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Preparation and Characterization of Aceclofenac Salt by Using Triethanolamine

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Abstract:

The objective of the present investigation was to prepare and characterize the aceclofenac salt by using triethanolamine as alkalyzing agent. Aceclofenac is an orally effective non-steroidal anti-inflammatory drug (NSAID) which exhibits very low aqueous solubility. The physico chemical properties of the prepared salt were investigated by solubility studies, micromeritic studies and characterized by FTIR, DSC and SEM studies. The FTIR, DSC spectra indicated that the aceclofenac formed salt with triethanolamine (ACE-TEA). ACE-TEA salt lowered the melting point of aceclofenac and the salt exhibit greater solubility than the drug alone. From the SEM studies, the surface morphology of aceclofenac and the prepared salt was irregular in shape and more crystalline nature of drug compared to prepared salt.

Keywords: Aceclofenac, Triethanolamine, Pharmaceutical Salt, Characterization.

1. INTRODUCTION:

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and lower medicine production costs. For the drug absorption into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. For hydrophobic drugs, dissolution process is the rate-controlling step and, therefore, determines the rate and degree of absorption. Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. About 50% of orally administered drug compounds suffer from formulation problems related to their water insolubility [1]. As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs. One way of improving solubility and dissolution properties is salt formation of aceclofenac.

Pharmaceutical salts are the important solid-state modifications that are formed by an ionic Active Pharmaceutical Ingredient (API) and a suitable, pharmaceutically acceptable counter ion. They have been a part of crystal form selection for a very long time as they offer diversity of composition and therefore can exhibit a wide range of physico-chemical properties. It is also used to enhance the solubility of poorly soluble APIs which represent approximately 40% of the drugs on the market and as many as 60% of APIs in development. To improve the solubility or dissolution rate of a BCS Class- II API's, it is possible via pharmaceutical salt formation [2].

Aceclofenac (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid) is an orally effective non-steroidal anti-inflammatory drug (NSAID) of the phenyl acetic acid group, which possesses remarkable anti-inflammatory, analgesic and antipyretic properties. The analgesic efficacy of aceclofenac 100 mg is more prolonged than that of acetaminophen 650 mg. Aceclofenac appears to be particularly well tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects. Aceclofenac exhibits very slight solubility in water and as a consequence it exhibits low bioavailability after oral administration [3,6,7,8].

In the present study, triethanolamine is used to prepare aceclofenac salt to improve the solubility and dissolution studies.

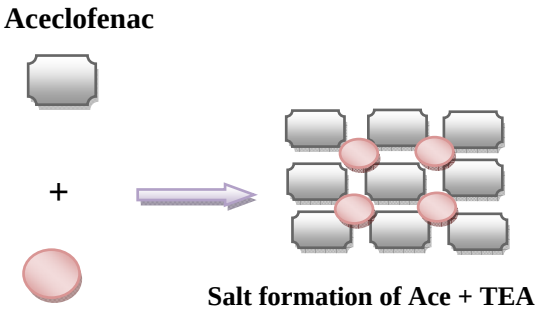

Figure 1: Salt formation of Aceclofenac-triethanolamine salt

2. MATERIALS AND METHODS:

Aceclofenac was obtained from Yarrow chemicals - Mumbai, triethanolamine was purchased from Merck Ltd-Mumbai. All other chemicals and solvents used were of analytical grade.

2.1. Preparation of aceclofenac-triethanolamine salt (Ace-TEA):

Aceclofenac was dispersed in acetone and an equimolar amount (1:1) of triethanolamine was added. Precipitated salt are collected by filtration. Filtrate is washed with acetone several times. The white solid filtrate is dried [4, 5].

2.2. Characterization of the pure drug and prepared salt:

2.2.1. Fourier transform infrared spectroscopy (FTIR):

FTIR spectra of aceclofenac and its prepared salt were recorded by using FTIR spectrophotometer. Potassium bromide pellet method was employed and the broad spectrum was collected under identical conditions. Each spectrum was derived from averaging 16 single scans collected in the region 4000 to 400cm^{-1}.

2.2.2. Differential Scanning Calorimetry (DSC):

DSC samples were analyzed by NETZSCH DSC 204. Samples were heated at scanning rate of 10^{0}C min^{-1} over the temperature range of 0- 300^{0}C under dry nitrogen purging (10mL/min).

2.2.3. Scanning Electron Microscopy (SEM):

SEM analysis was performed for the pure drug by using (HITACHI S-3000N SEM), to study about the shape and surface characteristics. The samples were mounted on alumina stubs using double adhesive tape coated with gold in HUS-5GB vacuum evaporator at an accelration voltage of 10 kv and a magnification of 5000x.

2.2.4. Solubility studies:

Solubility determination was performed by the synthetic method whereby, 5mg of prepared salt was taken in a screw capped glass vials to which incremental addition of solvent was added until the solution remained clear. The approximate visual solubility of the drug in solvents may be determined by noting the volume of solvent added until complete dissolution. After each addition of solvent, vial was shaken on a vial shaker for 2mins. All determinations were performed in triplicate.

2.2.5. Micromeritics:

Bulk and tapped density data was collected by doing density analysis by using bulk density apparatus. For tapped density, until no volume change occurred. In order to obtain an estimation of powder compressibility and flow, the compressibility index and the Hausner ratio were calculated according to the formulas below.

$$\text{Bulk density} = \frac{\text{Mass (M)}}{\text{Bulk volume } (V_0)}$$

$$\text{Tapped density} = \frac{\text{Mass (M)}}{\text{Final volume } (V_F)}$$

$$\text{Compressability index} = \frac{100\ (V_0 - V_F)}{V_0}$$

$$\text{Hausner ratio} = \frac{V_0}{V_f}$$

Where V_o = unsettled apparent volume

V_f = final tapped volume

2.2.6. Flow property:

Angle of repose was determined by fixed funnel method. Angle of repose was determined by fixed funnel method. A glass funnel was held in place with a clamp on a ring support over a glass plate. The glass plate is placed on a micro-lab jack. 2g of the drug and the prepared salts were transfered into the funnel keeping the orifice of the funnel blocked by the thumb. As the thumb was removed, the lab jack was adjusted so as to lower the plate and maintain about 1cm gap between the bottom of the funnel stem and top of the powder pile. When the powder was emptied from the funnel, the angle of the heap to the horizontal plane was measured. The height of the pile (h) and the radius of the base (r) was measured. The angle of repose was determined by the formula:

$$\text{Angle of repose } (\theta) = \tan^{-1}\left(\frac{h}{r}\right)$$

3. RESULTS AND DISCUSSION:

3.1. FTIR studies:

The OH peak in aceclofenac is observed at 3317.56cm^{-1} and the NH peak in diethanolamine is observed at 3381.93cm^{-1} and in the prepared salt a strong narrow characteristic narrow absorption peak is observed at 3352.28cm^{-1}, in which the negative charge on oxygen atom in aceclofenac and the positive charge on triethanolamine nitrogen interact electrostatically.

3.2. DSC studies:

The DSC studies have been performed for the pure drug and salt. It is observed that the sharp melting endotherm peak in aceclofenac is at 156.4^{0}C and for the prepared ACE-TEA salt has a sharp endotherm melting peak is observed at 132.3^{0}C due to reduced crystalline lattice energy of the prepared salt.

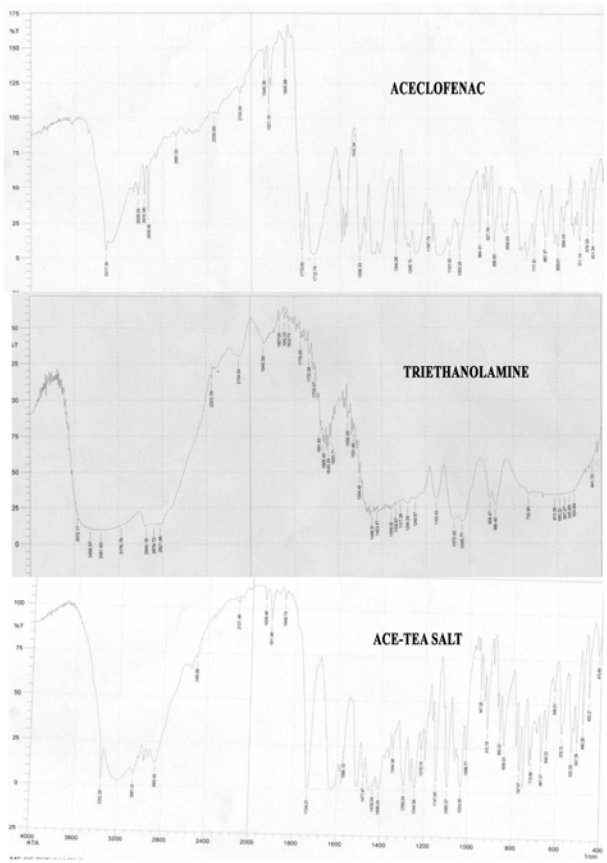

Figure 2: Comparitive FTIR spectra of Aceclofenac, triethanolamine and prepared salt (ACE-TEA)

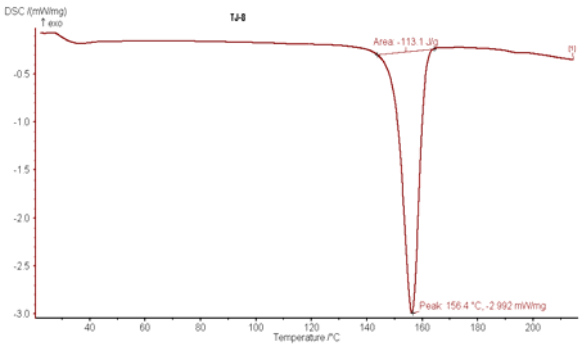

Figure no.3: DSC of Aceclofenac

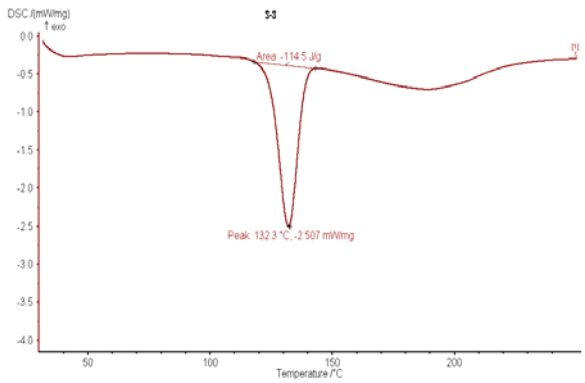

Figure no.4: DSC of the prepared salt (ACE-TEA)

3.3. SEM studies:

From the SEM studies, the surface morphology of aceclofenac and the prepared salt was irregular in shape and more crystalline nature of drug compared to prepared salt.

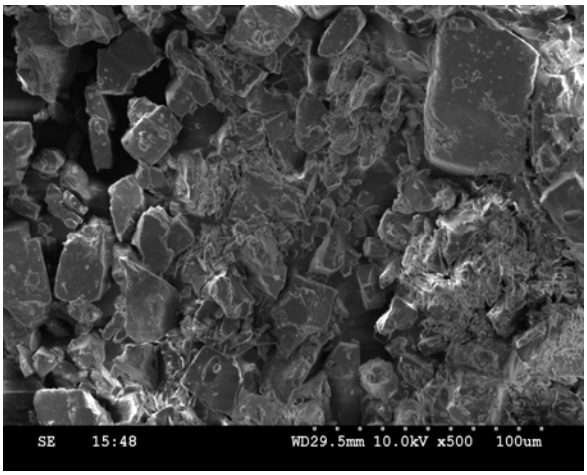

Figure no.5: SEM image of Aceclofenac

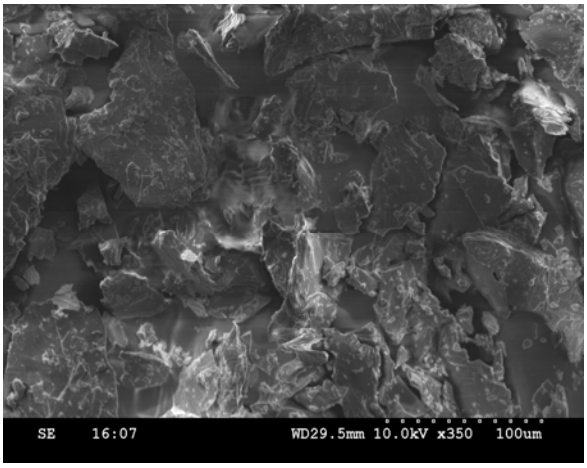

Figure no. 6: SEM image of prepared salt (ACE-TEA)

3.4. Solubility Studies:

The solubility studies have been performed for the drug and the prepared salt in three solvents. It has been observed that in distilled water the pure drug has 0.2mg/ml and in the prepared salt 500mg/ml. In pH 6.8 buffer, the drug shows 0.28mg/ml and 166.6mg/ml in salt. In pH 7.4 buffer, the drug shows 0.276mg/ml and 217.39mg/ml in salt. From this study, it has been observed that salt has a remarkable increase in the solubility compared to pure drug.

3.5. Micromeritics:

The density analysis can be determined by calculating the bulk density, tapped density, Hausner ratio and compressability index and the result as shown in table no.1.

Table 1: Micromeritics of the pure drug and for the prepared salt

Density Analysis	Aceclofenac	ACE-TEA Salt
Bulk density	0.54±0.025	0.3±0.032
Tapped density	0.73±0.035	0.44±0.021
Hausner ratio	1.37±0.085	1.44±0.085
Compressibility index	27.38±0.058	25.25±0.058

Based upon the bulk density the particles can be termed as heavy or light particles. Light particles have low bulk density and heavy particles have more bulk density. The pure drug aceclofenac exhibits more density (0.54±0.025) and for the prepared salt exhibits low bulk density (0.3±0.032) and this density is used for the selection of suitable container.

Carr's index and Hausner ratio have been widely used to estimate the flow properties of powders. A Hausner's ratio of less than 1.20 indicates good flow whereas above 1.5 indicates poor flow. Similarly Carr's index value less than 15% indicates good flow and the value greater than 25% indicates poor flow. Aceclofenac showed the Carr's index and Hausner ratio values of 27.38 and 1.37 respectively which indicates poor flow and for the prepared salt (Aceclofenac-Triethanolamine salt) showed the Carr's index and Hausner's ratio values of 27.38±0.058 and 1.37±0.085 lesser in comparision to aceclofenac (pure drug) thereby showing an improved flow behaviour.

3.6. Flow property:

The flow property for the pure drug and for the prepared salt was determined by angle of repose. The angle of repose for the pure drug was found to be 31.23±1.46 and for the prepared salt it was 33.54±1.83 which were passable.

4. CONCLUSION:

In this study prepared aceclofenac salt showed improved solubility and the micromeritic properties showed poor flow and this flow can be increased by adding glidants. This technology has the potential to provide the directly compressed aceclofenac tablets with improved bioavailability. However, extensive long-term stability, toxicity and clinical pharmacokinetic studies are required before commercialization.

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