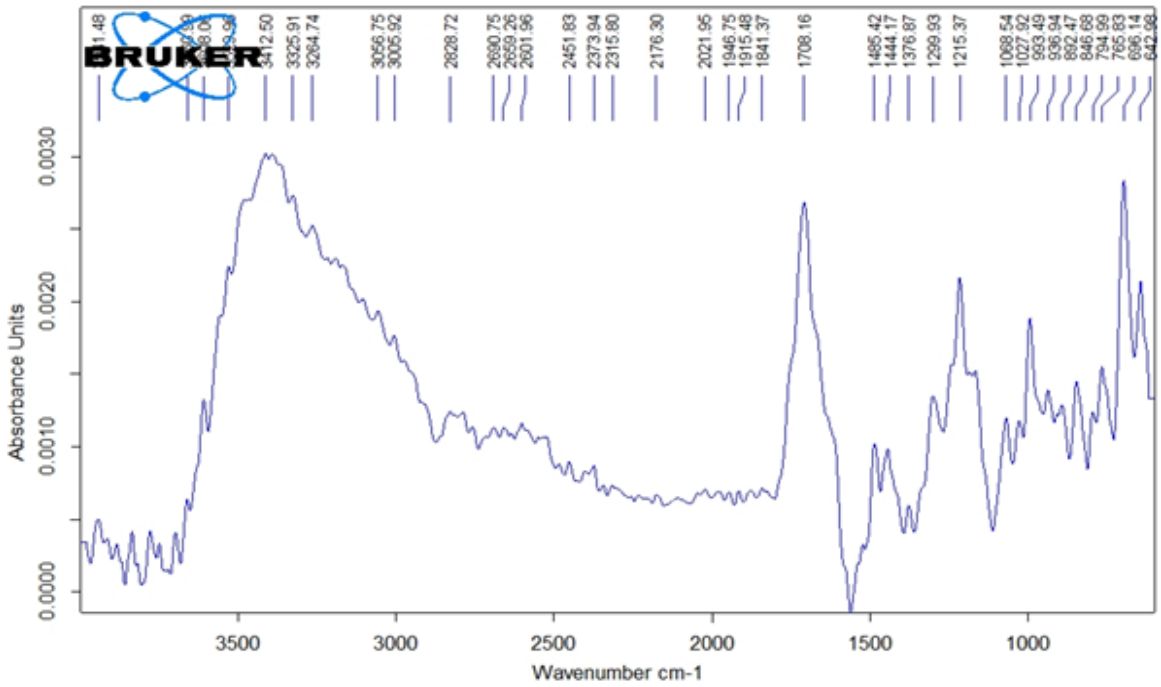

Fig 1: FT-IR spectrum of Benzoyl Peroxide

Table 3: Interpretation of FT-IR spectra of pure Benzoyl Peroxide

Infrared Spectrum Data IR Absorption Band (cm^{-1}) Experimental	Infrared Spectrum data IR absorption band (cm^{-1}) Literature	Functional group
3264	3200	C=H stretching
1708	1665-1700	C=O stretching
1444	1400	Aromatic Stretching
606	580-600	Ortho substituted ring

UV Visible Spectroscopy

The absorption maximum (λ_{max}) was found at 274 nm.

Melting point

Melting point of Benzoyl Peroxide was found to be between105 ± 1 °C.

Partition Coefficient

The partition coefficient of Benzoyl Peroxide was determined using n- octanol/water system by shake flask method and was found to be 3.2 ± 0.2.

Drug- Excipients Compatibility study

Table 4: Compatibility study of Benzoyl Peroxide with excipients used

Drug : Excipients (1:1 Ratio)	At Temperature 25 ˚C	At Temperature 40 ˚C
Benzoyl Peroxide+ β-cyclodextrin	NC	NC
Benzoyl Peroxide + PEG 6000	NC	NC

NC = No change observed

Characterization of Solid Dispersion

Table 5: Drug content of Benzoyl Peroxide: β-cyclodextrin Solid dispersion

S. No.	Formulation code	Absorbance	% Drug content (Mean ± S.D.)
1	B1	0.076	33.5±0.02
2	B2	0.481	23.6±0.04
3	B3	0.652	32.15±0.06
4	B4	0.868	42.95±0.08
5	B5	0.252	60.75±0.09

Table 6: Drug content of Benzoyl Peroxide: PEG 6000 solid dispersion

S. No.	Formulation code	Absorbance	% Drug content (Mean ± S.D.)
1	P1	0.366	3.57±0.02
2	P2	0.477	23.4±0.04
3	P3	0.135	31.5±0.06
4	P4	0.596	29.35±0.08
5	P5	0.437	21.35±0.05

Table 7: Drug content of Benzoyl Peroxide: β–cyclodextrin and PEG 6000 Solid dispersion

S. No.	Formulation code	Absorbance	% Drug content (Mean±S.D.)
1	F1	0.205	39.2±0.02
2	F2	0.159	30±0.04
3	F3	0.212	40.6±0.06
4	F4	0.367	71.6±0.08
5	F5	0.299	58±0.05

Result shows that the drug content of different batches of solid dispersions shown in graphs. The kneading method of preparing solid dispersions using β-cyclodextrin and PEG 6000 as a carrier was found to be satisfactory as it produced good product with high drug content. Out of the 15 formulations prepared formulation F4 showed marked increase in the solubility as well as the dissolution. The solid dispersion prepared by Kneading method showed improved dissolution. It is indicated β-cyclodextrin plays the role as dissolution rate promoter due to its ability to solubilize compounds via stabilization of supersaturated drug solutions presumably by inhibition of nucleation and arresting crystal growth. Lack of crystallinity, i.e. amorphization, increased wettability, dispersibility and particle size reduction are considered to be important factors for dissolution rate enhancement. Because of greater % drug content of solid dispersion prepared with 1:5:4 (F4) drug carrier ratios was selected as an ideal batch for incorporation into gels.

Characterization of optimized Solid Dispersion

Table 8: Drug content of optimized Solid dispersion

Optimized formulation	Absorbance	% Drug Content (Mean±S.D.)
F4	0.367	71.6±0.08

Determination of Percent Practical Yield (PY)

Practical yield = 3.510 gm

Theoretical yield =4.88 gm

% Practical yield = (Weight of Practical solid dispersions × 100)/ Theoretical weight (Benzoyl Peroxide + β-cyclodextrin + PEG 6000)

= (3.510x100)/ 4.88 = 71.92%

% Practical yield is 71.92

XRD of optimized solid dispersion of Benzoyl Peroxide

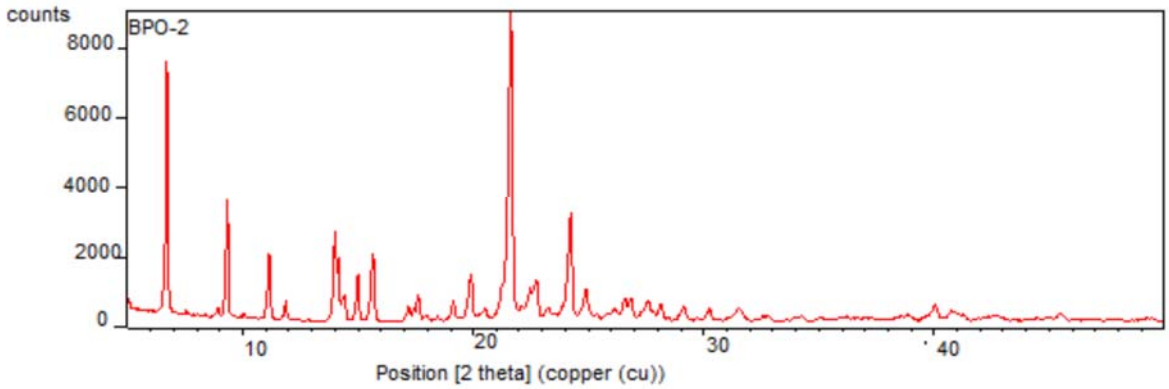

Fig 2: XRD Study of optimized solid dispersion of Benzoyl Peroxide

Powder x-ray diffraction analysis was performed for solid dispersion of Benzoyl Peroxide the X-Ray diffraction patterns were shown in Figure-2. The ternary systems of all the formulations with β-CD showed some diffraction 2θ peaks with little intensity, which is attributed to a crystalline nature of β-CD. Modified and hollow pattern suggesting the formation of amorphous inclusion complex of drug with and β-CD and PEG 6000.

Characterisation of optimised solid dispersion incorporated transdermal gel

Measurement of pH: The pH of various gel formulations was determined by using digital pH meter as follows:

Table 9: Measurement of pH

S. NO.	BATCH	pH
1	G1	6.4
2	G2	6.3
3	G3	6.9
4	G4	6.5
5	G5	7.2
6	G6	6.8

Results shows that G5 solid dispersion incorporated trandermal gel has more pH than all of the above which matches with the pH of the skin.

Table 10: Drug content of optimized solid dispersion incorporated transdermal gel of Benzoyl Peroxide

S. No.	Batch	Absorbance	%Drug Content
1	G1	0.169	80 ± 0.02
2	G2	0.145	68 ± 0.04
3	G3	0.152	71.5 ± 0.06
4	G4	0.178	84.5 ± 0.08
5	G5	0.189	90 ± 0.05
6	G6	0.175	83 ± 0.03

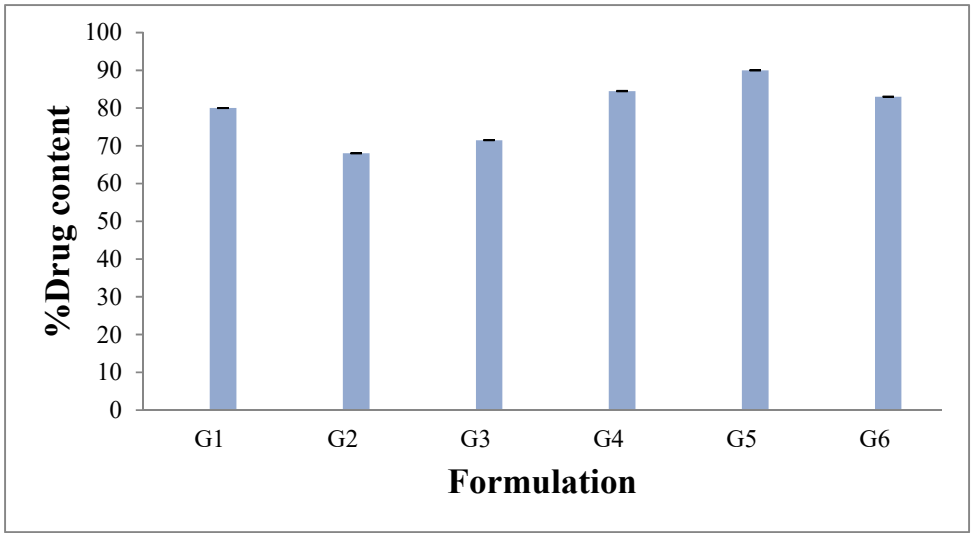

Fig 3: Drug content of optimized solid dispersion incorporated transdermal gel

Determination of Viscosity

The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. Viscosity of optimized solid dispersion incorporated as shown in Table-11.

Table 11: Determination of Viscosity

S.NO.	Batch	RPM	Torque	Spindle	Viscosity (Cp)
1	G1	10	60%	S-62	1015
2	G2	10	80.2%	S-62	2402
3	G3	10	82.1%	S-62	1230
4	G4	10	84.7%	S-62	2630
5	G5	10	72.2%	S-62	2166
6	G6	10	68.2%	S-62	2046

Results shows that G5 has higher viscosity, higher the conc. of gel higher the viscosity

Homogeneity

Table 12: Homogeneity of optimized solid dispersion transdermal gel

S. No.	Batch	Homogeneity
1	G1	Good
2	G2	Good
3	G3	Good
4	G4	Good
5	G5	Good
6	G6	Good

***In -vitro* diffusion study**

In-vitro drug release study was performed by Franz diffusion cell method using phosphate buffer (pH 7.4) as dissolution media. Drug release profile and a comparison of its release profile with pure drug as shown in Figure-4.

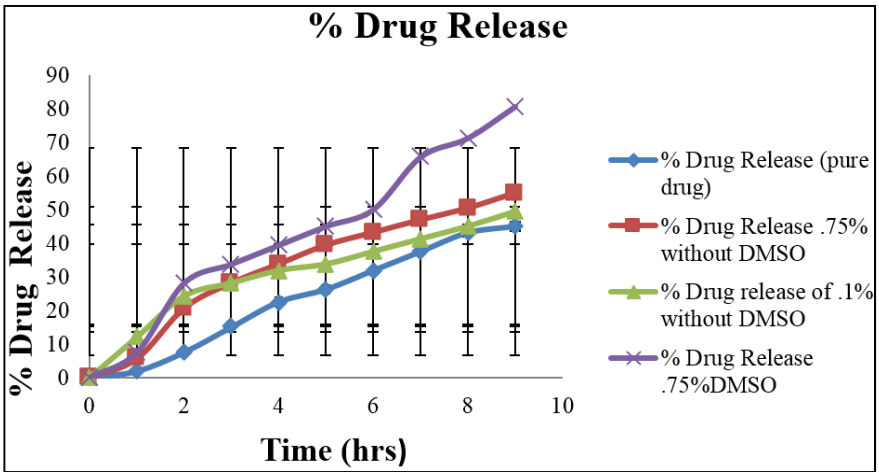

Fig 4: *In-Vitro* Drug release study

Table 13: % Drug release of optimized solid dispersion incorporated transdermal gel of Benzoyl Peroxide

S. No.	Time (hrs)	% Drug Release (Mean ± S.D.)			
		Pure Benzoyl Peroxide	G3	G5	G6
1	0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
2	1	1.875±0.02	5.625±0.02	12± 0.02	7.5± 0.02
3	2	7.5±0.04	20.625±0.03	22.25±0.03	28.125±0.03
4	3	15±0.06	28.125±0.05	28.125±0.05	33.75±0.05
5	4	22.5±0.08	33.75± 0.08	31.75±0.08	39.375±0.08
6	5	26.25±0.07	39.375±0.06	33.75±0.06	45± 0.06
7	6	31.875±0.05	43.125±0.04	37.5±0.04	50±0.04
8	7	37.5±0.03	46.875±0.07	41.25±0.07	65.625± 0.07
9	8	43.125±0.01	50.375±0.09	45±0.09	71.25 ±0.09
10	9	45±0.09	54.875±0.12	49±0.12	80.625± 0.12

Results shows that 0.75% Solid dispersion incorporated Transdermal gel of Benzoyl Peroxide containing DMSO as a permeation enhancer shows much higher % Drug Release as compared with the pure drug. The increased drug release of formulation G5 (0.75% optimized solid dispersion incorporated trandermal gel containing DMSO) *in vitro* release may be due to decreased viscosity of the gel.

Conclusion

In the present work, solid dispersion of Benzoyl Peroxide was prepared in β-cyclodextrin, PEG 6000 by kneading method and were characterized for Drug Content. β-Cyclodextrin plays the role as dissolution rate promoter due to its ability to solubilize compounds via stabilization of supersaturated drug solutions presumably by inhibition of nucleation and arresting crystal growth. PEG was found to be the most suitable auxiliary substance in terms of superior complexation efficiency and stability constant. Higher stability constant values in the presence of PEG suggest a significant improvement in the complexation efficiency between Benzoyl Peroxide and β-cyclodextrin. Out of the fifteen formulations, F4 showed marked increase in the solubility as well as the dissolution. The solid dispersion prepared by Kneading method showed improved dissolution. It is indicated β-cyclodextrin plays the role as dissolution rate promoter due to its ability to solubilize compounds via stabilization of supersaturated drug solutions presumably by inhibition of nucleation and arresting crystal growth. Then solid dispersion of Benzoyl Peroxide was incorporated into the different concentrations of Carbopol. Solid dispersion incorporated gel was formulated and further, characterized for *In-vitro* Drug Release and Drug Content. Out of which optimized gel showed the best *in-vitro* drug release having better dissolution, permeation and stability used for the treatment of Acne. Formulation G5 (0.75% Solid dispersion incorporated transdermal gel of Benzoyl Peroxide containing DMSO) as a permeation enhancer shows much higher % Drug Release as compared with the pure drug. The increased drug release of formulation G5 (0.75% Solid dispersion incorporated transdermal gel of Benzoyl Peroxide containing DMSO) *in-vitro* release may be due to decreased viscosity of the gel.

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