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# Study of diabietic acid as matrix forming material

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**Abstract**

Abietic acid was extracted from rosin N grade and further standardized. Diabietic acid, a derivative of abietic acid was prepared by dimerization with sulfuric acid and evaluated for different physicochemical properties. A yellowish brown colour product with an acid value of 98 mg KOH, a softening point of 142–145°C and an acid/alkali resistant property was obtained. Moisture absorption study indicated its hydrophobic nature. Water vapour transmission and scanning electron micrography showed that the free films of diabietic acid are smooth, flexible, nonporous with 0.024 g $h^{-1}$ mmHg of water vapour transmission rate at 82.5% relative humidity (RH). Matrix tablets of Diclofenac sodium were formulated using diabietic acid as a matrix-forming material and evaluated for hardness, friability, release characteristics and material balance study. The results showed that diabietic acid having good film forming, acid/alkali resistant properties could be successfully used to prolong release of water-soluble drug for up to 24 h.

*Keywords:* Abietic acid; Diabietic acid; Rosin; Diclofenac sodium; Matrix forming material; Prolonged release formulation

## 1. Introduction

Abietic acid, a product obtained from rosin N grade by extraction, and its various derivatives, possesses excellent film-forming properties and therefore has wide applications in paints, varnishes (Miller, 1947), lacquer (Kono, 1972) and cosmetics (Gelinsky, 1934). Glycerol esters of abietic acid were used in fluid surgical dressings to form a hydrophobic film over a wound surface to protect it from water (Gallienne et al., 1957). The recent investigation in our laboratory indicated that abietic acid and its several derivatives can be used as microencapsulating material for pharmaceutical formulation (Puranik et al., 1992). Abietic acid sorbitol and abietic acid pentaerythritol are useful microencapsulating materials for prolonged release dosage form (Puranik and Dorle., 1991).

Diclofenac sodium is a potent nonsteroidal anti-inflammatory (NSAID) drug advocated for use in painful and inflammatory rheumatic and nonrheumatic conditions. It however undergoes first pass metabolism after oral administration (Todd and Sorkin, 1988), and possesses a very short biological half life (1.1–4.0 h), consequently a repetitive dosing schedule (25–50 mg, three

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Table 1
Physicochemical properties: yellowish brown; acid value: 98 mg of KOH; softening point: 142–145°C

| Product | Solubility in different solvents | | Solubility in different pH solutions | |
|---|---|---|---|---|
| | Solvent | Solubility (g/ml) | pH | Solubility (g/ml) |
| Diabietic acid | Chloroform | 0.35 ± 0.043 | 1.2 | $1.0 \pm 0.20 \times 10^{-5}$ |
| | Acetone | 0.30 ± 0.024 | 4.5 | $1.4 \pm 0.35 \times 10^{-5}$ |
| | Isopropanol | 0.20 ± 0.037 | 6.8 | $4.0 \pm 0.85 \times 10^{-5}$ |
| | Ethanol | 0.20 ± 0.021 | 7.2 | $5.0 \pm 0.65 \times 10^{-5}$ |
| | Carbontetrachloride | 0.15 ± 0.019 | 7.5 | $12.0 \pm 2.17 \times 10^{-5}$ |
| | Ethyl acetate | 0.25 ± 0.033 | | |
| | Water | Insoluble | | |

times a day) becomes necessary. In view of the need for repetitive dosing it was felt that a sustained release formulation of diclofenac sodium which may be administered as a single dose would prove useful. The present work was undertaken with a view to devise such a sustained release formulation of diclofenac sodium and also to ascertain the usefulness of diabietic acid as a sustained release and matrix-forming material.

## 2. Experimetnal

### 2.1. Materials

Rosin N grade (ISI), abietic acid (isolated and standardized in our laboratory), chloroform (SD Fine chemicals), carbon tetrachloride (Runa chemicals), sulfuric acid (SD Fine chemicals), sodium chloride (Sarabhai chemicals), isopropyl alcohol (Runa chemicals), absolute alcohol (MSSIDC Industries, India), magnesium stearate (Apex chemicals), talc (Apex chemicals), methanol (SD Fine chemicals), and hydrochloric acid (SD Fine chemicals) were the chemicals used. All were of laboratory grade.

Table 2
Moisture absorption studies

| Product | %Relative humidity | %Moisture absorbed[a] |
|---|---|---|
| Diabietic acid | 17.5 | 0.00 ± 0.00 |
| | 57.0 | 0.01 ± 0.001 |
| | 82.5 | 0.87 ± 0.02 |

[a]Average of three readings.

### 2.2. Methods

#### 2.2.1. Isolation and standardization of abietic acid

Abietic acid was extracted from alcoholic solution of rosin N Grade (ISI) by isomerization of rosin acids into *l*-abietic acid using hydrochloric acid as a catalyst at room temperature (Bose et al., 1948). The precipitated product was recrystallized in methanol. The yield of the product was 50%. The product was subjected to the following tests.

#### 2.2.2. Identification test

Abietic acid gives a green colour with copper nitrate (Budu and Simon, 1983). One hundred mg of product was reacted with 5 ml of 1% copper nitrate solution which turns green indicating the presence of abietic acid.

#### 2.2.3. Acid value

Acid value was determined according to the Indian Pharmacopoeia method (The Indian Pharmacopoeia, 1985).

#### 2.2.4. Optical activity

Alcoholic solution (1% w/v) of product was subjcted to an optical activity test in a polarimeter.


Fig. 1. Electron micrograph scanning: free films of diabietic acid: magnification, 56 000 × .

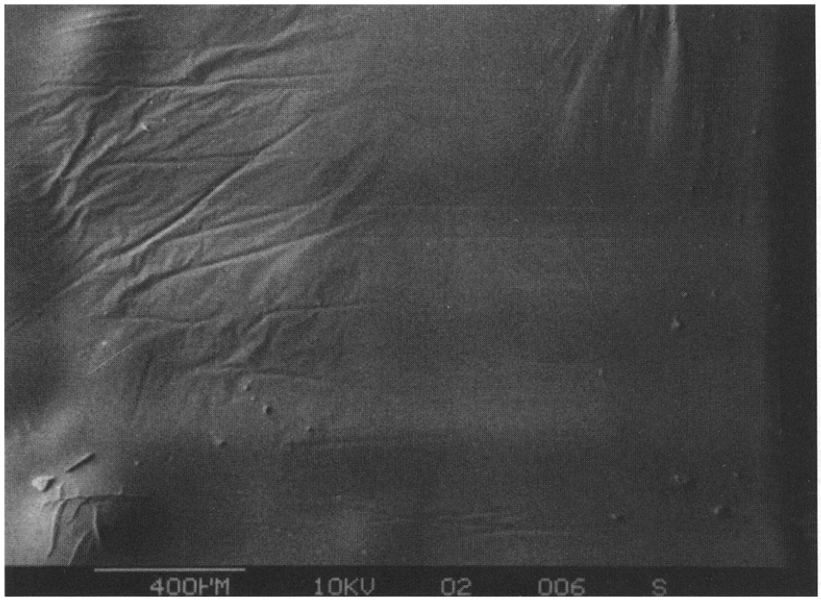


Fig. 2. Electron micrograph scanning: free films of diabietic acid: magnification, 55 × .

*2.2.5. Abietic acid content (Shukla et al., 1979)*

Ten mg of sample was taken in an iodine flask, 20 ml of 0.05 N iodine monochloride solution was added, and the flask was stoppered, and placed in the dark for 20 min at room temperature. After the expiry of 20 min, 10 ml of 15% potassium iodide solution was added to the flask and the contents were titrated against 0.02 N sodium thiosulphate solution using starch as an indicator.

Table 3
Water vapour transmission studies of free film

| Product | %Relative humidity | Thickness of film in mm | %RWVT g $h^{-1}$ mmHg[a] |
|---|---|---|---|
| Diabietic acid | 17.5 | 0.13 | 0.0027 ± 0.0004 |
| | 57.0 | | 0.0190 ± 0.0020 |
| | 82.5 | | 0.0240 ± 0.0050 |

[a]Average of three readings.

The amount of abietic acid in sample was obtained by

$$\text{mg of sample} = \frac{(B - A) \times M \times N}{4 \times 2} \quad (1)$$

where $A$ = ml of sodium thiosulphate solution for sample; $B$ = ml of sodium thiosulphate solution for blank; $M$ = molecular weight of abietic acid; $N$ = normality of sodium thiosulphate solution; 4 = mol iodine monochloride for sample.

### 2.3. Preparation of diabietic acid

Diabietic acid was prepared by the method described by Sinclair et al. (1970). To the solution of abietic acid (50 g) in chloroform (760 ml), 17.5 ml of concentrated sulphuric acid (98%) was added. The reaction flask was warmed at 44°C on an oil bath; heating and stirring was continued for 5 h after which the reaction was quenched with 1 l of water. The quenched product yielded a dark to yellow brown solution which was then washed with saturated sodium chloride solution until aqueous wash was neutral. The chloroform layer was seperated and evaporated. The product obtained was dried in vacuo at 60°C for 16 h.

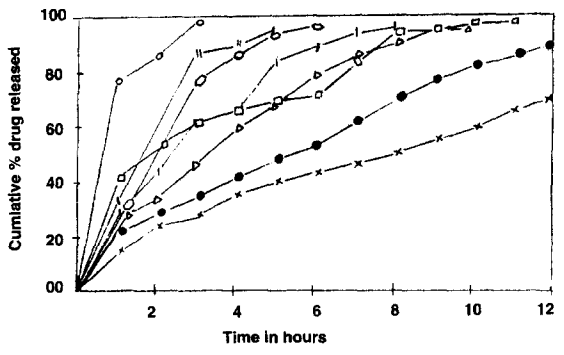


Fig. 3. Release characteristics: matrix tablets prepared by using different concentrations of diabietic acid. Drug:coating material: 100:00 (○); 100:06 (‖); 100:11 (○); 100:18 (□); 100:25 (/); 100:35 (△); 100:43 (●); 100:47 ( × ).

### 2.4. Physicochemical properties

#### 2.4.1. Acid value

Acid value was determined by using the Indian Pharmacopoeia method (The Indian Pharmacopoeia, 1985).

#### 2.4.2. Colour

Colour comparison in all the cases was visual against a white background.

#### 2.4.3. Softening point

Herculus drop softening point method was employed for determining softening point.

#### 2.4.4. Relative solubility

Three g of material with 50 ml of solvent was placed in an airtight screwcapped tube and agitated at 25°C for 24 h. Two ml of supernatant was withdrawn in a tared dish. Solvent was evaporated by a mild heat and the tared dish was weighed again. The difference in weight gives the amount of material dissolved in the solvent. Different solvents were used for this purpose and the experiment was repeated three times for each solvent.

Table 4
Evaluation of matrix tablets of diclofenac sodium

| S. no. | Drug:coating material | Hardness (kg/cm$^2$) | Friability (%) | $D_{t50\%}$ (%) | %Drug released after 12 h |
|---|---|---|---|---|---|
| 1 | Control[a] | - | - | 0.6 | - |
| 2 | 100:06 | 2.5 | 2.54 | 1.0 | - |
| 3 | 100:11 | 3.0 | 2.85 | 1.5 | 96.00 ± 3.20 |
| 4 | 100:18 | 3.2 | 3.06 | 2.2 | 90.00 ± 4.56 |
| 5 | 100:25 | 3.4 | 3.33 | 2.7 | 88.00 ± 2.08 |
| 6 | 100:34 | 3.1 | 3.52 | 3.2 | 78.00 ± 3.87 |
| 7 | 100:43 | 3.6 | 3.20 | 5.8 | 52.00 ± 2.75 |
| 8 | 100:47 | 3.8 | 2.85 | 8.5 | 43.00 ± 4.09 |
| 9 | 125:60[b] | 5.8 | 1.20 | 9.5 | 60.00 ± 3.93 |

[a]Plain drug.
[b]SRDF.

*2.4.5. Moisture absorption study*

Ten g of diabietic acid were powdered and dried at 50°C until constant weight was obtained, and kept in different desicators maintained at controlled humidity conditions brought about by different percentages of sulfuric acid as follows (weight of % sulfuric acid/relative humidity): 25/82.5%; 40/57.0%; 60/17.5%. The diabietic acid was kept for 7 days at these humidities. The difference in weight gives the amount of moisture absorbed by the material at different humidities.

*2.4.6. Preparation of free films of diabietic acid*

The free films of diabietic acid were prepared by following method.

Preliminary trials showed that diabietic acid in chloroform forms good films. A 10% w/v solution of diabietic acid in chloroform, using propylene glycol (5% w/w of coating material) as a plasticizer was prepared and 1.5 ml of this solution was placed on a mercury surface (13.6 mm) in a petri dish. The solvent was evaporated at room temperature and the petri dish was kept at 37 ± 1°C for 24 h. The dried films were removed and subjected to water vapour transmission rate study (Patel et al., 1964) at different relative humidities. The thickness of the film was determined at different points on the film by screw gauge. The experiment was repeated three times at each relative humidity, viz. 17.5, 57 and 82.5%.

Rate of water vapour transmission was given by:

$$\mathrm{RWVT} = W/AP \quad (2)$$

RWVT = rate of water vapour transmission in g $h^{-1}$ mmHg; $W$ = amount of moisture transmitted; $A$ = area of film exposed; $P$ = vapour pressure gradient across the film (28.96 mmHg).

*2.5. Preparation of matrix tablets*

Diabietic acid was dissolved in sufficient chloroform in different concentrations viz. 6, 11, 18, 25, 34, 43 and 47% w/v to obtain the tablets with different drugs: coating material ratios, keeping the drug quantity constant, i.e., 100 mg/tablet. The solution of diabietic acid in chloroform (25 ml) was added to drug mass (for 100 tablets) and kneeded. The cohesive mass was forced through a hand granulator to obtain granules which were then dried in a dryer at 50°C. The granules were mixed with lubricants and compressed to form tablets on a Manesty single punch machine with a punch size of 6 mm.

The formulae for tablets were: diclofenac sodium (100 mg/tablet); diabietic acid (different concentrations); talc (3 mg/tablet); magnesium stearate (3 mg/tablet); granulating agent (chloroform q.s.).

*2.6. Evaluation of tablets*

The tablets were evaluated for following parameters: (i) hardness; (ii) friability; and (iii) dissolution rate.

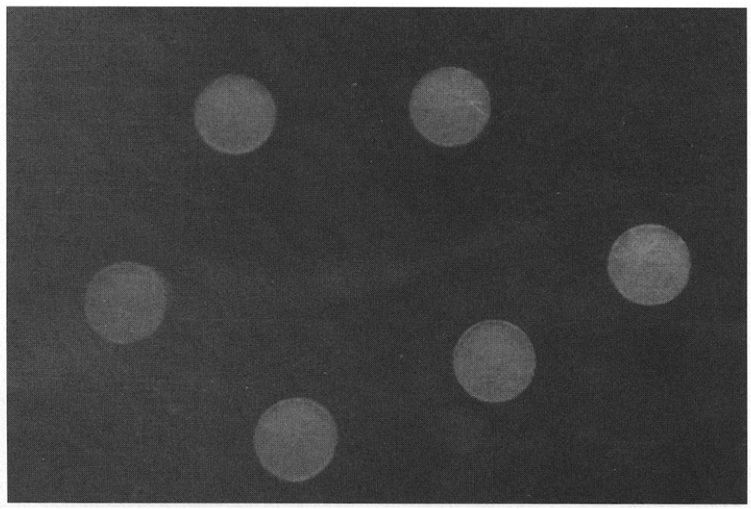

Fig. 4. Tablets before dissolution.

Dissolution studies were carried out using USP XIX Dissolution Test Apparatus in 900 ml of phosphate buffer (pH 6.8) at 37 ± 1°C and 100 rpm. Samples were withdrawn from dissolution media at fixed intervals and analysed for drug content spectrophotometrically at 276 nm. The calibration curve at pH 6.8 was prepared and affirmed that diclofenac sodium was accurately determined in the concentration range of 0.1–4.0 μg/ml. One tablet was employed in a dissolution study and the test was repeated three times for each type of tablet.

Fig. 5. Tablets after dissolution showing porous structure with intact tablet.

### 2.7. Formulation of sustained release matrix tablets

The mathematical design of sustained release dosage form incorporates all concepts and assumption of the biopharmaceutics, i.e., absorption, distribution, metabolism and elimination. Pharmacokinetics studies show that a dose of 25 mg produces an effective blood level concentration of 0.7–1.5 μg/ml within 1.5–2.5 h with the half life of 1.1–4.0 h (Todd and Sorkin, 1988).

Thus the elimination rate constant $k$

$$k = \frac{0.693}{t_{1/2}} \tag{3}$$

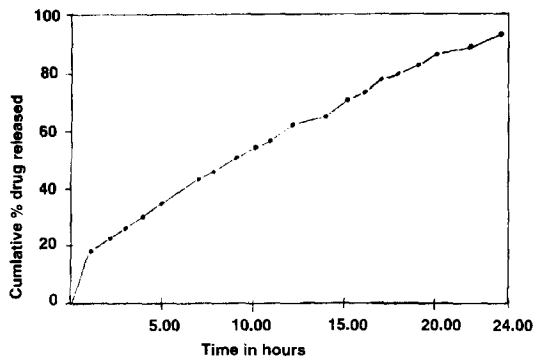


Fig. 6. Release characteristics: sustained release formulation.

Table 5
Release kinetics of sustained release formulation

| Eq. no. | Slope | Correlation coefficient |
|---|---|---|
| 1 | 3.5360 | 0.9976 |
| 2 | 18.5737 | 0.9900 |
| 3 | −0.0690 | −0.9913 |

Eq. 1, zero order release; Eq. 2, matrix type release; Eq. 3, first order release.

$$k = \frac{0.693}{4.0} = 0.1732 \text{ mg h}^{-1} \quad (4)$$

Hence the availability rate $R$

$$R = k \times D = 0.1732 \times 25 = 4.3 \text{ mg h}^{-1}$$

where $D$ is the usual dose of the drug.

The maintenance dose $D_m$

$$D_m = R \times h = 4.3 \times 25 = 107.5 \text{ mg}$$

where $h$ is number of hours for which sustained action is desired.

Therefore total dose

$$D = D + D_m = 25 + 107.5 = 132.5 \text{ mg}$$

$$D_{corrected} = D - R_{tp} = 25 - (2 \times 4.3) = 16.4 \text{ mg}$$

where $R_{tp}$ is the time required to reach peak blood level.

Therefore

$$\text{total dose}_{corrected} = D_{corrected} + D_m = 16.4 + 107.5 = 123.9 \text{ mg}$$

The preliminary dissolution study indicated that a 100:47 diclofenac sodium:diabietic acid ratio prolongs the release of drug for more than 12 h with $D_{t50\%}$ value of 8.5 h ($D_{t50\%}$, time required to release 50% of the drug). Hence the same ratio was considered for the formulation of sustained release tablets. The tablets were prepared with following formulae: diclofenac sodium (125 mg/tablet); diabietic acid (60 mg/tablet); talc (3 mg/tablet); magnesium stearate (3 mg/tablet); chloroform q.s. as granulating agent.

### 2.8. Release kinetics

Release kinetics study was carried out by computer programming (Bhanja et al., 1990) using the following equations.

Equation 1: zero order mechanism: $M_t = f(t)$
Equation 2: matrix mechanism: $M_t = f(t)^{1/2}$
Equation 3: first order mechanism: $\log M_o - M_t = f(t)$

where $M_t$ is the amount of drug released at time $t$ and $M_o$ is initial drug loading.

## 3. Results and discussion

Abietic acid undergoes dimerization at the conjugated diene system at the ring which is characteristic of abietic acid. Diabietic acid has a lower acid value (98 mg of KOH) than abietic acid (185 mg of KOH). Optical activity of 1% alcoholic solution of abietic acid was found to be $\alpha\}_D^{20} - 95$. A study of relative solubility was carried out in different solvents and under different pH conditions. Diabietic acid is insoluble in water and soluble in all organic solvents tested, i.e., isopropanol, alcohol, chloroform, ethyl acetate and benzene (solubility $> 20\%$ w/v). Chloroform was used as solvent for preparation of film because it yielded a fairly satisfactory film as compared to other solvents. The solublity of diabietic acid increases with increasing pH of the solution. Up to pH 7.2 there was a gradual increase in the solubility followed by abrupt increase in the solublity at pH 7.5. This indicates that solublity of diabietic acid is relatively higher in alkaline pH than in acidic (Table 1).

Moisture absorption studies at different relative humidities revealed that diabietic acid absorbs only 0.87% moisture at 82.5% relative humidity indicating a very low moisture absorbing capacity and hydrophobic nature of diabietic acid (Table 2). Free films of diabietic acid were obtained with the use of 5% w/v propylene glycol as plasticizer. The films were shiny, transperent and flexible.

Scanning electron micrography of the film shows that the films were smooth, continuous and free from any pores (Figs. 1 and 2).

The rate of water vapour transmission was low even at high humidities, i.e., 0.024 g $h^{-1}$ mmHg at 82.5% and 0.0027 g $h^{-1}$ mmHg at 17.5% RH, which is indicative of a strong moisture protecting ability for the film. This also indicates the continuity and nonporous nature of the film (Table 3).

### 3.1. Evaluation of tablets

Hardness of the tablet increases with an increase in the amount of matrix forming material (Table 4). However, no statistically significant difference in the hardness of the tablets was noticed. The tablets were comparatively friable at all concentrations of matrix-forming material with more than 2% friability. Fig. 3 depicts the in vitro release characteristics of the drug in phosphate buffer (pH 6.8). A correlation exists between the amount of drug released, $D_{t50\%}$ value and the drug:diabietic acid ratio in the tablets. The drug release rate decreased with increase in concentration of diabietic acid in the tablets presumbly because of an increase in the hydrophobic nature of material. The tablets successfully sustained the release of the drug for 24 h with about 93.41% drug release and $D_{t50\%}$ value of 9.5 h (Table 4). The initial burst effect of the tablet releases about 20% of the drug which was considered to be the loading dose of the drug after which, release was sustained for 24 h. The shape of the tablet remained intact with porous matrix (Figs. 4 and 5) even after the dissolution. The material balance study showed that after dissolution, the intact, porous tablet contains 6–9% of the drug and 54–56 mg of diabietic acid, i.e. 90 $\pm$ 3% of diabietic acid in the tablet. This indicates that diabietic acid forms a plastic type of matrix. Fig. 6 illustrates the drug release characteristics from sustained release dosage forms. The release pattern shows initial instant release followed by a slow zero order release of the sustained component.

Release kinetics studies revealed that sustained release formulation follows overall zero order release, since computer base programming gives the highest correlation coefficent of 0.9976 for zero order release (Table 5).

## 4. Conclusion

The above study indicates that diabietic acid, a dimer of abietic acid has good film forming qualities; moisture absorption studies show its hydrophobic nature and hence it can be used to cover moisture-sensitive drugs. Matrix tablets prepared using diabietic acid as a matrix-forming agent, successfully sustained the release of the water-soluble drug, diclofenac sodium, for 24 h. Hence it can be employed in the formulation of sustained release dosage forms.

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