Title: EXTENDED RELEASE FORMULATION OF ACETAMINOPHEN

Abstract: The present invention relates to a dry ready to use modified release dosage formulation for Acetaminophen dosage forms and its salts and derivatives thereof, a process for preparing extended release tablet using INSTAMODEL (A43D00050) 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 Acetaminophen at various dosage strength, a process for production thereof and also use thereof as formulated pharmaceutical compositions.
Description
EXTENDED RELEASE FORMULATION OF ACETAMINOPHEN

Technical Field

[1] The present invention relates to a dry ready to use modified release dosage formulation for Acetaminophen dosage forms and its salts and derivatives thereof, a process for preparing extended release tablet using INSTMODEL (A43D00050) 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 Acetaminophen at various dosage strength, a process for production thereof and also use thereof as formulated pharmaceutical compositions.

Background Art

[2] In general Acetaminophen is an analgesic and antipyretic agent which is widely used in prescription and non-prescription medicines, often in combination with other biologically active compounds. The elimination half-life of Acetaminophen is reported to be in the range of 1.9-2.5 hours. Its absorption following oral doses of conventional immediate release tablets is characterized by passive absorption with high bioavailability (80%) and rapidly occurring maximum plasma concentration (30-90 min).

[3] Acetaminophen is administered through solid dosage ranges of 1000 mg every 4 to 6 hours. In June 2009, a U.S. Food and Drug Administration advisory committee recommended maximum dosage at any given time would be decreased from 1000 mg to 650 mg.

[4] 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. Some prior art documents that disclose sustained release compositions of acetaminophen include US 4968509, WO 200180834 and WO 2004006904. In principle, the 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.

[5] 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 drug 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 facilitated by diffusion of the acetaminophen. WO 2011026125, US 2011212173 and US 2001014353 disclose use of cellulosic polymers for the modified release of drugs like
acetaminophen.

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 released 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 Acetaminophen extended release or modified release formulation.

**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 Acetaminophen Hydrochloride using INSTAMODEL (A43D00050) manufactured by Ideal Cures Private Limited Mumbai India.

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

In another aspect, present invention also provides thrice or four times a day Acetaminophen table dosage form.

Extended release 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 stearyl 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-particulate 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®.

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 dichloride, isopropyl alcohol, water or their mixture thereof.

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 pyrrolidone K30 (PVP K30) and there derivatives thereof.

[25] The ready to use polymeric composition Instamod A43D00045 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.

[26] According to inventors it was surprisingly found that extended release solid oral dosage form for Aceclofenac can be created with ready to use Instamodel (A43D00045) 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.

[27] 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.

[28] 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.

[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 optionally coated.

[30] 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.

[31] 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:-

[32] 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.

[33] 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.

[34] 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 Acetaminophen, its intermediates and derivatives thereof.

[35] The term 'Acetaminophen' is in context of the invention includes its polymorphic forms, the pharmaceutically acceptable salts, including salts esters and pother chemical derivatives or intermediates etc. The solid pharmaceutical composition comprises Acetaminophen from 1 to 90 w/w % of dosage form.

[36] 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.

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

[38] 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 stearyl fumarate and there derivatives thereof.

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

[40] 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.

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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 pyrrolidone K30 (PVP K30) and there derivatives thereof.

[42] The ready to use polymeric composition Instamodel A43D00050 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 Once a day administration.

[43] According to inventors it was surprisingly found that extended release solid oral dosage form for Acetaminophen can be created with ready to use Instamodel (A43D00050) system and dosage form have advantageous modified release properties. The ready to use composition in accordance with present invention comprise INSTAMODEL (A43D00050). In one of the embodiment of present invention Acetaminophen is formulated with ready to use composition to prepare modified release dosage form. In accordance with present invention different salts, derivatives, polymorphs of Acetaminophen could be combined to achieve ready-to-use composition to achieve extended or modified release dosage form.

[44] In a dosage form according to the invention Acetaminophen 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.

[45] In yet another embodiment of present invention Acetaminophen 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.

[46] In yet another embodiment of present invention Acetaminophen 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.

[47] 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.

[48] Inventive dosage form may be prepared by blending Acetaminophen, 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 (A43D00050) with Ac-
etaminophen.

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

According to one of the embodiment inventive dosage form is prepared by blending ready to use composition (Instamodel A43D00050), process blending is performed by conventional dry blender or a food processor or 'V-blender' or a similar function device. Further Acetaminophen 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 Acetaminophen along with Instamodel (A43D00050). 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 pharmacopoeial equipment to get a controlled release oral dosage formulation of the correct desired weight and strength.

In one of the embodiment solid dosage formulation of Acetaminophen is prepared as in plurality of layers, including but not limited to more than one layers for example bi-layer solid oral dosage formulation, for which one or more layer is/are immediate release and other one or more layers are of extended release profile.

Immediate release layer of tablet is created using sifted Acetaminophen and microcrystalline cellulose in rapid mixture granulator. Sifting is done using appropriate sieved for example through 20, 40 or 60 mesh screen. It is noted that other size screen could be used to get similar results. Sifted blend is then granulated using binding solution of PVP K30 and Purified water which were premixed till clear binding solution is formed and in rapid mixture granulator (RMG). It is recommended that RMG should be at slow speed for some time followed by high speed. Granulation step requires proper optimization of water quantity and continuous monitoring to avoid heavy granulation. Generated wet mass is sieved using screen dried in tray drier at temperature not more than 50°C-65°C. Subsequently sifting the dried granule using #30 mesh and about 1.00 mm sieve. To promote efficient tablet punching further dis-
integrant, glidant, and lubricant, optionally colorant and flavourant are added to above
dried blended formulation for final granule generation.

[54] In one embodiment extended release profile layer are made by taking Acetaminophen with Instamodell optionally Colorant. Additionally binders can be added PVP K30 in rapid mixture granulator, all ingredients are sieved to get uniformly granulated powder through appropriate mesh screen. It is noted that other size screen could be used to get similar results. Sieved Acetaminophen with above ingredients is granulated using purified water 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. Generated wet mass is sieved using 4mm 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%. Subsequently sift the dried granule using #20 #40 mesh sieve on vibratory sifter and again sift on 1.0 -2.0 mm screen at slow speed.

[55] To promote efficient tablet punching further magnesium stearate and Colloidal 
Silicon Dioxide are added to dry blended formulation in blender for subsequent 5 minutes.

[56] On a solid oral dosage form plurality of layer are created using alternate tablet 
punching sequences generally known in the state of the art. In one of the embodiments immediate and extended release layers are then compressed in a way to form a bilayer shaped oral dosage form. Immediate layer formulation granules are filled in one 
hopper of tablet compressing machine and punched in capsule shaped punches at an 
average weight of 395 mg. Further extended release granules are filled in another 
hopper of tablet compressing machine punched . Generated dosage form tablets are 
then subjected to film coating using Instacoat Universal.

[57] Both immediate and extended release layers are then compressed in a way to form 
a bilayer shaped oral dosage form. Immediate layer formulation granules are filled in 
one hopper of tablet compressing machine and punched with 18.0 ×7.5 mm capsule 
shaped punches at an average weight of 395 mg and hardness NLT 4 Kg/cm². Further 
extended release granules are filled in another hopper of table compressing machine 
and set average weight of the final tablet at 820 mg and punched hardness of 8 - 10 
Kg/cm² . Final screened granules are compressed using 10.0 mm (for 300 mg average 
weight) circular, standard concave circular punches at hardness not less than 10-15 kg/ 

[58] cm². Generated dosage form tablets are then subjected to film coating using Instacoat 
Universal.

According to one of the main embodiment wherein hardness of tablets produced is 
in range of 5 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 Acetaminophen is formulated in oral dosage form for modified or extended release delivery. Inventive composition comprising 500, 750, 820, 950 mg or 1000 mg of Acetaminophen in plurality of dosage formulations. Controlled release formulation can have combination of one or more additional drugs.

Suitable APIs that can be used with the present invention include, but are not limited to: adrenergic blocking agent; acetyl-cholin-esterase inhibitor; analgesic or antipyretics; angiotensin modulator; anthelmintic agents; anti anxiety agent; antibacterial; 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.

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

Mode for Invention

Example 1.
Preparation of Acetaminophen modified release tablets (650 mg)
The dosage formulation for 100,000 Tablets of Acetaminophen is prepared using composition as stated in table:- 1 and 2. Present tablets are prepared as bi-layer solid oral dosage formulation, for which one of the layer is immediate release and other layer is of extended release profile.

Immediate release layer of tablet is created using composition of Acetaminophen is 32.5 kg and 3.8 kg of microcrystalline cellulose 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 Acetaminophen with above ingredients is granulated using binding solution of 1.10 Kg of PVP K30 in 9.50 Kg of Purified water premixed till clear binding solution and used as granulating solvent in rapid mixture granulator (RMG). It is recommended that RMG should be at slow speed for 10 min followed by high speed for 2-5 mins. 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 4mm screen (Multi-mill/ Fitzmill) dried in tray drier (or Fluidized bed dryer) at temperature not more than 50°C-65°C keeping loss on drying at 1-2%. Subsequently sift the dried granule using #30 mesh sieve on vibratory sifter and again sift on 1.0 mm screen at slow speed. To promote efficient tablet punching further 1.40 kg of Croscarmelllose sodium is sifted and mixed with generated granules in blender. Further 0.40 kg of magnesium stearate and 0.30 Kg of Colloidal silicon
dioxide are sieved through 60 mesh screen and added to above dried blended formulation in blender for subsequent 5 minutes.

Further extended release profile layer is created using composition of Table 2 wherein Acetaminophen is 32.5 kg with 8.0 kg of Instamodle (A43D00050) and 0.008 kg of Colour sunset yellow along with 1.000 kg of PVP K30 are weighed, sifted in rapid mixture granulator for 20 minutes, 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 Acetaminophen with above ingredients is granulated using purified water 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. 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 4mm 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%.

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

### 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</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>82.28</td>
<td>325.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>9.63</td>
<td>38.0</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone(PVP K30)</td>
<td>2.78</td>
<td>11.0</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s.</td>
<td>q.s</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>3.54</td>
<td>14.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.01</td>
<td>4.0</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>0.76</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Total Weight</strong></td>
<td><strong>100.00</strong></td>
<td><strong>395.0</strong></td>
</tr>
</tbody>
</table>

### Table 2
<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</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>76.47</td>
<td>325.0</td>
</tr>
<tr>
<td>Instamold (A43D00050) 1H</td>
<td>18.82</td>
<td>80.0</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (PVP K30)</td>
<td>2.35</td>
<td>10.0</td>
</tr>
<tr>
<td>Water</td>
<td>q.s.</td>
<td>q.s</td>
</tr>
<tr>
<td>Magnesium Stearate,</td>
<td>1.18</td>
<td>5.0</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>1.16</td>
<td>4.92</td>
</tr>
<tr>
<td>Colour sunset yellow</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100.00</strong></td>
<td><strong>425.0</strong></td>
</tr>
</tbody>
</table>

| Total Weight of Bilayer tablet | 395 + 425 = 820 | 39.5 + 42.5 = 82.0 |
| IR part (I layer) + ER part (II layer) |                     |                     |

To promote efficient tablet punching further 0.50 kg of magnesium stearate and 0.492 kg of Colloidal Silicon Dioxide are sieved through 60 mesh screen is added to above dried blended formulation in blender for subsequent 5 minutes.

Both immediate and extended release layers are then compressed in a way to form a bilayer shaped oral dosage form. Immediate layer formulation granules are filled in one hopper of tablet compressing machine and punched with 18.0 x 7.5 mm capsule shaped punches using Karnavati Tablet Compression M/C-17 Stn. GMP machine at an average weight of 395 mg and hardness NLT 4 Kg/cm². Further extended release granules are filled in another hopper of table compressing machine and set average weight of the final tablet at 820 mg and punched hardness of 8 - 10 Kg/cm².

**Example 2**

Dissolution Profile Evaluation of Acetaminophen tablet
Acetaminophen dose form dissolution study was performed. Drug dissolution profiles of tablet prepared are measured by USP 35 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 is as per table 2:-

<table>
<thead>
<tr>
<th>Time</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>Between 45 - 65 %</td>
</tr>
<tr>
<td>1 hour</td>
<td>Between 60 - 85 %</td>
</tr>
<tr>
<td>3 hours</td>
<td>NLT 85 %</td>
</tr>
</tbody>
</table>

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

**ACETAMINOPHEN IN VITRO % DRUG RELEASE USING INSTATMODEL (A43D00050) DISSOLUTION COMPARISON**

<table>
<thead>
<tr>
<th>Time Intervals (Test)</th>
<th>Dissolution Limits (USP)</th>
<th>% Drug Release Reference Product : Lanol</th>
<th>% Drug Release Test Product : Acetaminophen 650 mg using Instamodel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Min</td>
<td>Max</td>
</tr>
<tr>
<td>15 min</td>
<td>45% - 65%</td>
<td>49.96</td>
<td>51.14</td>
</tr>
<tr>
<td>60 min</td>
<td>60% - 85%</td>
<td>62.64</td>
<td>65.41</td>
</tr>
<tr>
<td>180 min</td>
<td>NLT 85%</td>
<td>81.47</td>
<td>83.65</td>
</tr>
</tbody>
</table>
The drug dissolved profile of the Reference products and Acetaminophen having dose strength of 650 mg using Instamold (A43D00050) formulations are compared. The release exponents for the Reference and formulated Acetaminophen 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 Acetaminophen 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 solvent is selected from water, isopropyl alcohol and like.

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

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

[7] A process for preparing Acetaminophen tablet according to claim 1 comprising
   a. Blending Acetaminophen with disintegrant and binder
   b. Granulating and sieving,
   c. Blending Instamold (A43D00050) with Acetaminophen.
   d. Thorough mixing and Wet granulation with binder and solvent
   e. Sieving and drying
   f. Addition of lubricant and glidant
   g. Final tablet compression

[8] The solid pharmaceutical composition prepare using process for preparing Acetaminophen tablet according to claim 1 comprising
   a. Blending Instamold (A43D00050) with Acetaminophen.
   b. Thorough mixing and Wet granulation with binder and solvent
   c. Sieving and drying
   d. Addition of lubricant and glidant
   e. Final tablet compression
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/16, A61K09/22, A61P19/00 Version=2014.01

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)
A61K, A61P

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)
IPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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<td>WO 0180834 A1 (SMITHKLINE BEECHAM PLC[GB]) 01 NOVEMBER 2001 (01-11-2001). The whole document</td>
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☐ Further documents are listed in the continuation of Box C.  ☒ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search 16-03-2015

Date of mailing of the international search report 16-03-2015

Name and mailing address of the ISA/Indian Patent Office
Plot No.32, Sector 14, Dwarka, New Delhi-110075

Authorized officer K Janardana

Telephone No. +91-1125300200

Form PCT/ISA/210 (second sheet) (January 2015)
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