Abstract: The present invention relates to a process for the preparation of dimethyl fumarate of formula (1) from fumaric acid of formula (3). The present process is simple, cost effective and feasible in large scale production. Dimethyl fumarate obtained by the present process is free of genotoxic impurities.
FIELD OF THE INVENTION:
The present invention relates to an improved process for the preparation of pharmaceutical grade dimethyl fumarate (DMF) of formula (1). The chemical name of dimethyl fumarate is dimethyl (E)-butenedioate. Dimethyl fumarate is a white crystalline solid.

\[
\begin{array}{c}
\text{H}_3\text{C} & \text{O} & \text{O} & \text{C}_2\text{H}_3
\end{array}
\]

(1)

BACKGROUND OF THE INVENTION:
The medical use of fumaric acid esters (FAE) was first described in 1959 by the German chemist W. Schweckendiek who reported on successful internal and external treatment of his own psoriasis. Today, FAE are the most frequently prescribed medication for systemic treatment of psoriasis in Germany. FAE were also found to be effective in other conditions, including necrobiosis lipoidica, granuloma annulare, sarcoidosis, alopecia areata, cheilitis granulomatosa, recurrent oral aphthae, pityriasis rubra pilaris, annular elastolytic giant-cell granuloma or non-infectious chronic uveitis.

Dimethyl fumarate is the methyl ester of fumaric acid. Dimethyl fumarate is chemically known as dimethyl (E)-butenedioate and structurally represented as below.

\[
\begin{array}{c}
\text{H}_3\text{C} & \text{O} & \text{O} & \text{C}_2\text{H}_3
\end{array}
\]

Dimethyl fumarate

Dimethyl fumarate is marketed under the brand name of TECFIDERA®. It is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

Conversion of dialkyl maleate to dialkyl fumarate by heating around 100° C in presence of catalysts like phosphorus oxychloride, thionyl chloride or phosphorus trichloride is disclosed in US2764609 patent.
In another patent application US200200023 06, process for the preparation of dimethyl fumarate using heterogeneous group VIII catalyst is disclosed.

In another patent application WO201270923, dimethyl fumarate is prepared by esterifying fumaric acid with methanol in the presence of sulfuric acid as catalyst.

In another patent application WO2014203231, dimethyl fumarate is prepared from fumaric acid, methanol in the presence of C₂-C₄-alkanoyl halide as catalyst. However, in spite of having the choice of variety of methods for preparation of dimethyl fumarate of formula (1), there is still a need to develop commercially viable process for large scale operations since, in general, the processes reported for preparation of dimethyl fumarate of formula (1) have the following disadvantages:
1. The processes cited above, require toxic reagents like thionyl chloride, phosphorous oxychloride, etc.
2. Removal of genotoxic impurities like dimethyl sulphate to the acceptable level from the drug substance requires several crystallizations.

**SUMMARY OF THE INVENTION:**

Keeping in view of the drawbacks associated with the processes disclosed in the literature for the preparation of dimethyl fumarate of formula (1) we aimed at developing a simple and economically viable process for commercial production of dimethyl fumarate of formula (1).

Accordingly, the main aspect of the present invention is to provide an improved process for the preparation of dimethyl fumarate of formula (1), which comprises simple, safe, economical, and commercially viable process which surpasses the above mentioned disadvantages.

Accordingly, another aspect of the present invention is to provide an improved process for the preparation of dimethyl fumarate of formula (1), by using readily and cheaply available raw materials in the process.

Accordingly, still another aspect of the present invention is to provide an improved process for the preparation of dimethyl fumarate of formula (1), by avoiding multiple purifications and adopting commercially feasible single purification method in the process.

Accordingly, another aspect of the present invention is to provide a process for the preparation of dimethyl fumarate by reacting fumaric acid with methanol in the presence of aqueous hydrochloric acid or methanolic HCl.

Accordingly, yet another aspect of the present invention is to provide an improved process for the preparation of dimethyl fumarate of formula (1), which produces
pharmaceutically acceptable grade dimethyl fumarate of formula (1) having more than 99.9\% HPLC purity.

Accordingly, still another aspect of the present invention is to provide an improved process for the preparation of dimethyl fumarate of formula (1), which produces dimethyl fumarate of formula (1) free from genotoxic impurities.

The present invention is shown in scheme-1.

**Scheme-1**

**DETAILED DESCRIPTION OF THE INVENTION:**

Accordingly, in the present invention, fumaric acid of formula (3) (prepared from maleic anhydride using literature process, CS243823), is reacted with methanol in the presence of catalysts like aqueous hydrochloric acid or anhydrous methanolic HCl preferably aqueous hydrochloric acid at temperatures ranging from 20-75° C and preferably at 60-70° C for 4-5 hours. Later the reaction mixture is cooled to 0-20° C preferably to 0-5° C and filtered. Thereafter, the wet product is suspended in water and the pH of the product mixture is adjusted to neutral pH using aq. base selected from aqueous sodium bicarbonate, aqueous sodium carbonate, aqueous potassium bicarbonate or aqueous potassium carbonate preferably aqueous sodium bicarbonate and filtered at 20-35° C preferably at 25-30° C to get dimethyl fumarate having > 99.8\% HPLC purity. The product is crystallized from 5-70\% aqueous methanol preferably 50\% aqueous methanol to get pharmaceutical grade dimethyl fumarate of formula (1) having HPLC purity of dimethyl fumarate obtained by present process is >99.95\% having monomethyl fumarate impurity at 0.01-0.02\% level and genotoxic impurity, maleic anhydride, at less than 0.9 ppm level (Limit of maleic anhydride as per ICH guidelines is NMT 3.125 ppm). Particle size distribution of dimethyl fumarate obtained by present process is as given below, d90 is 350-500 micron, d50 is 200-250 micron and d10 is 80-120 microns.

Accordingly, the present invention provides an improved process for the preparation of dimethyl fumarate of formula (1),
which comprises :-

i) reaction of maleic anhydride of formula (2)

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

(2)

with water in the presence of thiourea to get fumaric acid of formula (3),

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{H} \\
\end{align*}
\]

(3)

ii) esterification of compound of formula (3) with methanol in the presence of an acid catalyst to get technical grade of dimethyl fumarate of formula (1),

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{CH}_3 \\
\end{align*}
\]

(1)

iii) recrystallization of technical grade dimethyl fumarate of formula (1) from aqueous methanol to get pharmaceutical grade compound of formula (1).

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{CH}_3 \\
\end{align*}
\]

(1)

In a preferred embodiment of the present invention:-

The acid catalyst employed in step (ii) is selected from aqueous hydrochloric acid or methanolic HCl, preferably, aqueous hydrochloric acid.
In step (ii) the reaction temperature employed for the conversion of fumaric acid of formula (3) to dimethyl fumarate of formula (1) is 20-75°C, preferably, 60-70°C.

The temperature at which crude dimethyl fumarate of formula (1) isolated in step (ii) is between 0-20°C, preferably, 0-5°C.

The pH at which dimethyl fumarate isolated in step (ii) is between 6.5-8.0, preferably, 7.0-7.5.

The base employed for pH adjustment in step (ii) is selected from aqueous sodium bicarbonate, aqueous sodium carbonate, aqueous potassium bicarbonate or aqueous potassium carbonate, preferably, aqueous sodium bicarbonate.

The temperature at which technical grade dimethyl fumarate of formula (1) isolated in step (ii) is between 20-35°C, preferably, 25-30°C. HPLC purity of the isolated product of formula (1) is >99.8%.

The solvent employed to dissolve technical grade dimethyl fumarate of formula (1) in step (iii) is selected from 5-70% aqueous methanol, preferably, about 50% aqueous methanol. Yield of dimethyl fumarate is > 82% and HPLC purity is above 99.95% having monomethyl fumarate impurity at 0.01-0.02% level, genotoxic impurity, maleic anhydride, at 0.9 ppm level, particle size distribution of dimethyl fumarate obtained by present process is d90 is 350-500 micron, d50 is 200-250 micron and d10 is 80-120 microns.

**Advantages of the present process:**

- Present process avoids anhydrous reaction conditions.
- Dimethyl fumarate produced is free from genotoxic impurities.
- Present process is feasible on large scale production.
- Present process is cost effective.
- No metal catalysts required in the present process
- Easy to scale-up the process on commercial scale
- Raw materials used in the process are commercially available

**Brief Description of drawings:**

- Figs-1: XRD pattern of dimethyl fumarate prepared as per present invention.
- Figs-2: DSC of dimethyl fumarate prepared as per present invention.

The following examples are provided for illustration purpose only and are not intended to limit the scope of invention.
Example-1: Preparation of fumaric acid of formula (3) from maleic anhydride of formula (2):
Into a 3L, 4-necked RB flask, 1.25 L of water and 250 g of maleic anhydride were charged at 25-35 °C and stirred the reaction mixture at 25-30°C for complete dissolution. After dissolution, 7.5g of thiourea was charged and maintained the reaction mixture at 25-30°C for 8-9h under stirring. After completion of reaction, resulting product was filtered and washed with 750 ml water, suck dried for 30 min, and dried at 50-55°C to get 247.5 g (83.6%) of fumaric acid of formula (3) as white crystalline powder.
HPLC purity: >99.0%

Example-2: Preparation of dimethyl fumarate of formula (1) from fumaric acid of formula (3):
Into a 2L, 4-necked RB flask, 200 g of fumaric acid was reacted with methanol (800 ml) in the presence of concentrated hydrochloric acid (40 ml) at reflux temperature for about 5 hours. After completion of reaction, reaction mixture cooled to 0-5°C and filtered. Later, the wet cake was suspended in 800 ml of water and adjusted the pH to 7.0-7.5. The resulting product was filtered and dried at 25-30°C to get 210.5g (84.8%) technical grade white crystalline dimethyl fumarate. HPLC purity: >99.8%

Example-3: Preparation of dimethyl fumarate of formula (1) from fumaric acid of formula (3):
Into a 500 mL, 4-necked RB flask, 25 g of fumaric acid and methanolic HCl (192 ml) were charged and reacted at reflux temperature for about 12-14 hours. After completion of reaction, cooled the reaction mixture to 0-5°C and filtered. Later, the wet cake was suspended in 800 ml of water and adjusted the pH to 7.0-7.5. The resulting product was filtered and dried at 25-30°C to get 24.0 g (77.0%) of technical grade white crystalline dimethyl fumarate.
HPLC purity: >99.8%

Example-4: Purification of technical grade dimethyl fumarate of formula (1)
Into a 5L, 4-necked RB flask equipped with reflux condenser, thermometer socket, 1.40 L of methanol, 1.40 L of water and 175.0 g of technical grade dimethyl fumarate were charged. The reaction mixture was heated to reflux temperature to dissolve completely. After complete
dissolution, filtered and the solution cooled the filtrate to 0-5°C. The product was filtered and
dried at 25-30°C under vacuum to get 134.6 g (87.8%) of pharmaceutical grade dimethyl
fumarate. HPLC purity: >99.95%
We Claim:

1. An improved process for the preparation of dimethyl fumarate comprising the steps of:
   
i) esterification of fumaric acid of formula (3) with methanol in the presence of an acid catalyst to get technical grade dimethyl fumarate of formula (1),

   \[
   \text{H}_3\text{C}-\text{O}\text{CH}=\text{C}-(\text{O})\text{O}\text{H} \quad \text{H}_3\text{C}-\text{O}\text{CH}=\text{C}-(\text{O})\text{O}\text{CH}_3
   \]

   (3)  (1)

   ii) recrystallization of dimethyl fumarate of formula (1) from aqueous methanol to get pure compound of formula (1).

   \[
   \text{H}_3\text{C}-\text{O}\text{CH}=\text{C}-(\text{O})\text{O}\text{CH}_3
   \]

   (1)

2. An improved process for the preparation of dimethyl fumarate of formula (1) as claimed in claim 1, wherein in step (i)
   
   (a) The acid catalyst employed for the esterification of fumaric acid of formula (3) with methanol is selected from aqueous hydrochloric acid or methanolic HCl, preferably aqueous hydrochloric acid.

   (b) The reaction temperature employed for the conversion of fumaric acid of formula (3) to dimethyl fumarate of formula (1) is 20-75°C, preferably 60-70°C.

   (c) The temperature at which crude dimethyl fumarate of formula (1) isolated is between 0-20°C, preferably 0-5°C.

   (d) The pH at which dimethyl fumarate isolated is between 6.5-8.0, preferably 7.0-7.5.

   (e) The base employed for pH adjustment is selected from aqueous sodium bicarbonate, aqueous sodium carbonate, aqueous potassium bicarbonate or aqueous potassium carbonate, preferably aqueous sodium bicarbonate.

   (f) The temperature at which technical grade dimethyl fumarate of formula (1) isolated is between 20-35°C, preferably 25-30°C.
3. An improved process for the preparation of dimethyl fumarate of formula (1) as claimed in claims 1 & 2, wherein in step (ii)
   a) The solvent employed to dissolve technical grade dimethyl fumarate of formula (1) is selected from 5-70% aqueous methanol preferably, 50% aqueous methanol.
   b) Dimethyl fumarate prepared according to present process is having a peak in DSC at 105-108°C.

4. Dimethyl fumarate, which is free of genotoxic impurity maleic anhydride.
### A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C67/52 C07C69/657

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### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

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### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C. See patent family annex.

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Name and mailing address of the ISA:
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Authorized officer: Panday, Narendra
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