Abstract: The present invention relates to a dry ready to use modified release dosage formulation for Aceclofenac dosage forms and its salts and derivatives thereof, a process for preparing extended release tablet using INSTAMODEL (A43D00045) manufactured by Ideal Cures Private Limited Mumbai India thereof also use thereof as additive to animal feeds, foods and food supplements and also cosmetic and pharmaceutical compositions. Invention also relates to ready-to-use modified release compositions capable of regulating release of Aceclofenac at various dosage strength, a process for production thereof and also use thereof as formulated pharmaceutical compositions.
Description
EXTENDED RELEASE FORMULATION OF ACECLOFENAC

Technical Field
The present invention relates to a dry ready to use modified release dosage formulation for Aceclofenac dosage forms and its salts and derivatives thereof, a process for preparing extended release tablet using INSTAMODEL (A43D00045) manufactured by Ideal Cures Private Limited Mumbai India thereof also use thereof as additive to animal feeds, foods and food supplements and also cosmetic and pharmaceutical compositions. Invention also relates to ready-to-use modified release compositions capable of regulating release of Aceclofenac at various dosage strength, a process for production thereof and also use thereof as formulated pharmaceutical compositions.

Background Art
In general Aceclofenac are indicated for use as non-steroidal anti-inflammatory drug (NSAID). Aceclofenac is the glycolic acid ester of diclofenac. It is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Aceclofenac has higher anti-inflammatory action than conventional NSAIDs. It is a cytokine inhibitor. Aceclofenac works by blocking the action of a substance in the body called cyclo-oxygenase. Cyclo-oxygenase is involved in the production of prostaglandins (chemicals in the body) which cause pain, swelling and inflammation. It belongs to class II of the biopharmaceutical classification (BCS) in which dissolution rate is the controlling step in drug absorption. Aceclofenac is known for Anti-inflammatory and Analgesic action. It is poorly soluble in water leading to erratic dissolution, oral absorption and therefore poor bioavailability is also observed. Aceclofenac is administered through solid dosage ranges from 100 mg to 200 mg daily. In standard doses of 200 mg is taken in two equally divided doses, one tablet in the morning and one tablet in the evening. Prescription of Aceclofenac recommend that it should be taken with meals if possible and daily. Dosage generally should not exceed 200 mg daily.

It's well known in the art that Aceclofenac is poorly soluble in water leading to erratic dissolution, oral absorption and therefore poor bioavailability (less than 70%) is also observed. Aceclofenac is a BCS Class-II drug (Biopharmaceutical Classification System) i.e. Low solubility and High permeability. Further as Aceclofenac has poor solubility in water, it leads to erratic dissolution, oral absorption and therefore poor bioavailability.

In state of the art modified release compositions are developed to provide relatively constant drug plasma levels and sustained efficacy for longer period of time. In principle aim of extended and modified release composition is to get required therapeutic concentration of the active in the blood stream and maintain its therapeutic
concentration without deviation from strength during specified period. Prior art
documents disclosing such extended release compositions of aceclofenac are WO
201109037 1, WO 201214502, IN 223582 and 998/DEL/2008.

In state of art various grades of cellulosic polymers are used in the modified release
compositions e.g. HPMC polymer. These polymers extend the release of daig by
showing osmosis nature in aqueous conditions. Cellulosic matrix based system work
by the swelling and gelling function i.e. these polymer swell through influx of liquids
and a gel like physical structure is formed which provides extended release effect fa-
cilitated by diffusion of the Aceclofenac.

In theory it is known that with high viscosity grade polymer after attaining gelling
effect drug release is lower but as time progresses drug release is increased. On the
contrary with low viscosity grade polymer after attaining gelling effect drug is release
at faster speed due to larger pore sized and concentration of drug decrease as time
progresses.

In order to minimize difficulties associated in ratios of polymers, batch to batch
variations, formulating, storing and preserving many loose components of differently
textured and sized ingredients means have been desired in industry to make ready to
use extended release or modified release composition which are convenient to handle.

The object of the present invention was to provide a ready-to-use matrix system
and method of preparation for Aceclofenac extended release or modified release for-
mulation.

Disclosure of Invention

Summary of Invention

Accordingly, the present invention provides hydrophilic matrix system based ready
to use technology for Modified or Extended Release Formulation of Aceclofenac Hy-
drochloride: using INSTAMODEL(A43D00045) manufactured by ideal Cures Private
Limited Mumbai India.

Accordingly, the present invention also provides method for making ready to use
Aceclofenac modified or extended release formulation, involving steps of aqueous
granulation, drying, lubrication and punching of tablets.

In another aspect, present invention also provides Once a day Aceclofenac table
dosage form.

Extended released or modified release tablet formulation can be in the form of
single or multilayer tablets, capsule shaped oral dosage form, caplet, granules, disc,
pellets, granules in capsule, mini-tablets in oral dosage form and other possible oral
dosage form mean thereof.

In yet another embodiment, the solid oral dosage form can optionally include one
or more pharmaceutically acceptable excipients.

The details of one or more embodiments in the practice of the inventions are set
forth in the description below. Other features, objects and advantages of the inventions
will be apparent from the appended examples and claims.

**Detailed Description**

Below description specify various scientific terms unless stated with context, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

Unless stated to the contrary, The feature 'ready-to-use', in the context of the present invention, is taken to mean the property that the composition according to the invention can be used directly for its purposes by the user by simply dispersing it in required quantity of water.

The term ‘modified release’ is in context of the invention as a way of active drug delivery, where the rate of release of the active drug from the composition is not exclusively dependent on the concentration of active drug remaining in the dosage form and/or the solubility of the active drug in the liquid surrounding the composition, and where the time course with or without respective location of release of active drug from an oral dosage form are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms. For the purpose of invention active drug is selected from Aceclofenac, its intermediates and derivatives thereof.

The term 'Aceclofenac' is in context of the invention includes, its polymorphic forms, the pharmaceutically acceptable salts, including salts esters and other chemical derivatives or intermediates etc. The solid pharmaceutical composition comprises Aceclofenac from 1 to 80 w/w % of dosage form.

The term 'dosage', 'solid pharmaceutical composition' may include one or more of tablet, capsule, powder, disc, caplet, granules, pellets, granules in capsule, minitablets, minitablets in capsule, pellets in capsule, sachet and the like. The solid pharmaceutical composition also includes multilayer tablets. The solid pharmaceutical compositions are meant for oral administration.

The term 'tablet' includes pharmaceutical compositions of all shapes and sizes, whether coated or uncoated.

The term 'Lubricant' in the context of the present invention, is taken to mean that an ingredient, added to prevent the adhesion of tablet materials to the punches and dies, reduce inter-particle friction and facilitate the ejection of oral dosage forms from the die cavity. Lubricant of present invention includes but not limited to talc, magnesium stearate, stearic acid, sodium stearoyl fumarate and there derivatives thereof.

The term 'Glidant' in the context of the present invention, is taken to mean that an ingredient which enhance product flow by reducing inter-particle friction. Glidant can be used in present invention includes but not limited to silicon dioxide, colloidal silicon dioxide and there derivatives thereof. It is available under several brand names.
like AEROSIL® and CAB-O-SIL®.

[24] The term 'Solvent' in the context of the present invention, is taken to mean ingredient that facilitate mixing of components in wet granulation process. Solvent can be used in present invention includes but not limited to Acetone, ethanol, methylene di chloride, isopropyl alcohol, water or their mixture thereof.

[25] The term 'Binder' or 'Binding agent' in the context of the present invention, is taken to mean ingredient that facilitate binding of components in wet granulation process. Solvent can be used in present invention includes but not limited to dextrin and their derivatives, maltodextrin, polyvinyl polymers, Polyvinyl pyrrol idone K30 (PVP K30) and there derivatives thereof.

[26] The ready to use polymeric composition Instamodel A43 D00045 for extended and modified release formulation was supplied by Ideal Cures Private Limited, Mumbai, www.idealcures.co.in. This product was used to create inventive dosage form having ideal modified release profile for twice a day administration.

[27] According to inventors it was surprisingly found that extended release solid oral dosage form for Aceclofenac can be created with ready to use Instamodel (A43 D00045) system and dosage form have advantageous modified release properties. The ready to use composition in accordance with present invention comprise INSTAMODEL (A43D00045). In one of the embodiment of present invention Aceclofenac is formulated with ready to use composition to prepare modified release dosage form. In accordance with present invention different salts, derivatives, polymorphs of Aceclofenac could be combined to achieve ready-to-use composition to achieve extended or modified release dosage form.

[28] In a dosage form according to the invention Aceclofenac is blended with the ready to use polymer and aqueous granulated further the granulated mixture is compressed to produce a solid formulation. The ingredients are blended to form a uniform powder and then compressed with means generally known to skilled in the art.

[29] In yet another embodiment of present invention Aceclofenac and INSTAMODEL are blended together with binding agent and thereafter wet granulated and dried. These dried granules are then processed in presence of lubricant and glidant, and thereafter compressed to form appropriate dosage form and finally coated.

[30] In yet another embodiment of present invention Aceclofenac and INSTAMODEL are blended together with binding agent and thereafter wet granulated and dried. These dried granules, are then processed in presence of lubricant and glidant, and thereafter compressed to form appropriate dosage form and optionally coated.

[31] This system of formulation uses simple and economic polymers hence cost effective to the customer. Another advantage of the present formulation is its robust and reproducible results for extended release dose form without batch to batch variations. Further by using aqueous solvent system for granulation dosage form does not have any residual solvent or hazardous effect found in many organic solvent based
formulations.

Inventive dosage form may be prepared by blending Aceclofenac, their derivatives or combination thereof along with ready to use composition. Therefore inventive formulation preparation comprise steps as:-

1. Blending of ready to use formulation Instamodel (A43D00045) with Aceclofenac.
2. Thorough mixing to form dry powder
3. Wet granulation with active drug and solvent
4. Sieving through appropriate size
5. Tray drying or fluidized bed drying
6. Optionally addition of lubricant
7. Final tablet compression
8. Optional film coating

According to one of the embodiment inventive dosage form is prepared by blending ready to use composition (Instamodel A43D00045), process blending is performed by conventional dry blender or a food processor or 'V-blender' or a similar function device. Further Aceclofenac are processed using aqueous solvent with binder through wet granulation or a similar wet mixing method to generate dosage formulation. Dosage formulation is further dried, sieved and compressed optionally with addition of lubricant, binder, glidant to form modified release oral dosage form.

In one of the embodiment of present invention, inventive dosage formulations are prepared by blending Aceclofenac along with Instamodel (A43D00045). Initially all components are blended by conventional dry blending in a food processor or 'V-blender' or a similar function device. Other solid oral dosage formulation components like binders, lubricants, glidants, detackifier, excipients can be added to create inventive formulation. Further mixture is then processed with appropriate quantity of aqueous solvent with binder and wet granulated. Obtained sieved granulated is then uniformly mixed with premeasured amount of the lubricant to improve industrial acceptability and oral dosage compression quality. Subsequently uniform mixed inventive formulation is compressed in standard pharmaceopoeial equipment to get a controlled release oral dosage formulation of the correct desired weight and strength.

According to one of the main embodiment wherein hardness, of tablets produced is in range of 7 Kg/cm² to 15 Kg/cm². In one of the embodiment oral dosage forms produced by inventive composition having human administrable active ingredient is suitable for human use. Alternatively drug suitable for veterinary purpose formulated in accordance, with present composition will be suitable for veterinary use.

According to the objective of present invention Aceclofenac is formulated in oral dosage form for modified or extended release delivery. Inventive composition comprising 50 to 300 mg or 200 mg of Aceclofenac in plurality of dosage for-
mulations. Controlled release formulation can have combination of one or more additional drugs.

[38] Suitable APIs that can be used with the present invention include, but are not limited to: adrenergic blocking agent; acetyl-cholivesterase inhibitor; analgesic or antipyretics; angiotensin modulator; anthelmintic agents; anti anxiety agent; anti-tibacterial; antibiotic; anticoagulant; anticonvulsant; antidepressant; antifungal; anti-histamine; antimalarial; antimicrobial agent; antipsychotic agent; Antiviral agents; blood glucose lowering drug; calcium channel modulator; diuretic; erectile dysfunction; gastric acid secretion inhibitor; histamine H2-receptor antagonist; inhibitor of steroid Type II 5[alpha]- reductase including; lipid regulating agents; selective H1-receptor antagonist; vasodilator; vitamins.

[39] Following examples are offered to more fully illustrate the invention, but are not to be construed as limiting the scope thereof.

Mode for Invention

[40] Example 1.

[41] Preparation of Aceclofenac modified release tablets (200 mg)

[42] The dosage formulation for 100,000 (28.00 kg) Tablets of Aceclofenac is prepared using composition as stated in table-1 wherein Aceclofenac is 20.0 kg and 6.5 kg of Instamold (A43D00045) are weighed, sifted in rapid mixture granulator accordingly, subsequently sieved to get uniformly granulated powder through 40 mesh screen. It is noted that other size screen could be used to get similar results. Sieved Aceclofenac with above ingredients is granulated using 5.5 kg of water and 1.0 kg of binder (PVPK-30) as granulating solvent in rapid mixture granulator (RMG). It is recommended that RMG should be at slow speed for 15 min followed by high speed for 3-5 mins (Total qty of water used approx. 5-6 kg). Granulation step requires proper optimization of water quantity and continuous monitoring to avoid heavy granulation. If required extra water can be added gradually under continuous observation (to avoid heavy wet mass). Generated wet mass is sieved using #20 mesh screen (Multi-mill/ Fitzmill) dried in tray drier (or Fluidized bed dryer) at temperature not more than 50°C-55°C keeping loss on drying at 1-2%.

[43] Subsequently sift the dried granule using #30 mesh sieve on vibratory sifter and again sift on 1.0 mm screen at slow speed.

[44] Table 1

<table>
<thead>
<tr>
<th>Formulation ingredients</th>
<th>Composition</th>
<th>Quantity for Batch size of 100,000 Tabs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% w/w</td>
<td>mg/ tablet Kg</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>43%</td>
<td>00</td>
</tr>
<tr>
<td>Component</td>
<td>Quantity</td>
<td>Composition</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Instamodel (A43D00045) I (H)</td>
<td>1</td>
<td>21%</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>1</td>
<td>57%</td>
</tr>
<tr>
<td>Purified Water</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
<tr>
<td>Magnesium Stearate, USPN/F BP/Eur. Ph</td>
<td>1</td>
<td>07%</td>
</tr>
<tr>
<td>Colloidal silicon dioxide (Aerosil 200)</td>
<td>1</td>
<td>72%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.00</strong></td>
<td><strong>200.0</strong></td>
</tr>
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</table>

Coating ingredients

<table>
<thead>
<tr>
<th>ingredient</th>
<th>Amount</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instacof Universal (ICU-3849) white I (H)</td>
<td>7.00</td>
<td>84 kg (includes 20% extra to compensate process losses)</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s.</td>
<td>6.8 kg</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>287.00</strong></td>
<td></td>
</tr>
</tbody>
</table>

To promote efficient tablet punching further 0.2 kg of Colloidal silicon dioxide and 0.3 kg of magnesium stearate sieved through 40 mesh screen is added to above dried blended formulation in blender for subsequent 5 minutes. Final screened granules are compressed using 9.5 mm (for 280 mg average weight) circular, standard concave circular punches using Karnavati Tablet Compression Machine at hardness not less than 6-10 kg/cm². Generated dosage form tablets are then subjected to film coating using Instacoat Universal. Coating composition is weighed in accordance with table 1 and 11% coating suspension is prepared in water with stirrer and mixed for about 45 minutes subsequently it is passed through 80 mesh screen. Coating is preformed on dosage form using INSTACOAT Pharma RnD coaler (6' pan) at 25 rpm with inlet temperature being 53 °C and bed temperature at 40 °C coating was done using 1mm nozzle sprayer with peristaltic pump injecting coating suspension at the rate of 1ml/min. Coated tablets are then dried and packed as per pharacopoeial guidelines.

Example 2

Dissolution Profile Evaluation of Aceclofenac tablet

Aceclofenac dose form dissolution study was performed. Drug dissolution profiles
of tablet prepared are measured by USP 3.5 dissolution test of rotating basket method <711>. It is evident from standard state of the art that active ingredient may have its own dissolution testing parameters which can be found in their respective monographs. The active ingredient content for present invention is standardized for sustained release profile as per table 2:-

[50] Medium: Phosphate Buffer pH 6.8; 900 ml
[51] Time interval: 1, 4, 10, 16, 20 hour

<table>
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<tr>
<td>Time (Hour)</td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

[53] It was observed that it shows maximum absorbance at 284 nm on Double Beam (UV-VIS Spectrophotometer (UV 2700- Thermo Fisher Scientific)).

[54] ACECLO FENAC IN VITRO % DRUG RELEASE USING INSTAMODE L (A43D0M45 ) DISSOLUTION COMPARISON

<table>
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<tr>
<th>Time (Hrs)</th>
<th>Acceptance Criteria</th>
<th>% Drug Release (minimum)</th>
<th>% Drug Release (maximum)</th>
<th>% Drug Release (Average)</th>
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<tbody>
<tr>
<td>1</td>
<td>NMT 35 %</td>
<td>27.7</td>
<td>33.7</td>
<td>29.9</td>
</tr>
<tr>
<td>4</td>
<td>30 - 50 %</td>
<td>39.8</td>
<td>48.0</td>
<td>43.1</td>
</tr>
<tr>
<td>10</td>
<td>50 - 70 %</td>
<td>54.3</td>
<td>60.4</td>
<td>57.1</td>
</tr>
<tr>
<td>16</td>
<td>65 - 85 %</td>
<td>72.0</td>
<td>78.1</td>
<td>75.2</td>
</tr>
<tr>
<td>20</td>
<td>NLT 80 %</td>
<td>83.0</td>
<td>89.3</td>
<td>86.0</td>
</tr>
</tbody>
</table>

[55]
The drug dissolved profile of the Reference products and Aceclofenac having dose strength of 200 mg using Instamodul (A43D00045) formulations are compared. The release exponents for the Reference and formulated Aceclofenac is found to be having similar modified release profile indicating a predominantly diffusion based drug release mechanism.
Claims


[2] The solid pharmaceutical composition of claim 1, wherein Aceclofenac can be in form of salt, polymorphic form, its derivatives or mixture thereof.

[3] The solid pharmaceutical composition of claim 1, wherein binder is selected from polyvinyl polymers, Polyvinyl pyrrolidone K30 (PVP K30) and like.

[4] The solid pharmaceutical composition of claim 1, wherein lubricant is selected from talc, magnesium stearate, stearic acid, sodium stearyl fumarate and combination thereof.

[5] The solid pharmaceutical composition of claim 1, wherein glidant is selected from silicon di-oxide, colloidal silicon dioxide and there derivatives thereof.

[6] A process for preparing Aceclofenac tablet according to claim 1 comprising
   a. Blending Instamodel (A43D00045) with Aceclofenac.
   b. Thorough mixing and Wet granulation with binder and solvent
   c. Sieving and drying
   d. Addition of lubricant and glidant
   e. Final tablet compression
   f. Optional film coating.

[7] The solid pharmaceutical composition prepare using process for preparing Aceclofenac tablet according to claim 1 comprising
   a. Blending Instamodel (A43D00045) with Aceclofenac.
   b. Thorough mixing and Wet granulation with binder and solvent
   c. Sieving and drying
   d. Addition of lubricant and glidant
   e. Final tablet compression
   f. Optional film coating
A. **CLASSIFICATION OF SUBJECT MATTER**
A61K47/30, A61K0 9/54, A61K0 9/22, A61K0 9/24  Version=2 014.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. **FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A 6 1 K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

ORBIT, IPO- INTERNAL DATABASE, STN

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/ Authorized officer**

Indian Patent Office
Plot No. 32, Sector 14, Dwarka, New Delhi-110075

Facsimile No. Authorized officer

Telephone No. +91-1125300200

Form PC17ISA/210 (second sheet) (January 2015)
**INTERNATIONAL SEARCH REPORT**

**DOCUMENTS CONSIDERED TO BE RELEVANT**

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