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# SYNTHESIS OF DIETHYL PHTHALATE AND ITS APPLICATION IN CREAMS AND OINTMENTS

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## ABSTRACT

Diethyl phthalate (DEP) was synthesized using phthalic anhydride, absolute ethanol and p-toluene sulphonic acid as a catalyst. DEP was evaluated as per B.P. procedures. Purity of DEP was determined by Gas Chromatographic method. This DEP was used in different concentrations like 1, 3, 5, 10 % to prepare creams and ointments. Creams and ointments were evaluated for pH, homogeneity, content of uniformity, spreadability, and consistency. Effect of DEP on drug release from creams and ointments was studied by drug diffusion test apparatus. Drug release and spreadability of creams and ointments was found to be increase with increase in the concentration of DEP. Drug release from marketed preparations of creams and ointments were found to be comparable with batches of creams and ointments which were prepared using 5% of DEP. Results showed that DEP in 5% concentration can be suitably employed to prepare creams and ointments.

## INTRODUCTION

Diethyl phthalate (C.A.S. 84-66-2) is a, colorless, oily liquid with a slight aromatic odor and a bitter taste. It is commonly used to make plastics more flexible, in products such as toothbrushes, automobile parts, tools, toys, and food packaging. It is also used in insecticides, mosquito repellents, aspirin, and cosmetics, including bath preparations, eye shadows, hair sprays, wave sets, nail polish, nail polish remover, nail extenders, detergents, aftershave lotions, and skin care preparations. [1] Creams are semisolid emulsions for external application. Oil in water emulsion is most useful as water washable bases whereas water in oil emulsion is emollient and cleansing. Oil in water creams rub into skin; the continuous phase evaporates and increases concentration of a water-soluble drug in the adhering film. Ointments are greasy, semisolid preparations, often anhydrous and containing dissolved or dispersed medicaments.

## MATERIAL AND METHODS

### 1. Procedure for synthesis of DEP

Phthalic anhydride and absolute ethanol were used to synthesize diethyl phthalate. Weighed quantity of phthalic anhydride was added to four necked round bottom flask (RBF). Quantity of catalyst of 1% p- toluene sulphonic acid with 30% of required quantity of ethanol was added to RBF. Temperature of reaction mixture was maintained at $130^0$C. Dropping funnel containing fresh ethanol was kept in second neck of RBF. Condenser was attached to third neck of RBF. Receiver flask was attached to condenser with receiver tube. Rate of ethanol addition was matched with rate of condensation of ethanol-water mixture. Reaction was continued till the acidity of mixture remained 3-4%. Reaction mixture was neutralized with sodium carbonate. Acidity was determined by acid-base titration using phenolphthalein as an indicator. Batches were prepared using different catalyst.

### 2. Evaluation of DEP

Percent acidity, density, refractive index, ester content was determined as per B.P. procedures. Purity was determined by gas chromatography. Skin irritation was studied on hairless mice skin. Drug (Diclofenac sodium) and DEP compatibility was studied by FTIR. [2]

### 3. Formulation of ointments

Four batches of ointments were prepared by fusion method with different percentages of DEP like 1, 3, 5 and 10.The composition of ointments is as shown in Table 1.

**Table 1:** Ingredients and their quantities used for preparation of ointments

| **Ingredients** | **OD 1 (%)** | **OD 2 (%)** | **OD 3 (%)** | **OD 4 (%)** |
|---|---|---|---|---|
| Diclofenac sodium | 03 | 03 | 03 | 03 |
| Wool fat | 05 | 05 | 05 | 05 |
| Hard Paraffin | 05 | 05 | 05 | 05 |
| Cetostearyl alcohol | 05 | 05 | 05 | 05 |
| White soft paraffin | 76 | 74 | 72 | 70 |
| Diethyl phthalate | 01 | 03 | 05 | 10 |
| Castor oil | 05 | 05 | 05 | 05 |
| Perfume | q.s. | q.s. | q.s. | q.s. |

**4.**

**Formulation of creams**

Four batches of creams were prepared with different percentages of DEP like 1, 3, 5 and 10.

The composition of creams is as shown in Table 2.

**Table 2**: Ingredients and their quantities used for preparation of creams

| **Ingredients** | **CD 1 (%)** | **CD 2 (%)** | **CD 3 (%)** | **CD 4 (%)** |
|---|---|---|---|---|
| Stearic acid | 07.00 | 07.00 | 07.00 | 07.00 |
| Cetostearyl alcohol | 10.00 | 10.00 | 9.00 | 9.00 |
| White bees wax | 02.50 | 02.50 | 02.50 | 02.50 |
| Mineral oil | 05.00 | 05 | 05.00 | 05.00 |
| Propyl paraben | 00.08 | 00.08 | 00.08 | 00.08 |
| Diethyl phthalate | 01.00 | 03.00 | 05.00 | 10.00 |
| Diclofenac sodium | 03.00 | 03.00 | 03.00 | 03.00 |
| Triethanolamine | 02.00 | 02.00 | 02.00 | 02.00 |
| Methyl paraben | 00.40 | 00.40 | 00.40 | 00.40 |
| Purified water | q.s. up to 100% | q.s. up to 100% | q.s. up to 100% | q.s. up to 100% |
| Perfume | q.s. | q.s. | q.s. | q.s. |

**5. Evaluation of creams and ointments**

5.1 Physical properties

Physical parameters like colour and odor were examined visually.

5.2 pH

The pH meter was calibrated using buffer solution of pH 7.4 and 9.2. About 0.5 g of each formulation was dissolved in 50 ml of distilled water and pH was recorded.

5.3 Homogeneity

The developed formulations were tested for homogeneity by visual inspection. Formulations were tested for their appearance with no lumps.

5.4 Content of uniformity

Samples of 0.5 g of each formulation were taken randomly from the container and dissolved in 20 ml of pH 6.8 phosphate buffer. Diclofenac sodium is assayed using UV absorbance at 276 nm.

5.5 Spreadability test

It was determined by an apparatus suggested by Muttimer et al. It was suitably modified in the laboratory. It consisted of a wooden block, which was provided by a pulley at one end. A rectangular glass plate was placed on this block. 1 g of formulation was placed on this plate. Formulation was then sandwiched between this plate and another glass plate of same dimension, provided with a hook. 1 kg weight was placed on the top of the two plates for 5 min to expel air and to provide a uniform film of the ointment between the plates. The top plate was then subjected to pull of 50 g with help of string attached to the hook and time (sec) required by the top plate to cover distance of 5 cm was noted. [3]

Spreadability = ml/t

Where, m = weight tied to upper slide,

l = length of glass slide

t = time in second.

5.6 Consistency Test

5.6.1 Penetrometer

Consistency of the formulation was determined by penetrometer model no. 2 Associated instrument Pvt. Ltd. Calcutta. The penetrometer stand was made up of a vertical shaft (length=162 mm, mass= 47.5g) to maintain and guide the penetrating object. The release and penetration of the object was maintained horizontally. It also consisted of a cone shaped penetrating object having mass 102.5 g to retain and release when the devise pressed down. A scale, showing the depth of penetration was graduated in tenths of a millimeter.

5.6.2 Procedure

Test samples were completely filled in containers without forming air bubbles. These samples were placed on the base of penetrometer. It was verified that its surface was perpendicular to the vertical axis of the penetrating object and its position was such that its tip just touches the surface of the sample. Measurements of the depth of penetration were taken. The penetration was expressed in tenths of millimeter.

5.7 Drug diffusion study

Diffusion of diclofenac sodium through cream and ointment was studied using diffusion cell apparatus manufactured by Orchid Scientifics ltd, Nasik. Isolated goat skin preparations were treated with 0.32M ammonium hydroxide solution followed by distilled water. Receiver medium was phosphate buffer of pH 6.8. Each 0.3 g of formulations was uniformly applied on the skin. Samples of 0.3 ml were withdrawn with the help of syringe for 6 hrs at each 30 min interval. UV absorbance of diclofenac sodium was measured at 276 nm. Percent drug release was then calculated. [4]

**Table 3:** Marketed formulations used for drug release study

| Formulation | Marketed Preparation |
|---|---|
| Cream | Medicream, B.E. Biologicals |
| Ointment | Relaxyl ointment, Perceps Pharmaceutical Pvt Ltd. |

5.8 Stability study

Stability may be defined as the capability of a particular formulation, in a specific container to remain within its physical, chemical, microbiological and toxicological specifications. The stability test was carried out for 60 days. The conditions were room temperature, $10^0$C and $45^0$C. The formulations were analysed for the change in physical properties like organoleptic characteristics, pH, spreadability and consistency. [5]

## RESULTS AND DISCUSSION

### 1. DEP

DEP when synthesized using absolute alcohol, phthalic acid and catalyst PTSA at 1%, acidity and purity was 0.006%, 99.985% respectively. Refractive index, density and ester content were 1.501, 1.121 and 99.86% respectively. DEP synthesized meets the specifications of B.P. Compatibility study of DEP and diclofenac sodium was done using FTIR and showed that DEP and diclofenac were compatible. Skin irritation test was carried out on mice skin and no irritation was produced.

### 2. Ointments

Color of the ointment was pale yellow with characteristic odour. Ointment was homogenous with pH 6.70. Results of different tests were shown in Table 4.

**Table 4:** Results of color, odor and pH tests of ointments

| Formula | Color | Odor | pH | Homogeneity |
|---|---|---|---|---|
| OD 1 | Pale yellow | Characteristic | 06.70 | No lumps |
| OD 2 | Pale yellow | Characteristic | 06.71 | No lumps |
| OD 3 | Pale yellow | Characteristic | 06.70 | No lumps |
| OD 4 | Pale yellow | Characteristic | 06.70 | No lumps |
| Marketed Preparation | Pale yellow | Characteristic | 06.70 | No lumps |

Consistency and spreadability of ointments was found to increase with increase in concentration of DEP. OD3 formulation (DEP 5%) was comparable to marketed formulation with 151 and 10.68 of consistency and spreadability respectively. OD3 formulation was then subjected to stability studies. Content of uniformity was found within limits. Results of different tests were shown in Table 5.

**Table 5:** Results of homogeneity, spreadability and content of uniformity of ointments

| Formula | Consistency | Spreadability | Content of uniformity (%) |
|---|---|---|---|
| OD 1 | 125 | 04.90 | 99.40 |
| OD 2 | 136 | 08.33 | 98.90 |
| OD 3 | 151 | 10.68 | 99.44 |
| OD 4 | 170 | 22.40 | 99.02 |
| Marketed Preparation | 153 | 11.13 | 99.30 |

Cumulative % drug release from OD1 after 0.5, 2.0, 4.0 and 6.0 h was 5.95, 11.40, 27.47 and 66.62% respectively. Drug release was found to be increased in OD2, OD3 and OD4 formulation consecutively; with an increase in DEP concentration to 1, 3, 5 and 10 respectively, which was due to increase in spreading power of formulation. After 6 h cumulative % drug release of marketed formulation was 78.36 % and was comparable to OD3 formulation having 76.32% of cumulative drug release. Results of different tests were shown in Table 6.

**Table 6:** Cumulative percent drug release from ointments

| Time (h) | Cumulative percent drug release | | | | |
|---|---|---|---|---|---|
| | OD1 | OD2 | OD3 | OD4 | Marketed Preparation |
| 0.5 | 05.95 | 06.87 | 11.40 | 12.56 | 10.13 |
| 1.0 | 06.50 | 07.40 | 12.44 | 13.50 | 12.45 |
| 1.5 | 07.80 | 10.13 | 15.00 | 12.18 | 12.89 |
| 2.0 | 11.40 | 13.00 | 16.60 | 17.75 | 15.95 |
| 2.5 | 14.38 | 15.70 | 19.70 | 21.00 | 18.32 |
| 3.0 | 17.40 | 19.18 | 23.53 | 23.85 | 22.12 |
| 3.5 | 23.75 | 24.62 | 27.73 | 41.48 | 39.62 |
| 4.0 | 27.47 | 29.95 | 34.73 | 44.98 | 43.38 |
| 4.5 | 33.95 | 35.38 | 41.22 | 56.00 | 54.92 |
| 5.0 | 40.70 | 42.30 | 48.48 | 66.23 | 65.34 |
| 5.5 | 49.26 | 52.23 | 63.12 | 76.22 | 72.82 |
| 6.0 | 66.62 | 67.14 | 76.32 | 82.31 | 78.36 |

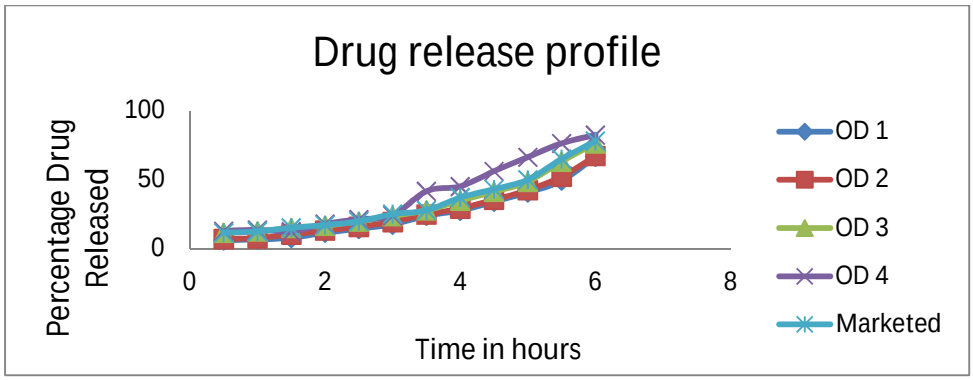


**Figure 1:** Drug release pattern from ointments

No significant variations were observed in respect to the appearance, pH, consistency, spreadability and drug content before and after storage under stability conditions for 20, 40 and 60 days at 10, 25 and 45 $^{o}$C. Results of different tests were shown in Table 7.

**Table 7:** Stability data of batch (OD3) of ointment

| **Parameter** | **Initial** | **10$^0$C** | | | **25$^0$C** | | | **45$^0$C** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Days** | | | **Days** | | | **Days** | | |
| | | 20 | 40 | 60 | 20 | 40 | 60 | 20 | 40 | 60 |
| Appearance | Pale yellow | No change | No change | No change | No change | No change | No change | No change | No change | No change |
| pH | 06.70 | 06.70 | 06.71 | 06.69 | 06.69 | 06.70 | 06.71 | 06.71 | 06.69 | 06.68 |
| Consistency | 151 | 150 | 148 | 145 | 150 | 149 | 148 | 151 | 152 | 152 |
| Spreadability | 10.68 | 10.44 | 10.31 | 10.67 | 10.65 | 10.51 | 10.42 | 10.62 | 10.58 | 10.62 |
| % Drug content | 99.44 | 99.36 | 99.34 | 99.25 | 99.33 | 99.28 | 99.21 | 99.33 | 99.20 | 99.18 |

**3. Creams**

Color of the creams was white with characteristic odour. Cream formulations were homogenous with pH 6.75. Results of different tests were shown in Table 8.

**Table 8:** Results of color, odor and pH tests of creams

| **Formula** | **Color** | **Odor** | **pH** | **Homogeneity** |
|---|---|---|---|---|
| CD 1 | White | Characteristic | 06.74 | No lumps |
| CD 2 | White | Characteristic | 06.74 | No lumps |
| CD 3 | White | Characteristic | 06.75 | No lumps |
| CD 4 | White | Characteristic | 06.75 | No lumps |
| CPG | White | Characteristic | 06.78 | No lumps |
| Marketed Preparation | White | Characteristic | 06.74 | No lumps |

Consistency and spreadability of creams was found to increase with increase in concentration of DEP. CD3 formulation (DEP 5%) was comparable to marketed formulation with 151 and 10.68 of consistency and spreadability respectively. CD3 formulation was then subjected to stability studies. Content of uniformity was found within limits. Results of different tests were shown in Table 9.

**Table 9:** Results of homogeneity, spreadability and content of uniformity of creams

| Formula | Consistency | Spreadability | Content of uniformity (%) |
|---|---|---|---|
| CD 1 | 175 | 09.32 | 99.10 |
| CD 2 | 189 | 11.79 | 98.90 |
| CD 3 | 206 | 14.88 | 99.04 |
| CD 4 | 218 | 25.20 | 98.02 |
| CPG | 198 | 14.21 | 99.32 |
| Marketed Preparation | 209 | 13.48 | 99.21 |

Cumulative % drug release from CD1 after 0.5, 2.0, 4.0 and 6.0 h was 7.12, 12.57, 27.35 and 67.77% respectively. Drug release was found to be increased in CD2, CD3 and CD4 formulation consecutively; with an increase in DEP concentration to 1, 3, 5 and 10 respectively, which was due to increase in spreading power of formulation. After 6 h cumulative % drug release of marketed formulation was 79.12% and was comparable to CD3 formulation having 77.52% of cumulative drug release. Results of different tests were shown in Table 10.

**Table 10:** Cumulative percent drug release from creams

| Time (h) | Cumulative percent drug release | | | | |
|---|---|---|---|---|---|
| | CD1 | CD2 | CD3 | CD4 | Marketed Preparation |
| 0.5 | 07.12 | 07.52 | 12.57 | 14.00 | 11.23 |
| 1.0 | 08.03 | 08.55 | 13.61 | 15.00 | 12.52 |
| 1.5 | 10.24 | 09.46 | 16.46 | 17.88 | 13.79 |
| 2.0 | 12.57 | 11.53 | 17.75 | 19.18 | 17.65 |
| 2.5 | 12.96 | 14.52 | 20.86 | 23.46 | 22.34 |
| 3.0 | 18.53 | 20.22 | 23.58 | 25.02 | 27.72 |
| 3.5 | 24.50 | 23.17 | 28.91 | 30.46 | 45.98 |
| 4.0 | 27.35 | 27.74 | 33.31 | 34.74 | 48.29 |
| 4.5 | 35.13 | 36.55 | 39.8 | 41.22 | 57.33 |
| 5.0 | 39.27 | 43.42 | 50.74 | 57.07 | 67.79 |
| 5.5 | 50.42 | 53.41 | 64.30 | 67.02 | 73.35 |
| 6.0 | 67.77 | 69.35 | 77.52 | 86.14 | 79.12 |

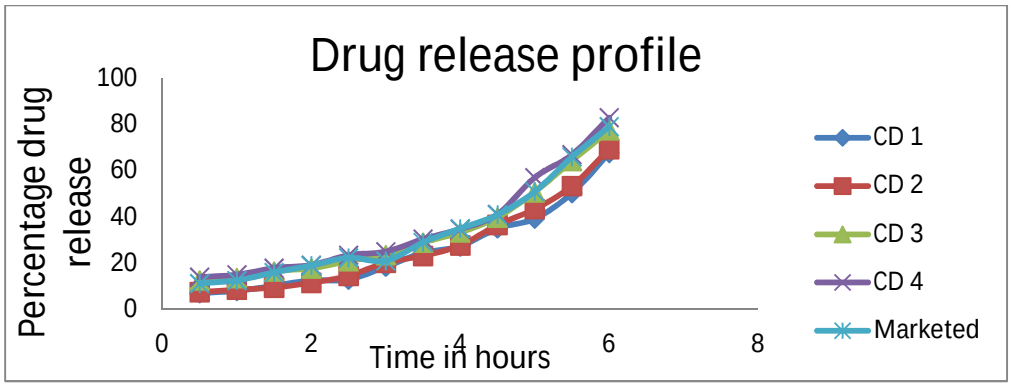


**Figure 2:** Drug release pattern from creams

No significant variations were observed in respect to the appearance, pH, consistency, spreadability and drug content before and after storage under stability conditions for 20, 40 and 60 days at 10, 25 and 45 $^{o}$C. Results of different tests were shown in Table 11.

**Table 11:** Stability data of batch (CD3) of cream

| **Parameter** | **Initial** | **10$^0$C** | | | **25$^0$C** | | | **45$^0$C** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Days** | | | **Days** | | | **Days** | | |
| | | 20 | 40 | 60 | 20 | 40 | 60 | 20 | 40 | 60 |
| Appearance | White | No change | No change | No change | No change | No change | No change | No change | No change | No change |
| pH | 06.75 | 06.74 | 06.73 | 06.72 | 06.75 | 06.74 | 06.73 | 06.74 | 06.73 | 06.72 |
| Consistency | 206 | 203 | 202 | 201 | 205 | 204 | 206 | 210 | 212 | 212 |
| Spreadability | 14.49 | 10.44 | 10.31 | 10.67 | 10.65 | 10.51 | 10.42 | 10.62 | 10.58 | 10.62 |
| %Drug content | 99.04 | 99.04 | 99.03 | 99.03 | 99.02 | 99.01 | 99.0 | 99.03 | 99.01 | 99.00 |

## CONCLUSION

DEP when synthesized using p-toluene sulphonic acid (PTSA) (1%) as catalyst, phthalic anhydride and absolute alcohol under reaction conditions for 12 h, meets B.P. specifications and no skin irritation was produced. DEP and diclofenac sodium found compatible, studied by IR spectra, hence it can be employed in formulations containing diclofenac sodium.

Formulation of ointment (OD3) and cream (CD3) when prepared using DEP in 5% concentration; observed good spreading, drug release, content of uniformity and consistency and were comparable with marketed preparations.

The study showed best results when DEP utilized in topical formulations at the concentrations of 5%, hence in future attempts can be made in the direction to utilize DEP in topical preparations having good spreading properties, optimum consistency, drug release and no skin irritation.

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