

Quantitative Estimation of Tableability of Aceclofenac after Incorporation of Titanium Dioxide using Area under the Curve

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ABSTRACT

Background: Tablet manufacturing with direct compression is one of the leading industrial technique that consumes less time, labour and economic also. But the choice of excipients are critical in this case which will allow the drug to get compressed without granulation techniques. **Purpose:** Aceclofenac is a BCS class II non-steroidal anti-inflammatory drug, which exerts a low oral bioavailability because of low solubility in aqueous medium. The drug also suffers from compressibility and also shows poor tableability. **Methods:** We have attempted to improve tableability by incorporating titanium dioxide (TiO_2) through kneading and solvent evaporation technique. **Results:** In the FTIR study revealed that NH and Cl aromatic stretching of aceclofenac has been affected significantly due to binding with TiO_2 . DSC thermogram ascertained the partial amorphization of the drug in the formulations. Evaluated tableability from the area under the applied pressure vs tensile strength curve (AUTC) of A1T1 has shown a poor value in contrast to other formulations.

Key words: Aceclofenac, Tableability, Titanium dioxide, Direct compression, Area under the curve.

INTRODUCTION

Tablet manufacturing with direct compression is one of the leading industrial techniques that consumes less time, labour and more economic also. But the choice of excipients are critical in the direct compression which allows the drug to get compressed without granulation techniques. The excipient must have symmetrical particle size distribution, must be compatible with the drug and other excipients and to bind a large amount of material while it is undergoing direct compression. Many research reports are available on directly compressible tablets but, quantitative estimation of tableability using non-linear approach are very few in number.

Aceclofenac, a BCS class II non-steroidal anti-inflammatory drug possesses remarkable analgesic and antipyretic properties and used to treat rheumatoid and osteoarthritis.¹⁻³ The drug also suffers from compressibility and shows poor tableability.^{4,5}

Talcum and magnesium stearate as the flow promoting agents even could not change in the flow properties of the drug in the presence of HPMC. The compression problem was observed in preparing aceclofenac mouth dissolving tablet by direct compression using microcrystalline cellulose and other excipients. Patil *et al.* 2012 has prepared aceclofenac agglomerates to improve its flowability and compressibility by emulsion solvent diffusion technique.⁶ The major limitations associated with the technique are the significant drug loss and polymer loss.⁷ Shete *et al.* 2018 have prepared cocrystals of Fenofibrate and Nicotinamide. In this study they have subjected the formulations to various tableting studies like hardness, thickness but they have not created any tableability profile of those prepared tablets.⁸

This study deals with the tableability behaviour of aceclofenac kneaded with TiO_2 in different ratios by direct compression

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technique. Quantitative estimation of tableability has rarely been studied earlier for any tablet formulation by direct compression technique. Non-linear approach for estimation of tableability quantitatively has been proposed in this work from simple relationship which is supposed to be more accurate relative to least square method. Titanium dioxide is having outstanding bio-compatibility and the drug releasing performance can be tuned by designing formulation/medical implants.^{9,10}

MATERIALS AND METHODS

Materials

Titanium dioxide was purchased from Merck Specialities Pvt. Ltd., Mumbai, India. Microcrystalline cellulose was obtained from HIMEDIA Laboratories Pvt. Ltd., Mumbai, India. Aceclofenac pure drug was obtained as a gift sample from Mannequin Pharmaceuticals Pvt. Ltd., Bhubaneswar, Odisha.

Preparation of Aceclofenac TiO₂ Kneaded mixture

Aceclofenac was dissolved in a minimal amount of acetone and a kneaded mixture was prepared with titanium dioxide at different ratios.¹¹ The mass was dried at 50°C until constant weight and preserved in a desiccator.

Characterization

FTIR Study

FTIR study of pure drug and formulated powder sample was done using KBr pellet method.¹² The FTIR spectrum was a mean of 80 times scan between the wave number of 400-4000cm⁻¹ in (Model: JASCO FTIR 4100type A).¹³

Direct Compression

The prepared formulation was mixed with microcrystalline cellulose by maintaining a ratio of 1:2. 200 mg of the prepared mixture then subjected to the punching cavity manually. The pressure was varied while preparing the compacts by using the previously stated formulations. The pressures which have been used were 0.5, 1, 1.5, 2 and 2.5 tons.¹⁴ The dimensions and hardness was then measured for determination of various physical and mechanical properties.⁸ Tensile strength was calculated by using formula:¹⁵

$$TS = \frac{2F}{\pi dh}$$

Here, F is compression force applied in Newton force (unit: kg.m/S²); d= diameter in meter, h=thickness of the tablet in meter.

Kawakita model

To relate between compaction pressure and volume reduction Kawakita and Ludde has proposed model as follows:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab}$$

In the above equation the 'P' signifies applied pressure, 'a' and 'b' both are constants which gives an idea of the maximum volume reduction and an inclination towards volume reduction respectively. 'C' can be described as degree of volume reduction and can be calculated from

$$C = 1 - \frac{V}{V_0}$$

(where, V₀ is the initial volume of the powder column and V is the volume under pressure).^{16,17}

RESULTS AND DISCUSSION

FTIR Study

An intense peak was observed at 3317 cm⁻¹ probably because of the amine group.¹⁸ (Figure 1) The peaks at 1715 and 1771 cm⁻¹ may be formed due to stretching of two carbonyl (C=O) groups in the aceclofenac structure.^{19,20} The peak at 2969 cm⁻¹ in both pure drug and formulations indicates the symmetric stretching of CH₂.²¹ In the formulations, the intensity of the peaks has decreased along with the increase of TiO₂ concentration which indicated a possible binding of TiO₂ and Aceclofenac.

Direct Compression

A model given by Sun *et al.* 2001 is mainly used in the case of expressing tableability. The equation is as follows:²²

$$TS = k_r P + C$$

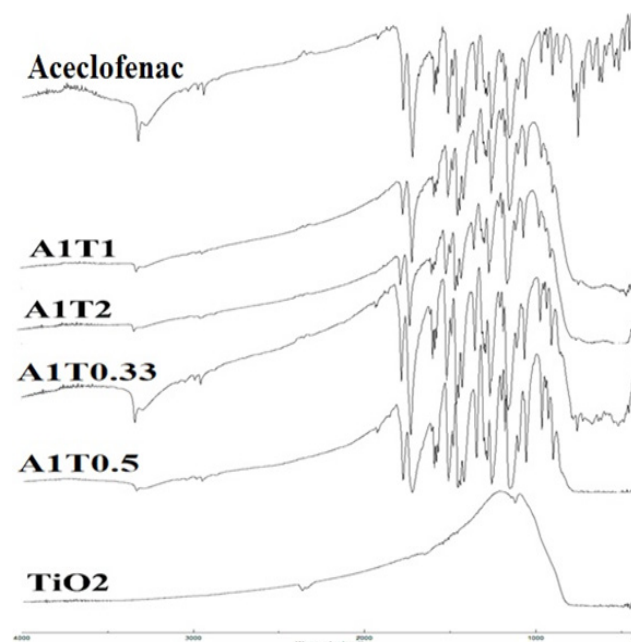


Figure 1: FTIR spectrum of aceclofenac and formulations

Tabletability of the composite powder material can be expressed by applied pressure vs tensile strength curve (Figure 2) where the slope value ' k_t ' signifies

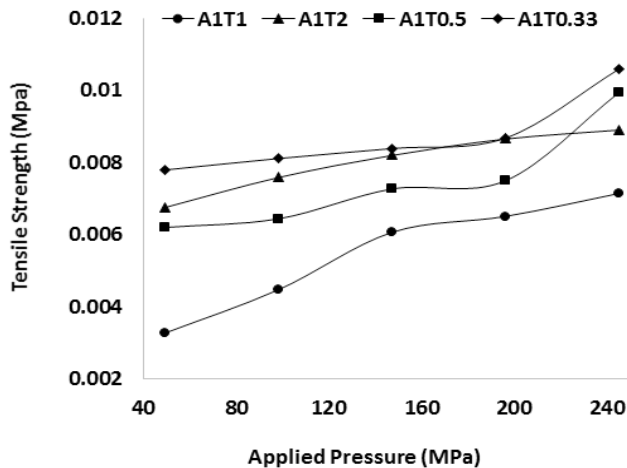


Figure 2: Tabletability profile of the formulations.

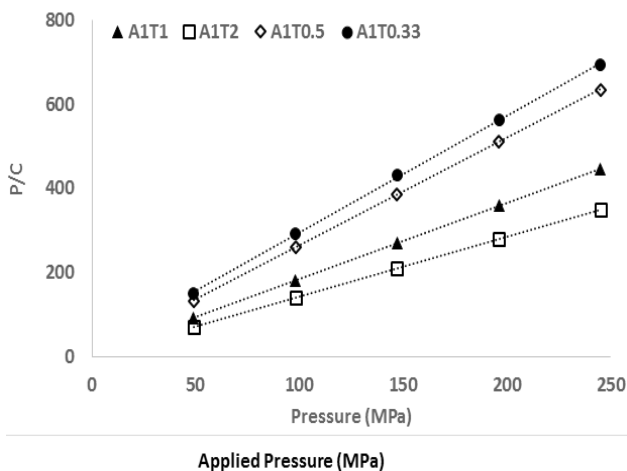


Figure 3: Kawakita pressure Plot of the prepared formulations.

tabletability coefficient. It can be quantified by Area under the applied pressure vs tensile strength curve (AUTC). (Table 1) The plot has clearly shown that the 1:1 formulation is poor in tabletability in contrast to the other formulations.²³

Kawakita Model

As per Kawakita linearity model, the highest compressibility (a) and inclination towards volume reduction (b) are seen with the formulation A1T2 (Figure 3) (Table 2).

Proposed binding of Aceclofenac with TiO₂

Proposed binding between TiO₂ and aceclofenac has been depicted in Figure 4a, b. Binding could be possible in either of the two ways. Titanium is getting attached to Chlorines while the amine group is getting attached with the oxygen present in TiO₂. Chlorine may bind with the titanium by opposite charge attraction (4a) or formation of hydrogen bond between chlorine and titanium (4b).

CONCLUSION

Aceclofenac alone could not be tableted because of very poor compressibility by direct compression. Tabletability of A1T2, A1T0.5 and A1T0.33 formulations has been improved compared to A1T1. The kawakita parameters suggested that the inclination towards

Table 1: Tabletability parameters.

Formulation Code	$K_t \cdot 10^6$	AUTC
A1T0.33	12.49	1.685
A1T0.5	17.32	1.435
A1T1	19.80	1.091
A1T2	10.94	1.584

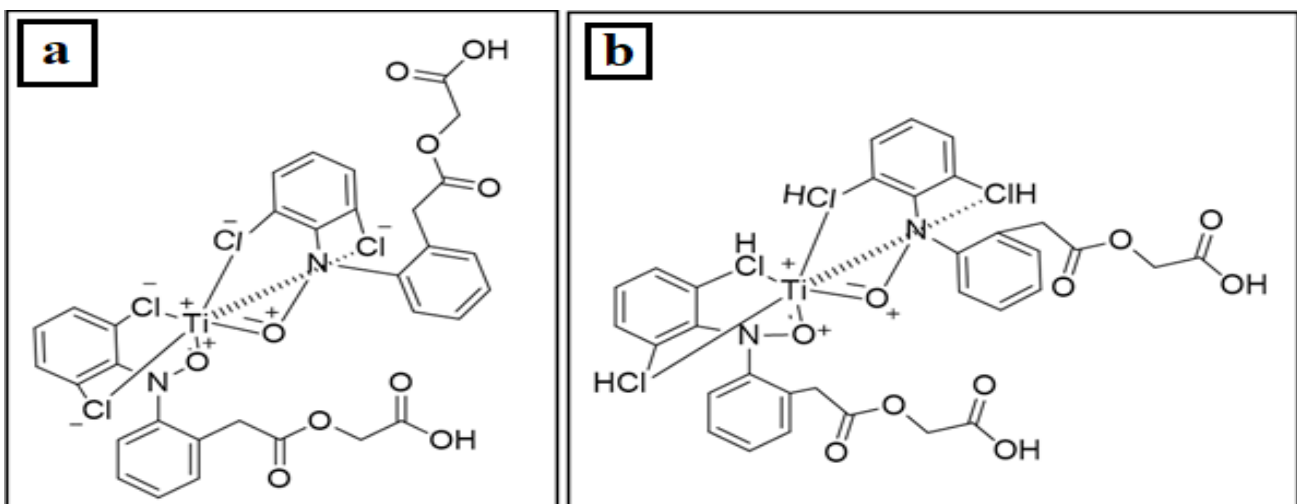


Figure 4: Proposed binding between TiO₂ and Aceclofenac. Chlorine may bind with the titanium by opposite charge attraction (4a) or formation of hydrogen bond between chlorine and titanium (4b).

Table 2. Kawakita Parameters of aceclofenac kneaded with TiO₂ in different ratios

Formulation Code	Drug:TiO ₂ (w/w)	Equation	1/a	1/ab	a	ab	b
A1T0.33	1:0.33	y=2.764x+19.17	2.764	19.176	0.361	0.052	0.144
A1T0.5	1:0.5	y=2.56x+8.16	2.560	8.160	0.390	0.122	0.313
A1T1	1:1	y=1.81x+3.14	1.810	3.146	0.552	0.317	0.575
A1T2	1:2	y=1.419x+1.26	1.419	1.261	0.704	0.793	1.125

volume reduction of the powder may be directly related to the amount of TiO₂ incorporation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

BCS: Biopharmaceutical Classification System; **TiO₂:** Titanium Dioxide; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier Transform Infrared Spectroscopy; **AUTC:** Area under the Tableability Curve; **HPMC:** Hydroxypropylmethylcellulose; **TS:** Tensile Strength.

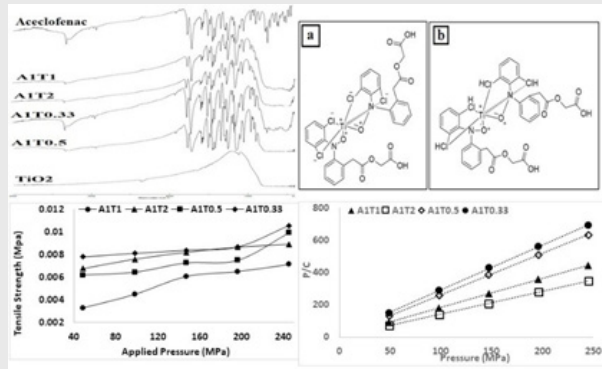
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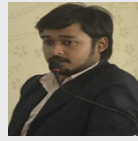
SUMMARY

Aceclofenac is a poorly compressible drug and has a low tableability. We have tried to overcome these drawbacks by incorporating TiO₂ in the formulation. An increase in tablet ability has been observed after the addition of TiO₂. Kawakita parameters also suggested that the inclination towards volume reduction of the powdered formulation is directly proportional to the amount of TiO₂ added.

PICTORIAL ABSTRACT



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