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(54) Title: SOLID ORAL PHARMACEUTICAL COMPOSITIONS COMPRISING FIXED DOSE COMBINATION OF ACET-
AMINOPHEN, DICYCLOMINE AND DEXTROPROPOXYPHENE OR SALTS THEREOF

(57) Abstract: The present invention relates to solid oral pharmaceutical compositions comprising fixed dose combination of acet-
aminophen, dicyclomine and dextropropoxyphene or salts thereof. In particular, the present invention relates to solid oral pharma-
ceutical compositions comprising fixed dose combination of acetaminophen, dicyclomine and dextropropoxyphene or salts thereof,
one or more alkalizers, and other pharmaceutically acceptable excipients. The compositions of the present invention exhibit im-
proved/faster dissolution profile of one or more active ingredients. The invention further relates to process of preparing said pharma-
ceutical compositions and their use as antispasmodic.



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**SOLID ORAL PHARMACEUTICAL COMPOSITIONS COMPRISING FIXED
DOSE COMBINATION OF ACETAMINOPHEN, DICYCLOMINE AND
DEXTROPROPOXYPHENE OR SALTS THEREOF**

Field of the Invention

The present invention relates to solid oral pharmaceutical compositions comprising fixed dose combination of acetaminophen, dicyclomine and dextropropoxyphene or salts thereof. In particular, the present invention relates to solid oral pharmaceutical compositions comprising fixed dose combination of acetaminophen, dicyclomine and dextropropoxyphene or salts thereof, one or more alkalizers, and other pharmaceutically acceptable excipients. The compositions of the present invention exhibit improved/faster dissolution profile of one or more active ingredients. The invention further relates to process of preparing said pharmaceutical compositions and their use as antispasmodic.

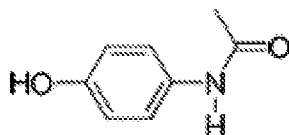
Background of the Invention

Muscle spasm is an involuntary contraction of a muscle. Muscle spasms occur suddenly, usually resolve quickly, and are often painful. Muscle spasm is most commonly refers to a muscle cramp which is often accompanied by a sudden burst of pain, but is usually harmless and ceases after a few minutes. There are a variety of other causes of involuntary muscle contractions, which may be more serious, depending on the cause.

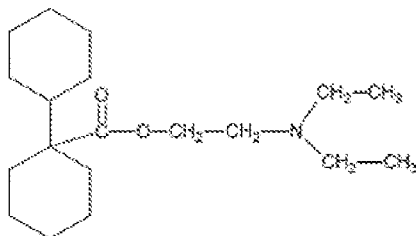
Antispasmodics are the agents used for smooth muscle contraction, especially in tubular organs of the gastrointestinal tract. Smooth muscles line most of the visceral organs. The peristalsis and muscular activity of the stomach, intestines, gall bladder, urinary bladder, lung, the uterus, and to a degree the heart are all largely controlled by smooth muscles. Smooth muscles are innervated by the autonomic nervous system. The effect is to prevent spasms of the stomach,

intestine or urinary bladder. Dicyclomine is used as an antispasmodic due to its anti-cholinergic action.

Acetaminophen is a non-salicylate antipyretic and non-opioid analgesic agent, indicated for management of mild to moderate pain with or without adjunctive opioid analgesics. Its chemical name is N-acetyl-p-aminophenol. Acetaminophen has a molecular weight of 151.16 with the following structural formula:

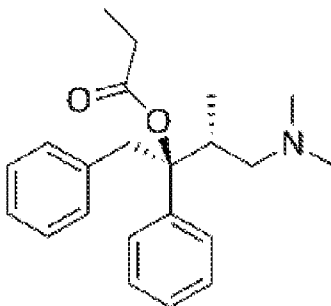


Dicyclomine is indicated for the treatment of patients with functional bowel/irritable bowel syndrome. It relieves muscle spasms and cramping in the gastrointestinal tract by blocking the activity of acetylcholine on cholinergic (or muscarinic) receptors on the surface of muscle cells. It is a smooth muscle relaxant. Dicyclomine is [bicyclohexyl]-1-carboxylic acid, 2-(diethylamino) ethyl ester, with a molecular formula of $C_{19}H_{35}NO_2$ and the following structural formula:



Hydrochloride salt of dicyclomine is currently marketed under brand name Bentyl® in US for treatment of functional bowel/irritable bowel syndrome.

Dextropropoxyphene is (1S,2R)-1-benzyl-3-(dimethylamino)-2-methyl-1-phenylpropyl propionate an analgesic in the opioid category, with a molecular formula $C_{22}H_{20}NO_2$ and the following structural formula:



Dextropropoxyphene is currently marketed under brand name Parvodex[®] in India as an analgesic (opioid).

These three active agents namely acetaminophen, dicyclomine and dextropropoxyphene are also available in fixed dose combination dosage form. For instance, in India the fixed dose combination product is available for treatment of spasmodic pains under trade name Spasmo-Proxyvon[®].

U.S. Patent No. 8,268,352 discloses modified release composition for highly soluble drugs comprising acetaminophen & dicyclomine.

U.S. Patent No. 8,263,125 discloses immediate release and modified release composition for highly soluble drugs comprising acetaminophen & dicyclomine.

U.S. Patent No. 7,776,844 discloses pharmaceutical formulation comprising acetaminophen & dicyclomine.

U.S. Patent No. 7,038,085 discloses pharmaceutical composition comprising acetaminophen & dextropropoxyphene.

U.S. Patent No. 6,730,321 & U.S. Patent No. 6,372,254 discloses press coated tablet, pulsatile drug delivery system comprising acetaminophen & dextropropoxyphene.

U.S. Patent No. 6,160,020 discloses pharmaceutical composition comprising acetaminophen & dicyclomine.

U.S. Patent No. 5,053,396 discloses pharmaceutical composition comprising acetaminophen & dextropropoxyphene hydrochloride.

U.S. Patent No. 4,952,402 discloses controlled release powder comprising acetaminophen & dicyclomine and process for its preparation.

Muscle spasms occur suddenly, and are often painful. Muscle spasm is accompanied by a sudden burst of pain. Antispasmodics, analgesics are the agents useful in these conditions, in presently available formulations not a single agent or combinations of these agents gives faster release. Hence it is necessary to develop the composition, which will give immediate as well as faster release of the agents useful in these conditions.

Within the pharmaceutical art, the formulation of multiple pharmaceutically active compounds into usable dosage forms, in which the release of one or more active ingredients is faster, may be challenging and, frequently, unpredictable. Although various methods have been suggested in the art to improve the drug release from the fixed dose combination formulations, it is highly uncertain to devise an ideal formulation of a particular drug combination by legitimate selection of excipients.

The inventors of the present invention have found that although several formulations have been suggested in the arts for combination of acetaminophen with either dicyclomine or dextropropoxyphene, or their fixed dose combination, these formulations still may not exhibit the desired release profile of the active ingredients.

Hence, there still exists an enduring need for an alternate, improved fixed dose combination formulation of acetaminophen, dicyclomine and dextropropoxyphene with an improved release of one or more of these active pharmaceutical agents.

The inventors of the present invention have surprisingly found that by using alkalizer in the fixed dose combination of acetaminophen, dicyclomine and dextropropoxyphene or salts thereof, or particularly by using the alkalizer in optimized amount, it is possible to achieve desirable or improved drug release.

Summary of the Invention

In one general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein the composition comprises one or more alkalizers.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine hydrochloride & dextropropoxyphene napsylate, wherein the composition comprises one or more alkalizers.

In another general aspect, there is provided an immediate release solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein the composition comprises one or more alkalizers.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein the composition comprises one or more alkalizers and pharmaceutically acceptable excipients.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein the composition comprises one or more alkalizers and one or more pharmaceutically acceptable excipient comprising fillers, glidants, alkalizers, lubricants, anti-adherents, disintegrants, flavours, colours, preservatives, sweeteners, and binders.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein acetaminophen or its salt is present in the form of at least two different portions of the particles each having different particle size.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein the composition further comprises one or more alkalizers and acetaminophen or its salt is present in the form mixture of particles having size less than about 300 microns and particles having size in the range of about 300 microns to about 1200 microns.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, and one or more alkalizers selected from alkali earth metal salts; alkali metal carbonates or bicarbonates such as lithium, sodium, or potassium carbonate, or lithium, sodium, or potassium bicarbonate; tertiary amines, such as triethylamine, tributylamine, N-methylmorpholine; salts of phosphoric acid such as sodium, potassium, calcium, magnesium and aluminium; citric acid or other suitable weak inorganic or organic acids, aluminium, calcium and magnesium hydroxides; magnesium oxide, trihydroxymethylaminomethane or mixtures thereof.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, sodium bicarbonate, and one or more pharmaceutically acceptable excipients.

In another general aspect, the composition of the present invention is in the form of powder, tablets, pellets, capsules, granules or pellets filled in capsule, tablet in capsule, multilayer tablet, a bilayer tablet, a trilayer tablet, or premixed powder filled in capsule.

In another general aspect, there is provided a method of improving the in-vitro dissolution profile (% drug release) of acetaminophen, dicyclomine or dextropropoxyphene or salts thereof, which method comprises using one or more alkalizers in the composition.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein the composition comprises one or more alkalizers and the amount of acetaminophen ranges from about 10% w/w to about 95% w/w, the amount of dicyclomine ranges from about 0.01% w/w to about 50% w/w and the amount of dextropropoxyphene ranges from about 0.5% w/w to about 70% w/w of the composition.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein the amount of alkalizer in the composition ranges from about 0.1% w/w to about 50% w/w of the composition.

In another general aspect, there is provides a process of preparing the solid oral pharmaceutical composition of acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, which process comprises steps of:

- (a) sifting acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, one or more alkalizers and one or more pharmaceutically acceptable excipients; and
- (b) formulating the mixture prepared in step (a) in a solid oral dosage form.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein the composition further comprises one or more alkalizers, characterized in that said composition exhibits a dissolution profile such that more than about 60% of the total acetaminophen is released until 10 minutes; more than about 90% of the total acetaminophen is released until 20 minutes; and more than about 95% of the total acetaminophen is released until 60 minutes when tested according to USP Apparatus 1 dissolution test method at 100 rpm using 900ml of pH 4.5 acetate buffer for 60 minutes.

In another general aspect, there is provided a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein the composition further comprises one or more alkalizers characterized in that said composition exhibits a dissolution profile such that more than about 60% of the total acetaminophen is released until 10 minutes; more than about 85% of the total acetaminophen is released until 20 minutes; more than about 95% of the total acetaminophen is released until 60 minutes when tested according to USP Apparatus 2 (paddle with sinker) dissolution test method at 30 rpm using 900ml of 0.05M HCl for 60 minutes.

In another general aspect, there is provided a method of treating muscle spasms, spasmodic pains, renal, ureteric, biliary or intestinal colic, spasmodic dysmenorrhoea in a patient in need thereof, wherein method comprises of administering the pharmaceutical composition as described herein.

Detailed Description of the Invention

The present invention provides a solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, and one or more alkalizers. The compositions of the invention are useful as antispasmodics in the treatment of muscle spasms, which requires immediate drug release and subsequently, its therapeutic action.

The term “alkalizer” used herein throughout the specification means an agent that counteracts or neutralizes acidity or creates alkaline pH around active ingredients.

The term "immediate release" used throughout the specification refers that within 2 hours, preferably within 1.5 hour, more preferably within 1 hour and most preferably within 20 minutes, at least 80%, preferably at least 85%, more preferably at least 90% of the drug being present in the compartment is dissolved or released.

The term “acetaminophen” as used herein refers to acetaminophen base or its salts, solvates, prodrugs, hydrates, enantiomers or polymorphs thereof.

The term “dicyclomine” as used herein refers to dicyclomine base or its salts, solvates, prodrugs, hydrates, enantiomers or polymorphs thereof.

The term “dextropropoxyphene” as used herein refers to dextropropoxyphene base or its salts, solvates, prodrugs, hydrates, enantiomers or polymorphs thereof.

In an embodiment, the solid oral pharmaceutical composition comprises acetaminophen, dicyclomine hydrochloride & dextropropoxyphene napsylate, and one or more alkalizers.

In a further embodiment, the dextropropoxyphene used in the composition is dextropropoxyphene hydrochloride or dextropropoxyphene napsylate. Preferred salt is dextropropoxyphene napsylate.

The inventors of the present invention have also surprisingly found that when at least two different types of particles of the active agents, differing in particle size, are used in the composition, the composition substantiates desired and improved release.

In an embodiment, the solid oral pharmaceutical composition comprising acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, wherein the composition further comprises an alkalizer and characterized in that acetaminophen or its salt is present in the form mixture of particles having size less than about 300 microns and particles having size in the range of about 300 microns to about 1200 microns.

The amount of acetaminophen in the composition may range from about 10% w/w to about 95% w/w of the composition. Preferably, the amount of acetaminophen in the composition ranges from about 40% w/w to about 80% w/w of the composition.

The amount of dicyclomine in the composition may range from about 0.01% w/w to about 50% w/w of the composition. Preferably, the amount of dicyclomine in the composition ranges from about 0.1% w/w to about 20% w/w of the composition.

The amount of dextropropoxyphene in the composition may range from about 0.5% w/w to about 70% w/w of the composition. Preferably, the amount of dextropropoxyphene in the composition ranges from about 2% w/w to about 40% w/w of the composition.

Suitable alkalizers for use in the present invention include, but not limited to alkali earth metal salts; alkali metal carbonates or bicarbonates, tertiary amines, buffering agents or mixtures thereof.

Suitable examples of alkalizers includes, but not limited to sodium carbonate, sodium bicarbonate, lithium carbonate, lithium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, tributylamine, N-methylmorpholine, sodium phosphate, potassium phosphate, calcium phosphate, magnesium phosphate, aluminium phosphate, citric acid, potassium citrate, aluminium hydroxide, calcium hydroxide, magnesium hydroxide, magnesium oxide, trihydroxymethylaminomethane or mixtures thereof. Preferably, alkali metal carbonates or bicarbonates are used. More preferably, sodium bicarbonate is used.

The amount of alkalizers in the composition may range from about 0.1% w/w to about 50% w/w of the composition. Preferably, the amount of alkalizers in the composition ranges from about 1% w/w to about 30% w/w of the composition. More preferably, the amount of alkalizers in the composition ranges from about 1% w/w to about 20% w/w of the composition.

The solid oral pharmaceutical composition of the invention further may comprise one or more pharmaceutical excipients suitable for oral administration. Such excipients may be selected from one or more binders, fillers, filler-binders, disintegrants, glidants, alkalizers, antiadherents, sweeteners, flavouring and colouring agents. In an embodiment, the composition comprises one or more alkalizers, glidants/lubricants and fillers.

Lubricants/glidants suitable for use in the solid oral pharmaceutical composition of the present invention may be selected from one or more of stearic acid, talc,

siliconised talc, sodium stearyl fumarate and magnesium stearate. Preferable lubricant/glidants is magnesium stearate.

Fillers or filler-binder suitable for use in the solid oral pharmaceutical composition of the present invention may be selected from starches, such as maize starch, potato starch, rice starch, wheat starch, pregelatinized starch, fully pregelatinized starch, cellulose, such as microcrystalline cellulose or silicified microcrystalline cellulose, mannitol, erythritol, lactose, such as lactose monohydrate and lactose anhydrous, calcium salts, such as calcium hydrogen phosphate dihydrate, anhydrous dibasic calcium phosphate, sorbitol, xylitol, or mixtures thereof. Preferable fillers and/or filler-binders are selected from pregelatinized starch, microcrystalline cellulose, lactose monohydrate, lactose, or mixtures thereof.

Binders suitable for use in the solid oral pharmaceutical composition of the present invention may be selected from one or more of polyvinyl pyrrolidone (Povidone), copolymers of vinylpyrrolidone with other vinyl derivatives (Copovidone), hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, powdered acacia, gelatin, guar gum, carbomer such as carbopol, polymethacrylates and starch.

In an embodiment, the solid oral pharmaceutical composition comprises-

- (a) about 40% w/w to about 80% w/w of acetaminophen or salts thereof;
- (b) about 0.1% w/w to about 20% w/w of dicyclomine or salts thereof;
- (c) about 2% w/w to about 40% w/w of dextropropoxyphene or salts thereof;
- (d) about 1% w/w to about 20% w/w of alkalizer;
- (e) about 1% w/w to about 60% w/w of filler; and
- (f) about 0.001% w/w to about 10% w/w of lubricant.

The invention further provides a process of preparing the solid oral pharmaceutical composition of acetaminophen, dicyclomine & dextropropoxyphene or salts thereof. The process comprises steps of:

- (a) sifting acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, one or more alkalizers and one or more pharmaceutically acceptable excipients; and
- (b) formulating the mixture prepared in step (a) in a solid oral dosage form.

In an embodiment, active ingredients and alkalizers are sifted either separately or together. Preferably, active ingredients are sifted together.

In a further embodiment, the process of preparing the solid oral pharmaceutical composition comprises steps of:

- (a) sifting a part quantity of acetaminophen or salts thereof;
- (b) sifting dicyclomine with part quantity of dextropropoxyphene or salts thereof
- (c) sifting mixture of step (b) with second part quantity of acetaminophen or salts thereof;
- (d) blending mixture of step (c) with remaining quantity of dextropropoxyphene or salts thereof;
- (e) blending mixture of step (d) with final quantity of acetaminophen or salts thereof;
- (f) blending mixture of step (e) with premixed and pre-sifted mixture of filler and alkalizer.
- (g) blending mixture of step (f) with lubricant; and
- (h) formulating the lubricated blend of step (g) in to a solid oral dosage form.

The solid oral pharmaceutical composition of the present invention may be formulated is in the form of powder, tablets, pellets, capsules, granules or pellets filled in capsule, tablet in capsule, multilayer tablet, a bilayer tablet, a trilayer tablet, or premixed powder filled in capsule.

The invention further provides a method of treating muscle spasms, spasmodic pains, renal, ureteric, biliary or intestinal colic, spasmodic dysmenorrhoea in a

human in need thereof, wherein method comprises of administering the solid oral pharmaceutical composition as described herein

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Acetaminophen, Dicyclomine HCl and Dextropropoxyphene Napsylate Capsules

Formulation of fixed dose combination of Acetaminophen, Dicyclomine HCl and Dextropropoxyphene Napsylate was prepared with and without sodium bicarbonate and was characterized for in-vitro % drug release of acetaminophen in Medium I & Medium II.

Table 1

Sr. No.	Ingredients	Quantity (mg/Cap)	
		Formulation I	Formulation II
1	Acetaminophen (Crystalline)	257.33	257.33
2	Acetaminophen (Fine)	67.67	67.67
3	Dicyclomine HCl	10.00	10.00
4	Dextropropoxyphene Napsylate	100	100.00
5	Siliconised Talc	42.00	42.00
6	Sodium bicarbonate	--	30.0
7	Magnesium stearate	2.00	2.00
	Total	479.00	509.00
8	Size '0' capsule, blue opaque cap and blue opaque body	01	01

Process:

Acetaminophen (crystalline) was sifted through 20 mesh. The retentions on 20 mesh was milled through multimill (Impact forward and slow speed) and by using 2.0 mm screen. The milled material was sifted through 20 mesh. The milling process was repeated by using 1.0 mm screen through multimill (Impact forward and fast speed) if retentions observed.

Dicyclomine Hydrochloride was co-sifted with half quantity of Dextropropoxyphene napsylate through 20 mesh to form Premix I. The premix I was co-sifted with Acetaminophen (fine) through 20 mesh to form Premix II. The premix II was loaded into blender and mixed for 20 minutes. Then remaining quantity of Dextropropoxyphene napsylate (presifted through 20 mesh) was loaded into blender and mixed for 10 minutes to form Premix III.

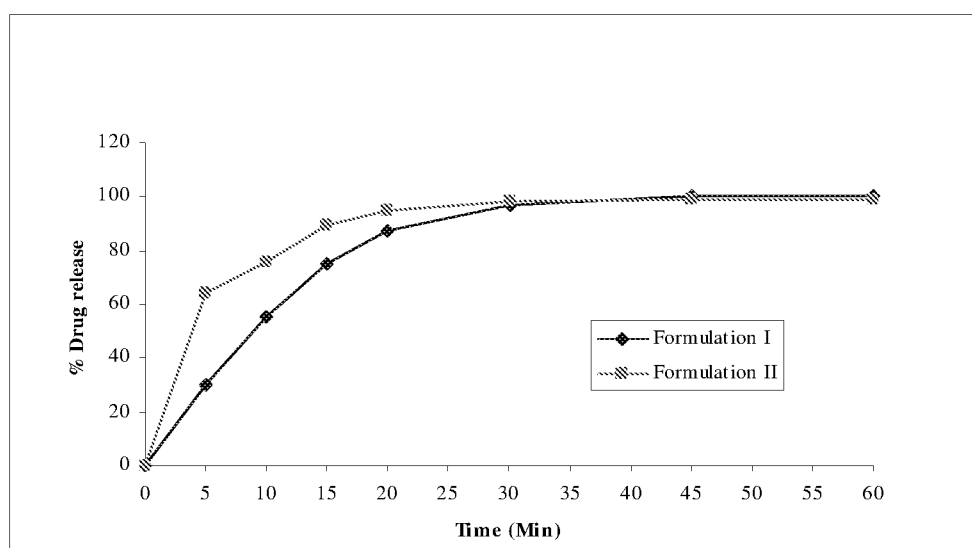
Acetaminophen (crystalline) was loaded with Premix III in a blender and mixed for 20 minutes to form Premix IV. Premixed and presifted (20 mesh) Siliconised talcum and sodium bicarbonate was loaded into Premix IV in blender and mixed for 20 minutes. Finally magnesium stearate was loaded into the blender & lubricated for 10 minutes. The resulting blend was then filled in size '0el' empty hard gelatine capsule using capsule filling machine.

Example 2: Dissolution study of Example 1 (USP Apparatus 1)

Dissolution study of formulation I and II of example 1 was carried out according to method USP Apparatus 1 (basket), by using 900ml of pH 4.5 acetate buffer for 60 minutes at 100 rpm.

Table 2

Time (min)	% Drug Release	
	Formulation I	Formulation II
0	0	0
5	30	64
10	55	76
15	75	89
20	87	95
30	97	98
45	100	99
60	100	99



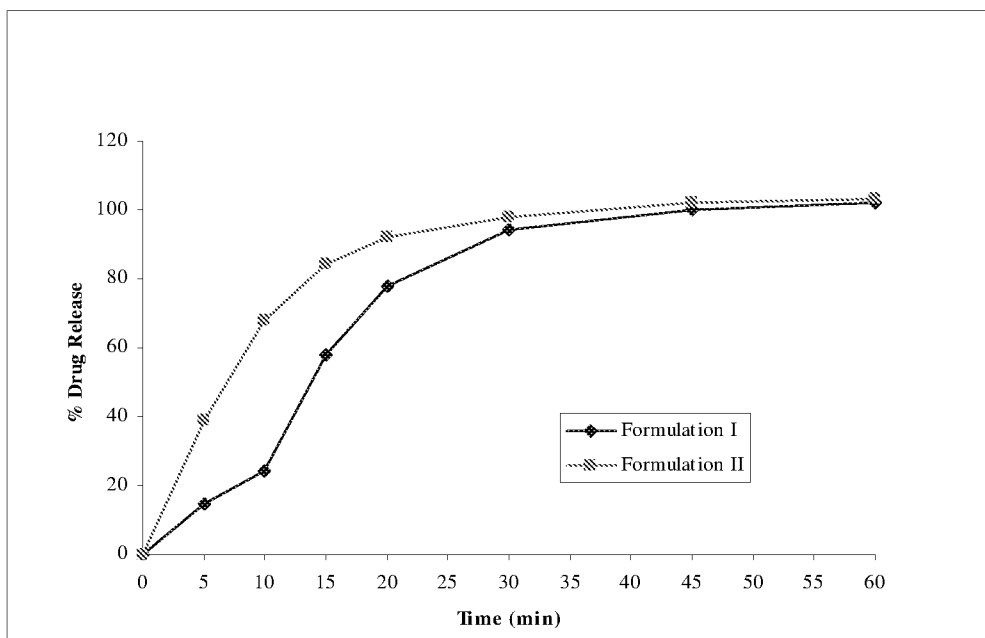
The dissolution profile indicates that use of alkalizer in formulation II has resulted in relatively faster/immediate release of acetaminophen than that exhibited by formulation I.

Example 3: Dissolution study of Example 1 (USP Apparatus 2)

Dissolution study of formulation I and II of example 1 was carried out according to method USP Apparatus 2 (paddle with sinkers), by using 900ml of 0.05M HCl for 60 minutes at 30 rpm.

Table 3

Time (min)	% Drug Release	
	Formulation I	Formulation II
0	0	0
5	15	39
10	24	68
15	58	84
20	78	92
30	94	98
45	100	102
60	102	103



The dissolution profile indicates that use of alkalizer in formulation II has resulted in relatively faster/immediate release of acetaminophen than that exhibited by formulation I.

Claims:

1. A solid oral pharmaceutical composition comprising acetaminophen, dicyclomine, dextropropoxyphene or salts thereof and one or more alkalizers.
2. The solid oral pharmaceutical composition of claim 1, wherein the amount of acetaminophen in the composition ranges from about 10% w/w to about 95% w/w, the amount of dicyclomine in the composition ranges from about 0.01% w/w to about 50% w/w and the amount of dextropropoxyphene in the composition ranges from about 0.5% w/w to about 70% w/w of the composition.
3. The solid oral pharmaceutical composition of claim 1, wherein alkalizer comprises one or more sodium carbonate, sodium bicarbonate, lithium carbonate, lithium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, tributylamine, and N-methylmorpholine, sodium phosphate, potassium phosphate, calcium phosphate, magnesium phosphate, aluminium phosphate, citric acid, potassium citrate, aluminium hydroxide, calcium hydroxide, magnesium hydroxide, magnesium oxide, trihydroxymethylaminomethane or mixtures thereof.
4. The solid oral pharmaceutical composition of claim 1, wherein the alkalizer comprises sodium bicarbonate.
5. The solid oral pharmaceutical composition of claim 1, wherein the alkalizer is present in amount of about 0.1% w/w to about 50% w/w of the composition.

6. The solid oral pharmaceutical composition of claim 1, wherein acetaminophen or its salt is present in the form of at least two different portions of the particles each portion having different particle size.
7. The solid oral pharmaceutical composition of claim 1, wherein acetaminophen or its salt is present in the form mixture of particles having size less than about 300 microns and particles having size in the range of about 300 microns to about 1200 microns.
8. The solid oral pharmaceutical composition of claim 1, wherein the composition exhibits a dissolution profile such that more than about 60% of the total acetaminophen is released until 10 minutes; more than about 90% of the total acetaminophen is released until 20 minutes; and more than about 95% of the total acetaminophen is released until 60 minutes when tested according to USP Apparatus 1 dissolution test method at 100 rpm using 900ml of pH 4.5 acetate buffer for 60 minutes.
9. The solid oral pharmaceutical composition of claim 1, wherein the composition exhibits a dissolution profile such that more than about 60% of the total acetaminophen is released until 10 minutes; more than about 85% of the total acetaminophen is released until 20 minutes; more than about 95% of the total acetaminophen is released until 60 minutes when tested according to USP Apparatus 2 (paddle with sinker) dissolution test method at 30 rpm using 900ml of 0.05M HCl for 60 minutes.
10. The solid oral pharmaceutical composition of claim 1, wherein the composition is in the form of powder, tablets, capsule, granules filled in capsule, tablet in capsule, multilayer tablet, a bilayer tablet, a trilayer tablet, premixed powder filled in capsule.

11. A process of preparing the solid oral pharmaceutical composition of claim 1, which process comprises steps of:
 - (a) sifting acetaminophen, dicyclomine & dextropropoxyphene or salts thereof, one or more alkalizers and one or more pharmaceutically acceptable excipients, and
 - (b) formulating the mixture prepared in step (a) in a solid oral dosage form.
12. A solid oral pharmaceutical composition of claim 1, wherein the composition exhibits immediate release of acetaminophen, dicyclomine and dextropropoxyphene or salts thereof.
13. A solid oral pharmaceutical composition comprising -
 - (a) about 40% w/w to about 80% w/w of acetaminophen or salts thereof;
 - (b) about 0.1% w/w to about 20% w/w of dicyclomine or salts thereof;
 - (c) about 2% w/w to about 40% w/w of dextropropoxyphene or salts thereof;
 - (d) about 1% w/w to about 30% w/w of alkalizer;
 - (e) about 1% w/w to about 60% w/w of filler; and
 - (f) about 0.001% w/w to about 10% w/w of lubricant.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/48 A61K31/167 A61K31/215 A61K31/216 ADD.		
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		
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) EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 16 September 2014		Date of mailing of the international search report 29/09/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Gómez Gallardo, S

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