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(71) Applicant *(for all designated States except US)*: **MEDREICH LIMITED** [IN/IN]; Medreich House, No.12/8, Saraswati Ammal Street, M.S. Nagar, Bangalore, Karnataka 560 033 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **NAIDU, Rongala, Appala, Swamy** [IN/IN]; c/o. Medreich Limited, Medreich House, No.12/8, Saraswati Ammal Street, M.S. Nagar, Bangalore, Karnataka 560 033 (IN). **BOTHRA, Chandanmal, Pukhraj** [IN/IN]; c/o. Medreich Limited, Medreich House, No.12/8, Saraswati Ammal Street, M.S. Nagar, Bangalore, Karnataka 560 033 (IN).

(74) Agent: **BHOLA, Ravi**; K & S Partners, # 134, First Floor, 60 Ft. Domlur Road, Indiranagar, Bangalore, Karnataka 560 008 (IN).

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(54) Title: A STABLE CONTROLLED RELEASE ORAL SOLID DOSAGE FORM COMPOSITION AND A PROCESS THEREOF

(57) Abstract: The present invention provides a solution to the problem encountered with conventional dosage forms of glucosamine for management of arthritis. The invention provides a controlled-release formulation of glucosamine and/ or glucosamine salts and a process for preparing the same.

# A STABLE CONTROLLED RELEASE ORAL SOLID DOSAGE FORM COMPOSITION AND A PROCESS THEREOF

## FIELD OF THE INVENTION

The present invention is in relation to film coated controlled release matrix formulations. More particularly the present invention relates to controlled release matrix formulations containing glucosamine and their salts. The formulation of the present invention is useful for the management of arthritis and its related disorders.

## BACKGROUND OF THE INVENTION

Natural ingredients, including Ayurvedic formulations, have been used to treat bone and joint inflammation, especially in eastern countries, and, increasingly, in western countries. Such natural ingredients include, for example, cartilage, chondroitin, glucosamine, proteolytic and other enzymes, and herbs, such as the gummy extract of *B. serrata*, Ashwagandha root and ginseng root. Although such natural ingredients generally do not lead to the kind of side effects observed with the steroidal and non-steroidal anti-inflammatory drugs (NSAIDS), many of these natural ingredients do not always provide sufficient relief of pain or restoration of significant function and use of inflamed tissue, e.g., joints. However, glucosamine and chondroitin have been found to contribute to restoring such function and use. Although glucosamine generally does not provide the same rapid temporary relief of inflammation and pain as aspirin or non-steroidal anti-inflammatory drugs (NSAIDS), it plays several key roles in the preservation and rebuilding of joint tissues. Namely, it stimulates the cartilage cells to produce glycosaminoglycans and proteoglycans, which maintain healthy joints and contribute to rebuilding connective tissue, and it, is one of the main ingredients of the synovial fluid that lubricates and provides nutrients for the joint structure. By participating in the preservation and rebuilding of joint tissues, it is believed that glucosamine can contribute to long term relief of a wide range of degenerative and inflammatory conditions such as rheumatoid arthritis, osteoarthritis, degenerative spinal disc disease, tendonitis, bursitis, and trauma to joints, tendons and ligaments, and may actually reverse the underlying disease process, in many cases.

Chondroitin, e.g., chondroitin sulfate, have also been found to play a role in the preservation and rebuilding of joint tissues. In a similar fashion to glucosamine,

chondroitin have been found to stimulate cartilage cells to produce the needed proteoglycans and to inhibit the enzymes that break down proteoglycans. Chondroitin sulfate in particular also functions to draw fluid into the proteoglycans molecules. This fluid acts as a shock absorber for the joint tissue and also carries nutrients into the cartilage.

Although the administration of glucosamine appears to be an effective treatment for many conditions having an inflammatory component, it is not free of side effects. In that regard, it has been found that high blood serum levels of glucosamine can interfere with glucose regulation in both normal individuals and individuals with diabetes mellitus. The high levels of glucosamine can induce an insulin resistance response, resulting in reduced rates of insulin-mediated glucose uptake by the liver, skeletal muscle, and adipose tissue (fat cells). If uncontrolled, insulin-resistance can lead to hyperglycemia and possibly glucose toxicity. In normal (i.e., non-diabetic) individuals, hyperglycemia can interfere with cellular metabolism and the mechanics for insulin-induced glucose disposal. The hyperglycemia itself can worsen insulin resistance, thus contributing to a vicious cycle that makes glycemic regulation more difficult. Moreover, hyperglycemia and insulin resistance are major contributing factors in the pathogenesis of non-insulin dependent diabetes mellitus (NIDDM).

The effects of high glucosamine levels on patients with NIDDM are typically more pronounced, since such patients generally affect glycemic regulation with dietary control. Thus, in such patients the cause and effect of insulin resistance and hyperglycemia on each other result in worsening the diabetic state and making glycemic regulation more difficult. Moreover, clinical studies have shown that hyperglycemia is the cause of most if not all of the chronic complications of diabetes. Insulin resistance induced by high levels of glucosamine can also have dramatic effects on patients with insulin dependent diabetes mellitus (IDDM) by again initiating a vicious cycle that worsens the diabetic state and makes glycemic regulation more difficult, possibly leading to glucose toxicity.

***Drawbacks of glucosamine conventional tablets and capsules:***

Glucosamine can be a stomach irritant in certain individuals, when glucosamine contacts the stomach lining.

Glucosamine capsule dissolves very quickly and leads to stomach irritation because of

the sudden release of the glucosamine.

Glucosamine tablets sudden dissolution provides high local concentrations and cause causes stomach lining irritation.

Significant fraction of the ingested glucosamine is catabolized by first-pass metabolism in the liver.

The bioavailability of oral glucosamine sulfate is only 26% of that seen with intravenous injection. The half life of glucosamine is short and is less than one hour

Irritation mechanisms that depend on the fast release into the stomach of the active substance contained in a tablet should be significantly off-set if the active substance is released slowly.

***Beneficial effects of Glucosamine slow and sustained release (SR) products:***

- Glucosamine SR product prevents stomach irritation due to controlled release of active release in the stomach.
- Glucosamine SR product is not suddenly dissolved in its entirety at any given spot, and consequently does not give rise to any locally high concentration of the active substance.
- Glucosamine SR composition is capable of forming a protective gel in the gastric environment. This composition acts as a stomach guard protecting the stomach lining from possible detrimental side effects of active substances such as glucosamine.

***Therapeutic Uses of Glucosamine:***

The formulation of the present invention is useful for the treatment of arthritis, including osteoarthritis and rheumatoid arthritis, rheumatism, tendonitis, bursitis, degenerative spinal disc disease, and trauma to joints, tendons, and ligaments, including sports trauma.

***Action of Glucosamine:***

Glucosamine is the main substrate for the biosynthesis of glycosaminoglycans and hyaluronic acid, the primary function of glucosamine is to stimulate the secretion of glycosaminoglycans in the articular cartilage. Therefore, glucosamine helps in addressing all arthritic related disorders such as osteoarthritis, rheumatoid arthritis, rheumatism, tendonitis, bursitis, degenerative spinal disc disease, trauma to joints,

tendons and ligaments, including sports trauma. It was also found to provide natural protection against the cartilage-damaging effects of some NSAIDs.

***Market available products:***

- Glucosamine IR tablets containing 250,400,500,750, 1000 mg and 1500 mg of glucosamine
- Glucosamine SR tablets containing 1000mg and 1500mg
- Glucosamine capsules 250mg, 500mg as conventional dosage forms.
- Glucosamine & Chondroitin sulphate 250/200mg SR capsules

**PRIOR ART OF THE INVENTION**

The related art of interest describes various processes for obtaining controlled release of glucosamine, but none discloses the present invention. There is a need for an effective process in obtaining controlled release of glucosamine and their salts which helps in management of arthritis, including osteoarthritis, rheumatoid arthritis, rheumatism, tendonitis, bursitis, degenerative spinal disc disease, trauma to joints, tendons and ligaments, including sports trauma. The related art will be discussed in the order of perceived relevance to the present invention.

**US PATENT NO: 7056531**

The aforementioned US patent document describes a sustained release composition comprising powdered cellulose and maltodextrin and a compound selected from the group consisting of glucosamine sulfate, glucosamine hydrochloride and mixtures thereof.

The drawbacks of the above prior art are: a) Formulations with the above materials as matrix components in the solid dosage forms are prone to discoloration and/or degradation during storage of drug product.

b) This composition controls drug release for about 2 hours.

**US PATENT NO: 6767899**

The aforementioned US patent document describes a controlled-release glucosamine composition comprising a therapeutically effective amount of a glucosamine component dispersed in a controlled-release matrix system, said matrix system comprising a continuum of material and controlled-release component finely dispersed throughout said matrix system capable of releasing said glucosamine in an amount and at a rate sufficient to maintain an effective glucosamine blood serum level over a designated time period, said controlled-release component comprising at least one

water soluble high molecular weight cellulose polymer. The above patent also describes composition of controlled-release component selected from the group consisting of hydroxypropyl methyl cellulose (HPMC), hydroxyl ethyl. cellulose (HEC), hydroxyl propyl cellulose (HPC), carboxy methyl cellulose (CMC), and mixtures thereof.

The drawbacks of the above prior art are that formulations with the above materials as matrix components in the solid dosage forms are prone to discoloration and/or degradation during storage of drug product

**US PATENT NO: 6,214,385**

The aforementioned US Patent document discloses controlled release of diltiazem wherein it was found using pH dependent and pH independent polymers. However, the document was failed in arriving at specific concentration ranges as proposed by the application of instant invention. In addition, the invention of aforementioned citation involves combining short lag and long lags pellets into a single formulation and to achieve the release of the drug completely after 24 hours. Thus, it is evident that the aforementioned citation does not motivate the applicant to arrive at the application of instant invention.

**US PATENT NO: 6,039,979**

The cited document is aimed at controlled release of active pharmaceutical ingredients such as diltiazem and verapamil. The citation does not disclose the same components of composition as proposed in instant invention. It uses a few addition excipients such as ethyl phthalate, aerosol and acetone and the same are not disclosed in the application of instant invention. Thus, the citation does not motivate the applicant to arrive at the application of instant invention.

**EP 1 721 602 A1**

The aforementioned patent application document discloses an invention relates to a liquid controlled release dosage form through complex formation of an acidic drug with glucosamine or a similar compound. The document is no where related to instant invention as it claims for a composition of glucosamine and/ or glucosamine slats, and a process to formulate the same as tablets, mini tablets and coating them with the polymer solution of Eudragit RL 100 and Eudragit RS 100.

**CN 1762379**

The aforementioned Chinese patent document discloses about dispersible tablets of glucosamine sulfate in combination with chondroitin sulfate along with auxiliary

material. However, it is no where related to the instant invention, wherein the applicant has formulated the solid dosage forms of glucosamine and/ or glucosamine slats by coating the dosage forms with polymer solution such as Eudragit RL 100 and Eudragit RS 100.

**CN 1634087**

The aforementioned Chinese patent document is in relation to a sustained release formulation of a glucosamine salt, its preparation and usage. The sustained formulation includes the actives along with slow release materials. The document is no where related to instant invention as it claims for a composition of glucosamine and/ or glucosamine slats, and a process to formulate the same as tablets, mini tablets and coating them with the polymer solution of Eudragit RL 100 and Eudragit RS 100.

**RU 2247563**

The aforementioned patent document talks about method of manufacturing a solid medicinal formulation – glucosamine hydrochloride tablets. However, the document is no where related to the application of instant invention.

None of the above patents, taken either singly or in combination, is seen to describe the instant invention as claimed. Thus, obtaining stable controlled-release glucosamine using the polymer matrix composition and process of instant invention will therefore helps in addressing the problems associated with the prior art.

## OBJECTIVES OF THE INVENTION

The principal object of the present invention is to develop a stable controlled-release formulation.

Another object of the present invention is to develop a stable controlled-release formulation of glucosamine and its salt (s).

Yet another object of the present invention is to develop a polymer matrix composition for attaining the controlled-release formulations of glucosamine and salts.

Yet another object of the present invention is to develop tablets comprising a) core comprising hydrophilic polymer matrix composition and b) coat comprising rate controlling pH-independent permeable polymer for attaining the controlled-release formulations of glucosamine and salts.

Yet another object of the present invention is to develop tablets comprising a) core comprising hydrophilic polymer matrix composition and b) coat comprising rate

controlling pH-independent polymers for attaining the controlled-release formulations of glucosamine and salts up to 12 hrs.

Still another object of the present invention is to develop a process for preparation of a stable controlled-release formulation of glucosamine and its salts in various dosage forms such as tablets, film coated tablets, multiparticulates and/or mini-tablets in capsules.

Still another object of the present invention is developing controlled-release formulation of glucosamine and its salts in various dosage forms such as tablets, tablets coated with pH-independent Eudragit RS and Eudragit RL, film coated tablets, multiparticulates and/or mini-tablets in capsules.

Still another object of the present invention is to provide a method for management of arthritis and its related disorders using the stable controlled-release formulation of glucosamine its salts for the management of arthritis, including osteoarthritis, rheumatoid arthritis, rheumatism, tendonitis, bursitis, degenerative spinal disc disease, trauma to joints, tendons and ligaments, including sports trauma.

**STATEMENT OF THE INVENTION**

Accordingly, the present invention is in relation to A stable controlled release oral solid dosage form(s) composition for management of arthritis and related disorders, said composition comprising glucosamine and/ or salt (s) of glucosamine at a concentration ranging from 50 % to 98 %, preferably at a concentration ranging from 70 % to 80 %, Eudragit RL 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.15 % to 0.5 % and Eudragit RS 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.2 % to 0.75 %, optionally along with pharmaceutically acceptable additives; A process for preparing a stable controlled release oral solid dosage form(s) composition comprising glucosamine and/ or salt (s) of glucosamine at a concentration ranging from 50 % to 98 %, preferably at a concentration ranging from 70 % to 80 %, Eudragit RL 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.15 % to 0.5 % and Eudragit RS 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.2 % to 0.75 %, optionally along with pharmaceutically acceptable additives for management of arthritis and related disorders, said process comprising steps of: (a) meshing and blending of glucosamine

and/ or glucosamine salt (s) with additives to obtain a mixture; (b)granulating the mixture followed by milling to obtain granules; (c) drying and lubricating the milled granules for compression to obtain solid dosage form (s); (d) coating the solid dosage forms followed by drying to obtain stable controlled-release oral solid dosage form (s); and a method for managing arthritis and related disorders in a subject in need thereof, said method comprising step of administering pharmaceutically acceptable amount of a stable controlled release oral solid dosage form(s) composition comprising glucosamine and/ or salt (s) of glucosamine at a concentration ranging from 50 % to 98 %, preferably at a concentration ranging from 70 % to 80 %, Eudragit RL 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.15 % to 0.5 % and Eudragit RS 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.2 % to 0.75 %, optionally along with pharmaceutically acceptable additives to the subject.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention is in relation to a stable controlled release oral solid dosage form(s) composition for management of arthritis and related disorders, said composition comprising glucosamine and/ or salt (s) of glucosamine at a concentration ranging from 50 % to 98 %, preferably at a concentration ranging from 70 % to 80 %, Eudragit RL 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.15 % to 0.5 % and Eudragit RS 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.2 % to 0.75 %, optionally along with pharmaceutically acceptable additives.

In another embodiment of the present invention, wherein said oral solid dosage forms are selected from a group comprising tablets, film coated tablets, pellets and mini-tablets in capsules.

In yet another embodiment of the present invention, wherein said oral solid dosage form is preferably film coated tablet.

In still another embodiment of the present invention, wherein the glucosamine salts are selected from a group comprising glucosamine sulphate, glucosamine hydrochloride, glucosamine 2 KCl and combinations thereof.

In still another embodiment of the present invention, wherein the pharmaceutically acceptable additives are selected from a group comprising polymers, diluents, binders, granulating agents and lubricants.

In still another embodiment of the present invention, wherein the additives are preferably polymers selected from a group comprising pH-independent permeable polymers such as Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.2, Eudragit RL, Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.1 and Eudragit RS 100, calcium hydrogen phosphate and dibasic calcium phosphate as diluent, carbopol preferably carbomer 974P as binder, stearic acid as lubricant, talc as anti-adherent, isopropyl alcohol as a granulating agent or combinations thereof.

In still another embodiment of the present invention, wherein the additives are preferably calcium hydrogen phosphate as diluent at a concentration ranging from 2 % to 25 % and preferably at a concentration ranging from 5 % to 15 %, dibasic calcium phosphate as diluent at a concentration ranging from 9 % to 13 %, carbopol preferably carbomer 974P as a binder at a concentration ranging from 1 % to 15 %, preferably at a concentration ranging from 2 % to 10 %, stearic acid as a lubricant at a concentration ranging from 0.5 % to 10 %, preferably at a concentration ranging from 2 % to 5 %, talc as anti-adherent at a concentration ranging from 0.1 % to 5 % and preferably at a concentration ranging from 0.15 % to 0.5 %.

In still another embodiment of the present invention, wherein said oral solid dosage forms are preferable dose forms selected from a group comprising 200 mg, 250 mg, 500 mg, 750 mg, 1000 mg and 1500 mg of glucosamine and/ or salts of glucosamine.

In still another embodiment of the present invention, wherein said related disorders of arthritis comprise osteoarthritis, rheumatoid arthritis, rheumatism, tendonitis, bursitis, degenerative spinal disc disease, sports trauma, trauma to joints, tendons and ligaments.

In still another embodiment of the present invention, wherein the ratio of Eudragit RL 100 and Eudragit RS 100 is ranging from 1.0:2.0 to 2.0:1.0 and preferably at a ratio ranging from 1.0:1.5 to 1.5:1.0.

In still another embodiment of the present invention, wherein said composition provides controlled release for a time period ranging from 4 hrs to 24 hrs and preferably for a time period ranging from 8 hrs to 12 hrs.

The present invention is in relation to a process for preparing a stable controlled release oral solid dosage form(s) composition comprising glucosamine and/ or salt (s) of glucosamine at a concentration ranging from 50 % to 98 %, preferably at a concentration ranging from 70 % to 80 %, Eudragit RL 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.15 % to 0.5 % and Eudragit RS 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.2 % to 0.75 %, optionally along with pharmaceutically acceptable additives for management of arthritis and related disorders, said process comprising steps of: (a) meshing and blending of glucosamine and/ or glucosamine salt (s) with additives to obtain a mixture; (b)granulating the mixture followed by milling to obtain granules; (c) drying and lubricating the milled granules for compression to obtain solid dosage form (s); (d) coating the solid dosage forms followed by drying to obtain stable controlled-release oral solid dosage form (s).

In another embodiment of the present invention, wherein coating the solid dosage form (s) with coating composition comprising pH independent controlled release coating materials and processing agents

In yet another embodiment of the present invention, wherein said coating materials are selected from a group comprising pH-independent permeable polymers such as Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio ranging from 1:2:0.2, Eudragit RL 100, Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio ranging from 1:2:0.1, Eudragit RS 100 and combinations thereof.

In still another embodiment of the present invention, wherein said processing agents are selected from a group comprising ethyl alcohol and a blend of dichloromethane with isopropyl alcohol.

In still another embodiment of the present invention, wherein said coating composition is prepared by dispersing Eudragit RL 100 and Eudragit RS 100 in ethanol: stirring with addition of talc followed by filtration so as to obtain coating composition.

In still another embodiment of the present invention, wherein the drying of granules is performed at a temperature ranging from $45^0$ C to $50^0$ C, preferably at a temperature ranging from $48^0$ C to $52^0$ C.

In still another embodiment of the present invention, wherein the dried granules have an LOD ranging from 0.5 % to 4.5 %, preferably between 1.0 % to 3.5 % and more preferably between 1.5 % to 2.0 %.

In still another embodiment of the present invention, wherein said glucosamine salts are selected from a group comprising glucosamine sulphate, glucosamine hydrochloride, glucosamine 2 KCl and combinations thereof.

In still another embodiment of the present invention, wherein the pharmaceutically acceptable additives are selected from a group comprising polymers, diluents, binders, granulating agents and lubricants.

In still another embodiment of the present invention, wherein the additives are preferably polymers selected from a group comprising pH-independent permeable polymers such as Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.2, Eudragit RL, Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.1 and Eudragit RS 100, calcium hydrogen phosphate and dibasic calcium phosphate as diluent, carbopol preferably carbomer 974P as binder, stearic acid as lubricant, talc as anti-adherent, isopropyl alcohol as a granulating agent or combinations thereof.

In still another embodiment of the present invention, wherein the additives are preferably calcium hydrogen phosphate as diluent at a concentration ranging from 2 % to 25 % and preferably at a concentration ranging from 5 % to 15 %, dibasic calcium phosphate as diluent at a concentration ranging from 9 % to 13 %, carbopol preferably carbomer 974P as a binder at a concentration ranging from 1 % to 15 %, preferably at a concentration ranging from 2 % to 10 %, stearic acid as a lubricant at a concentration ranging from 0.5 % to 10 %, preferably at a concentration ranging from 2 % to 5 %, talc as anti-adherent at a concentration ranging from 0.1 % to 5 % and preferably at a concentration ranging from 0.15 % to 0.5 %.

In still another embodiment of the present invention, wherein said oral solid dosage forms are selected from a group comprising tablets, film coated tablets, pellets and mini-tablets in capsules.

In still another embodiment of the present invention, wherein said oral solid dosage forms are preferably film coated tablet.

In still another embodiment of the present invention, wherein said oral solid dosage forms can optionally be prepared using direct compression method

The present invention is in relation to a method for managing arthritis and related disorders in a subject in need thereof, said method comprising step of administering pharmaceutically acceptable amount of a stable controlled release oral solid dosage form(s) composition comprising glucosamine and/ or salt (s) of glucosamine at a concentration ranging from 50 % to 98 %, preferably at a concentration ranging from 70 % to 80 %, Eudragit RL 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.15 % to 0.5 % and Eudragit RS 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.2 % to 0.75 %, optionally along with pharmaceutically acceptable additives to the subject.

In another embodiment of the present invention, wherein the subject is an animal or human being.

In yet another embodiment of the present invention, wherein the wherein the pharmaceutically acceptable additives are selected from a group comprising polymers, diluents, binders, granulating agents and lubricants.

In still another embodiment of the present invention, wherein the additives are preferably polymers selected from a group comprising pH-independent permeable polymers such as Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.2, Eudragit RL, Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.1 and Eudragit RS 100, calcium hydrogen phosphate and dibasic calcium phosphate as diluent, carbopol preferably carbomer 974P as binder, stearic acid as lubricant, talc as anti-adherent, isopropyl alcohol as a granulating agent or combinations thereof.

In still another embodiment of the present invention, wherein said oral solid dosage forms are preferable dose forms selected from a group comprising 200 mg, 250 mg, 500 mg, 750 mg, 1000 mg and 1500 mg of glucosamine and/ or salt (s) of glucosamine.

In still another embodiment of the present invention, wherein said related disorders of arthritis comprise osteoarthritis, rheumatoid arthritis, rheumatism, tendonitis, bursitis, degenerative spinal disc disease, sports trauma and trauma to joints, tendons and ligaments.

Binary mixtures of drug and excipients were prepared (1: 1 ratio) and packed in glass vials and kept in accelerated environmental condition (50°C) **for** 4 week period. At the end of 4 week period all the samples were observed for color change

Based on the drug: excipient compatibility study, the following excipients were considered as most compatible and used in the present invention

- Dicalcium phosphate anhydrous ( DC grade ,unmilled , A-TAB)
- Carbomer ( Carbopol 974P)
- Stearic Acid (Powder)
- Isopropyl Alcohol
- Ethanol (96%)
- Eudragit RL 100
- Eudragit RS 100

***Safety of ingredients used:***

**Polymethacrylate copolymers (Eudragit RL 100 and Eudragit RS 100)** are widely used as film-coating materials in oral pharmaceutical formulations. They are generally regarded as nontoxic and non-irritant. Included in the FDA Inactive Ingredients Guide (Oral capsules and tablets). Included in non-paretenteral medicines licensed in the UK (Ref: Handbook of Pharmaceutical Excipients Third Edition, page 405).

**Stearic acid**: Stearic acid is widely used in oral and topical pharmaceutical formulations; it is also used in cosmetics and food products. It is generally regarded as non-toxic and nonirritant material. GRAS listed. Accepted as a food additive in the UK. Included in the FDA Inactive Ingredients Guide (sublingual tablets, oral capsules, solutions, suspensions and tablets, topical and vaginal preparations. Included in nonparenteral medicines licensed in the UK. (Ref: Handbook of Pharmaceutical Excipients Third Edition, page 535)

**Carbomers** are extensively used in nonparenteral products. Carbomers designated with the letter 'P' are the only pharmaceutical grades of polymer accepted for oral or mucosal contact products. Carbomers are generally regarded as essentially nontoxic and nonirritant materials. Carbomers are included in the FDA Inactive Ingredients Guide (oral capsules, granules, suspensions and tablets, ophthalmic, rectal, and topical preparations). They are also included in nonparenteral medicines licensed in the UK (Ref: Handbook of Pharmaceutical Excipients Third Edition, page 81).

Dibasic calcium phosphate anhydrous is widely used in oral pharmaceutical products, food products, and toothpastes and is generally regarded as nontoxic and nonirritant. GRAS listed and included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in Europe, the UK and the US. Accepted as a food additive in Europe (Ref: Handbook of Pharmaceutical Excipients Third Edition, page 61)

**Solvents** (Isopropyl alcohol and Ethanol 96%) incorporated in the process of the present invention are used as processing agents which are removed during subsequent unit operations. However, the levels of residual solvents are well below the pharmacopoeial limits.

***Improved Formulation and Process Developed***

- All the materials used in the present product development were tested for their compatibility with Glucosamine HCl and Glucosamine 2 KCl
- In the present investigation matrix core tablets were prepared using non-aqueous granulation using the following materials:
- Glucosamine hydrochloride, Calcium hydrogen phosphate,anhydrous (A-TAB), Carbomer (Carbopol 974 P) and Stearic acid (Powder). Isopropyl alcohol was used as processing agent for granulation.
- The core tablets were coated using organic solution of Eudragit RL 100 Eudragit RS100 in Ethyl alcohol and purified talc as anti-adherent.
- Products having strength of 1500mg, 1000mg, 750mg and 500mg were developed with Sustained Release of Glucosamine up to 12 hrs for 1500mg, 1000mg and 750mg strengths and 8hrs for 500mg strength.
- All the samples of the products developed were found to be relatively more stable when compared to products available in market.
- Critical Process parameters: Drying of wet granules: LOD of dried granules must be between 0.5% to 4.5%, preferably between 1.0% to 3.5% and more preferably between 1.5% to 2.0%. Over dried granules produced tablets with more friability (more than 1.0%).
- Optionally the formulations of instant invention can even be prepared using direct compression method followed by coating with the coating composition of the instant invention.

The technology of the instant Application is further elaborated with the help of following examples. However, the examples should not be construed to limit the scope of the invention.

**Example: 1 Glucosamine HCl 1500 mg SR tablets**

| | | B.No. GHXA070507 | | B.No GHXA070107 | |
|---|---|---|---|---|---|
| **Sl No** | **Ingredients** | **mg/tablet** | **% w/w** | **mg/tablet** | **% w/w** |
| 1 | Glucosamine Hydrochloride | 1800 | 79.1 | 1800 | 78.2 |
| 2 | Dibasic calcium phosphate anhydrous (A-Tab) | 290 | 12.7 | 290 | 12.6 |
| 3 | Carbomer (Carbopol 974 P) | 90 | 3.9 | 90 | 3.9 |
| 4 | Stearic acid | 70 | 3.0 | 70 | 3.0 |
| 5 | Isopropyl alcohol | QS | QS | QS | QS |
| **Core weight** | | **2250** | --- | **2250** | --- |
| 6 | Eudragit RL 100 | 5.35 | 0.2 | 14.30 | 0.6 |
| 7 | Eudragit RS 100 | 12.50 | 0.5 | 21.40 | 0.9 |
| 8 | Purified Talc | 7.15 | 0.3 | 14.30 | 0.6 |
| 9 | Isopropyl Alcohol | -- | --- | QS | --- |
| 10 | Ethanol (96%) | Qs | Qs | -- | --- |
| **Coated tablet weight** | | **2275** | --- | **2300** | --- |
| **Coating Build up** | | **25mg** | | **50mg** | |
| **Assay** | | **100.50** | | **99.50** | |
| **Dissolution Profile** | **1st hour-** | 25.34% | | 16.89% | |
| | **4th hour-** | 62.78% | | 17.96% | |
| | **8th hour -** | 83.36% | | 32.17% | |
| | **12th hour-** | 103.15% | | 50.71% | |

**Manufacturing Procedure:**

**Step 1: Sifting**

Sift the following materials through the respective sieve specified

| Ingredients | Sieve no |
|---|---|
| Glucosamine Hydrochloride | 20# |
| Calcium hydrogen phosphate (anhydrous, granular, A-TAB) | 20# |
| Carbomer (Carbopol 974 P) | 20# |
| Stearic acid (Powder) | 40# |

**Step 2: Dry Mixing**

Take the following materials in a blender and blend for 5 minutes

- Glucosamine Hydrochloride

- Calcium hydrogen phosphate (anhydrous, granular, A-TAB)
- Carbomer (Carbopol 974 P)

**Step 3: Granulation**

Granulate the dry mix of step 2 with granulating solvent (isopropyl alcohol) by using Rapid Mixer Granulator (RMG).

**Step 4: Wet milling:**

Mill the wet mass through 8mm screen and collect in a double lined Polybag.

**Step 5: Drying:**

Dry granules of step 4 in Hot Air Oven at 45-50° C until optimum LOD is obtained. The LOD of dried granules must be between 0.5% to 4.5%, preferably between 1.0 % to 3.5 % and more preferably between 1.5 % to 2.0 %. Over dried granules produced tablets with more friability (more than 1.0%).

**Step 6: Dry milling:**

Mill the dried granules of step 5 through 2mm screen and collect in a double lined Polybag.

**Step 7: Dry Screening:**

Sift the Step-6 Milled granules through # 20 and collect in a Doubled Lined polybag and weigh the granules.

**Step 8: Lubrication:**

Add stearic acid powder to step 7 granules and blend for 3 minutes and collect into a HDPE containers containing doubled Lined polybag

**Step 9: Compression:**

Compress the granules of step 8

**Step 10: Preparation of coating Suspension:**

Disperse Eudragit RL100 and Eudragit RS100 in Ethanol.

- Stir for 90 min to dissolve.

- Add Purified talc to above clear solution.
- Stir for 5 min.
- Filter the above suspension through nylon cloth (200#).

**Step 11: Coating operation:**

Coat the core tablets of step 9 using coating solution of step 10 till achieving required weight gain and free from solvent.

The coated tablets obtained were subjected for assay followed by carrying out dissolution studies using water as a solvent by United States Pharmacopoeia method.

Here, the coating build up was made to have 25 mg and the dissolution profile had showed a release of 103.15 % at 12$^{th}$ hour. Thus, the prepared tablets were showing the controlled release up to 12 hours. In addition, any variation in concentration of components of composition had resulted in decrease in release of the drug as it is evident from the aforementioned example wherein it has shown a release of 50.71 % at 12$^{th}$ hour having a coating build up of 50mg for batch number (GHXA070107) E1. Similarly the procedure is followed with other examples provided in the below tables with slight variation in the concentration of the actives and excipients/ additives.

**Example: 2 Glucosamine HCl 1000 mg SR tablets**

| | | **B.No: GHAU020307** | | **B.No. GHAU020307** | |
|---|---|---|---|---|---|
| **Sl No** | **Ingredients** | **mg/Tab** | **% w/w** | **mg/Tab** | **% w/w** |
| 1 | Glucosamine Hydrochloride | 1000.00 | 79.0 | 1000.00 | 78.4 |
| 2 | Dibasic calcium phosphate anhydrous (A-Tab) | 161.00 | 12.7 | 161.00 | 12.6 |
| 3 | Carbomer (Carbopol 974 P) | 50.00 | 3.9 | 50.00 | 3.9 |
| 4 | Stearic acid | 38.70 | 3.0 | 38.70 | 3.0 |
| 5 | Isopropyl alcohol | Qs | Qs | Qs | Qs |
| **Average Wt** | | **1249.70** | --- | **1249.70** | --- |
| 6 | Eudragit RL 100 | 4.29 | 0.3 | 7.15 | 0.5 |
| 7 | Eudragit RS 100 | 6.42 | 0.5 | 10.70 | 0.8 |
| 8 | Purified Talc | 4.29 | 0.3 | 7.15 | 0.5 |
| 9 | Ethanol (96%) | Qs | Qs | Qs | Qs |
| **Total Weight** | | **1264.7** | --- | **1274.7** | --- |
| **Coating Build up** | | **15mg** | | **25mg** | |
| **Assay** | | **99.50%** | | **99.4%** | |

| | | | |
|---|---|---|---|
| **Dissolution Profiles** | **1st hour-** | 2.92% | 3.05% |
| | **4th hour-** | 42.82% | 39.66% |
| | **8th hour -** | 75.02% | 59.93% |
| | **12th hour-** | 98.77% | 69.55% |

Here, the coating build up was made to have 15 mg and the dissolution profile had showed a release of 98.77 % at 12th hour. Thus, the prepared tablets were showing the controlled release up to 12 hours. In addition, any variation in concentration of components of composition had resulted in decrease in release of the drug as it is evident from the aforementioned example wherein it has shown a release of 69.55 % at 12th hour having a coating build up of 25mg for batch number: GHAU020307.

**Example: 3 Glucosamine Sulphate 1000 mg SR tabs**

| | | **B.No GTS130207** | | **B.No. GTS170207** | |
|---|---|---|---|---|---|
| **Sl No** | **Ingredients** | **mg/Tab** | **% w/w** | **mg//Tab** | **% w/w** |
| 1 | Glucosamine Sulphate Potassium Chloride | 1333.30 | 78.5 | 1333.30 | 77.9 |
| 2 | Dibasic calcium phosphate anhydrous (A-Tab) | 162.00 | 9.5 | 164.00 | 9.5 |
| 3 | Carbomer (Carbopol 974 P) | 133.00 | 7.8 | 133.30 | 7.7 |
| 4 | Stearic acid | 40.00 | 2.3 | 40.00 | 2.3 |
| 5 | Isopropyl alcohol | QS | QS | QS | QS |
| | **Core tablet wt** | **1668.30** | --- | **1670.60mg** | --- |
| 6 | HPMC-E5 | -- | --- | -- | --- |
| 7 | Opadry white | -- | --- | -- | --- |
| 8 | Eudragit RL 100 | 8.58 | 0.5 | 8.56 | 0.5 |
| 9 | Eudragit RS 100 | 12.84 | 0.7 | 20.00 | 1.1 |
| 10 | Talc | 8.58 | 0.5 | 11.44 | 0.6 |
| 11 | IPA | QS | QS | -- | --- |
| 12 | Alcohol | -- | --- | Qs | Qs |
| 13 | Methylene Chloride | QS | Qs | -- | --- |
| | **Coated tablet wt** | **1698.3** | | **1710.6** | |
| | **Coating Build up** | **30mg** | | **40 mg** | |
| | **ASSAY** | **101.35** | | **100.98** | |
| **Dissolution Profile** | **1st hour-** | 17.99% | | 16.14% | |
| | **2nd hour-** | 23.15% | | -- | |
| | **4th hour-** | 27.91% | | 29.50% | |
| | **8th hour -** | 69.60% | | 58.55% | |
| | **12th hour-** | 99.69% | | 75.63% | |

Here, the coating build up was made to have 30 mg and the dissolution profile had showed a release of 99.69 % at 12th hour. Thus, the prepared tablets were showing the controlled release up to 12 hours. In addition, any variation in concentration of components of composition had resulted in decrease in release of the drug as it is evident from the aforementioned example wherein it has shown a release of 75.63 % at 12th hour having a coating build up of 40 mg for batch number GTS170207.

**Example: 4 Glucosamine HCl 750 mg SR tablets:**

| | | **B.No.** GHAUS040307 | | **B.No:** GHAUS010307 | |
|---|---|---|---|---|---|
| **Sl No** | **Ingredients** | **mg/tablet** | **% w/w** | **mg/tablet** | **% w/w** |
| 1 | Glucosamine Hydrochloride | 750 | 79.5 | 750 | 78.7 |
| 2 | Dibasic calcium phosphate anhydrous (A-Tab) | 132.25 | 14.03 | 121 | 12.7 |
| 3 | Carbomer (Carbopol 974 P) | 26.25 | 2.7 | 37.50 | 3.9 |
| 4 | Stearic acid | 29 | 3.0 | 29 | 3.0 |
| 5 | Isopropyl alcohol | Qs | Qs | Qs | Qs |
| **Core weight** | | **937.50** | --- | **937.50** | --- |
| 6 | Eudragit RL 100 | 1.43 | 0.15 | 4.29 | 0.4 |
| 7 | Eudragit RS 100 | 2.14 | 0.22 | 6.42 | 0.6 |
| 8 | Purified Talc | 1.43 | 0.15 | 4.29 | 0.4 |
| 9 | Ethanol (96%) | Qs | Qs | Qs | Qs |
| **Coated tablet weight** | | 942.5 | --- | 952.5 | --- |
| **Coating Build up** | | 5mg | | 15mg | |
| **ASSAY** | | **98.95** | | **99.20** | |
| **Dissolution Profile** | **1st hour-** | 19.35% | | 2.12% | |
| | **2nd hour-** | 43.18% | | 7.84% | |
| | **4th hour-** | 62.22% | | 39.59% | |
| | **6th hour -** | 85.31% | | 47.44% | |
| | **8th hour -** | 88.15% | | 73.98% | |
| | **12th hour-** | 97.99% | | -- | |

Here, the coating build up was made to have 5 mg and the dissolution profile had showed a release of 97.99 % at 12th hour. Thus, the prepared tablets were showing the controlled release up to 12 hours. In addition, any variation in concentration of components of composition had resulted in decrease in release of the drug as it is evident from the aforementioned example wherein it has shown a release of 73.98 % at 8th hour having a coating build up of 15 mg for batch number (GHAUS010307)1.

**Example: 5 Glucosamine Sulphate 500 mg SR tablets**

| | | B.No. GSSA030507 | | B.No. GSSA010307 | |
|---|---|---|---|---|---|
| **Sl No** | **Ingredients** | **mg/Tab** | **% w/w** | **mg/Tab** | **% w/w** |
| 1 | Glucosamine Sulphate Potassium Chloride | 666.65 | 77.9 | 666.65 | 78.9 |
| 2 | Dibasic calcium phosphate anhydrous (A-Tab) | 81.68 | 9.5 | 81 | 9.5 |
| 3 | Carbomer (Carbopol 974 P) | 66.67 | 7.7 | 66.50 | 7.8 |
| 4 | Stearic acid | 20 | 2.3 | 20 | 2.3 |
| 5 | Isopropyl alcohol | Qs | Qs | Qs | Qs |
| **Core weight** | | **835mg** | | **834.15mg** | |
| 6 | Eudragit RL 100 | 4.28 | 0.5 | 2.86 | 0.3 |
| 7 | Eudragit RS 100 | 10.0 | 1.1 | 4.28 | 0.5 |
| 8 | Purified Talc | 5.72 | 0.6 | 2.86 | 0.3 |
| 9 | Alcohol | QS | QS | QS | QS |
| 10 | Triethyl citrate | -- | --- | -- | --- |
| **Coated tablet weight** | | **855** | --- | **844.1** | --- |
| **Coating Build up** | | **20mg** | | **10mg** | |
| **ASSAY** | | **101.0** | | **99.76** | |
| **Dissolution Profile** | **1st hour-** | 30.75% | | 50.87% | |
| | **2nd hour-** | -- | | 70.38% | |
| | **4th hour-** | 69.17% | | 99.02% | |
| | **6th hour -** | 81.0% | | -- | |
| | **8th hour -** | 90.14% | | -- | |

Here, the coating build up was made to have 20 mg and the dissolution profile had showed a release of 90.14 % at 12th hour. Thus, the prepared tablets were showing the controlled release up to 12 hours. In addition, any variation in concentration of components of composition had resulted in decrease in release of the drug as it is evident from the aforementioned example wherein it has shown a release of 99.02 % at 4th hour having a coating build up of 10 mg for batch number GSSA010307. Thus, this batch number GSSA010307was not able to provide a controlled release of glucosamine. Therefore, concentration of components in the composition and the coating build up for each of the dose strengths was a challenge which has been addressed by the application of instant invention.

Any drastic variation in concentrations of the components of the composition may not result in even obtaining the solid dosage forms such as tablets etc. The present invention was successful in arriving at a concentration specific composition of

ingredients so as to achieve a controlled release of glucosamine for a time-period of up to 12 hours.

**Example: 6 Stability data of Glucosamine HCl SR 1500mg tablets.**

The details of the formulation subjected for stability studies.

**Batch No.** 470375

**Batch Size:** 5Lakh

**Pack:** White HDPE container with child resistant closure

| **Period of storage and condition** | **Appearance** | **Dissolution in %** | | | | **Assay (mg)** | **Microbial limit test (cfu/g)** |
|---|---|---|---|---|---|---|---|
| | | **1st hr** | **4th hr** | **8th hr** | **12th hr** | | |
| Initial | White colored oval shaped film coated tablets plain on both sides | 26.0 to 37.8 | 42.2 to 48.3 | 62.0 to 63.1 | 94.0 to 100.9 | 1558.4 | 20 |
| 3rd Month 30 deg C/65%RH | Complies | 15.7 to 21.1 | 45.2 to 52.5 | 66.6 to 72.5 | 89.0 to 95.2 | 1531.2 | 20 |
| 3rd Month 40 deg C/75%RH | Complies | 16.5 to 25.3 | 42.5 to 50.2 | 63.5 to 70.2 | 86.5 to 94.0 | 1520.9 | 25 |
| Limit | White to off-white colored oval shaped film coated tablets plain on both sides | NMT 30.0% | NMT 55.0% | NMT 75.0% | NLT 85.0% | 1350 to 1650 | NMT 1000 |

It is evident from the aforementioned stability data that the product of the application of instant invention is indeed stable as it complies with its appearance, dissolution percentage release, assay values and microbial limit test parameters.

**We Claim:**

1) A stable controlled release oral solid dosage form(s) composition for management of arthritis and related disorders, said composition comprising glucosamine and/ or salt (s) of glucosamine at a concentration ranging from 50% to 98%, preferably at a concentration ranging from 70 % to 80 %, Eudragit RL 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.15 % to 0.5 % and Eudragit RS 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.2 % to 0.75 %, optionally along with pharmaceutically acceptable additives.

2) The composition as claimed in claim 1, wherein said oral solid dosage forms are selected from a group comprising tablets, film coated tablets, pellets and mini-tablets in capsules.

3) The composition as claimed in claim 1, wherein said oral solid dosage form is preferably film coated tablet.

4) The composition as claimed in claim 1, wherein the glucosamine salts are selected from a group comprising glucosamine sulphate, glucosamine hydrochloride, glucosamine 2 KCl and combinations thereof.

5) The composition as claimed in claim 1, wherein the pharmaceutically acceptable additives are selected from a group comprising polymers, diluents, binders, granulating agents and lubricants.

6) The composition as claimed in claim 1, wherein the additives are preferably polymers selected from a group comprising pH-independent permeable polymers such as Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.2, Eudragit RL, Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.1 and Eudragit RS 100, calcium hydrogen phosphate and dibasic calcium phosphate as diluent, carbopol preferably carbomer 974P as binder, stearic acid as lubricant, talc as anti-adherent, isopropyl alcohol as a granulating agent or combinations thereof.

7) The composition as claimed in claim 1, wherein the additives are preferably calcium hydrogen phosphate as diluent at a concentration ranging from 2 % to 25 % and preferably at a concentration ranging from 5 % to 15 %, dibasic

calcium phosphate as diluent at a concentration ranging from 9 % to 13 %, carbopol preferably carbomer 974P as a binder at a concentration ranging from 1 % to 15 %, preferably at a concentration ranging from 2 % to 10 %, stearic acid as a lubricant at a concentration ranging from 0.5 % to 10 %, preferably at a concentration ranging from 2 % to 5 %, talc as anti-adherent at a concentration ranging from 0.1 % to 5 % and preferably at a concentration ranging from 0.15 % to 0.5 %.

8) The composition as claimed in claim 1, wherein said oral solid dosage forms are preferable dose forms selected from a group comprising 200 mg, 250 mg, 500 mg, 750 mg, 1000 mg and 1500 mg of glucosamine and/ or salts of glucosamine.

9) The composition as claimed in claim 1, wherein said related disorders of arthritis comprise osteoarthritis, rheumatoid arthritis, rheumatism, tendonitis, bursitis, degenerative spinal disc disease, sports trauma, trauma to joints, tendons and ligaments.

10) The composition as claimed in claim 1, wherein the ratio of Eudragit RL 100 and Eudragit RS 100 is ranging from 1.0:2.0 to 2.0:1.0 and preferably at a ratio ranging from 1.0:1.5 to 1.5:1.0.

11) The composition as claimed in claim 1, wherein said composition provides controlled release for a time period ranging from 4 hrs to 24 hrs and preferably for a time period ranging from 8 hrs to 12 hrs.

12) A process for preparing a stable controlled release oral solid dosage form(s) composition comprising glucosamine and/ or salt (s) of glucosamine at a concentration ranging from 50 % to 98 %, preferably at a concentration ranging from 70 % to 80 %, Eudragit RL 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.15 % to 0.5 % and Eudragit RS 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.2 % to 0.75 %, optionally along with pharmaceutically acceptable additives for management of arthritis and related disorders, said process comprising steps of: (a) meshing and blending of glucosamine and/ or glucosamine salt (s) with additives to obtain a mixture; (b)granulating the mixture followed by milling to obtain granules; (c) drying and lubricating the milled granules for compression to obtain solid dosage form (s); (d) coating the

solid dosage forms followed by drying to obtain stable controlled-release oral solid dosage form (s).

13) The process as claimed in claim 12, wherein coating the solid dosage form (s) with coating composition comprising pH independent controlled release coating materials and processing agents.

14) The process as claimed in claim 13, wherein said coating materials are selected from a group comprising pH-independent permeable polymers such as Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio ranging from 1:2:0.2, Eudragit RL 100, Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio ranging from 1:2:0.1, Eudragit RS 100 and combinations thereof.

15) The process as claimed in claim 13, wherein said processing agents are selected from a group comprising ethyl alcohol and a blend of dichloromethane with isopropyl alcohol.

16) The process as claimed in claim 12, wherein said coating composition is prepared by dispersing Eudragit RL 100 and Eudragit RS 100 in ethanol: stirring with addition of talc followed by filtration so as to obtain coating composition.

17) The process as claimed in claim 12, wherein the drying of granules is performed at a temperature ranging from $45^0$ C to $50^0$ C, preferably at a temperature ranging from $48^0$ C to $52^0$ C.

18) The process as claimed in claim 12, wherein the dried granules have an LOD ranging from 0.5 % to 4.5 %, preferably between 1.0 % to 3.5 % and more preferably between 1.5 % to 2.0 %.

19) The process as claimed in claim 12, wherein said glucosamine salts are selected from a group comprising glucosamine sulphate, glucosamine hydrochloride, glucosamine 2 KCl and combinations thereof.

20) The process as claimed in claim 12, wherein the pharmaceutically acceptable additives are selected from a group comprising polymers, diluents, binders, granulating agents and lubricants.

21) The process as claimed in claim 12, wherein the additives are preferably polymers selected from a group comprising pH-independent permeable polymers such as Poly(ethyl acrylate, methyl methacrylate,

trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.2, Eudragit RL, Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.1 and Eudragit RS 100, calcium hydrogen phosphate and dibasic calcium phosphate as diluent, carbopol preferably carbomer 974P as binder, stearic acid as lubricant, talc as anti-adherent, isopropyl alcohol as a granulating agent or combinations thereof.

22) The process as claimed in claim 12, wherein the additives are preferably calcium hydrogen phosphate as diluent at a concentration ranging from 2 % to 25 % and preferably at a concentration ranging from 5 % to 15 %, dibasic calcium phosphate as diluent at a concentration ranging from 9 % to 13 %, carbopol preferably carbomer 974P as a binder at a concentration ranging from 1 % to 15 %, preferably at a concentration ranging from 2 % to 10 %, stearic acid as a lubricant at a concentration ranging from 0.5 % to 10 %, preferably at a concentration ranging from 2 % to 5 %, talc as anti-adherent at a concentration ranging from 0.1 % to 5 % and preferably at a concentration ranging from 0.15 % to 0.5 %.

23) The process as claimed in claim 12, wherein said oral solid dosage forms are selected from a group comprising tablets, film coated tablets, pellets and mini-tablets in capsules.

24) The process as claimed in claim 12, wherein said oral solid dosage forms are preferably film coated tablet.

25) The process as claimed in claim 12, wherein said oral solid dosage forms can optionally be prepared using direct compression method.

26) A method for managing arthritis and related disorders in a subject in need thereof, said method comprising step of administering pharmaceutically acceptable amount of a stable controlled release oral solid dosage form(s) composition comprising glucosamine and/ or salt (s) of glucosamine at a concentration ranging from 50 % to 98 %, preferably at a concentration ranging from 70 % to 80 %, Eudragit RL 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.15 % to 0.5 % and Eudragit RS 100 at a concentration ranging from 0.1 % to 5 %, preferably at a concentration ranging from 0.2 % to 0.75 %, optionally along with pharmaceutically acceptable additives to the subject.

27) The method for managing as claimed in claim 26, wherein the subject is an animal or human being.

28) The method for managing as claimed in claim 26, wherein the wherein the pharmaceutically acceptable additives are selected from a group comprising polymers, diluents, binders, granulating agents and lubricants.

29) The method for managing as claimed in claim 26, wherein the additives are preferably polymers selected from a group comprising pH-independent permeable polymers such as Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.2, Eudragit RL, Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methaacrylate chloride at a ratio of 1:2:0.1 and Eudragit RS 100, calcium hydrogen phosphate and dibasic calcium phosphate as diluent, carbopol preferably carbomer 974P as binder, stearic acid as lubricant, talc as anti-adherent, isopropyl alcohol as a granulating agent or combinations thereof.

30) The method for managing as claimed in claim 26,wherein said oral solid dosage forms are preferable dose forms selected from a group comprising 200 mg, 250 mg, 500 mg, 750 mg, 1000 mg and 1500 mg of glucosamine and/ or salt (s) of glucosamine.

31) The method for managing as claimed in claim 26, wherein said related disorders of arthritis comprise osteoarthritis, rheumatoid arthritis, rheumatism, tendonitis, bursitis, degenerative spinal disc disease, sports trauma and trauma to joints, tendons and ligaments.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2007/000530

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

*A61K 47/32* (2006.01) *A61K 9/26* (2006.01) *A61K 9/58* (2006.01)
*A61K 9/14* (2006.01) *A61K 9/32* (2006.01) *A61K 31/726* (2006.01)

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)

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)
WPIDS, MEDLINE, CA: eudragit rl, eudragit rs, modified, sustained, release, matrix, glucosamine and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | AU 758299 B2 (LABORATOIRES PROGRAPHARM) 16 December 1999 -see whole document | 1-31 |
| Y | US 4980170 A (SCHNEIDER G et al) 25 December 1990 - in particular Abstract, cols 6-8, Examples | 1-31 |
| Y | WO 2002/060385 A2 (SMITHKLINE BEECHAM PLC) 8 August 2002 - in particular Abstract, pages 22, 24-26, Example 3) | 1-31 |

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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"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

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 April 2008 | 8 MAY 2008 |
| Name and mailing address of the ISA/AU<br>AUSTRALIAN PATENT OFFICE<br>PO BOX 200, WODEN ACT 2606, AUSTRALIA<br>E-mail address: pct@ipaustralia.gov.au<br>Facsimile No. +61 2 6283 7999 | Authorized officer<br>**JENNIFER FERNANCE**<br>AUSTRALIAN PATENT OFFICE<br>(ISO 9001 Quality Certified Service)<br>Telephone No : (02) 6283 2269 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2007/000530

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2004/0166157 A1 (THOMBRE, AG) 26 August 2004<br>- in particular paragraphs 0034-0039, Examples 11, 19, 20 claims 7 and 18 | 1-31 |
| Y | Derwent Abstract Acc No: 2004-700650/69 Class B02<br>CN 1511524 A (DONG J) 14 July 2004<br>-see Abstract | 1-31 |
| Y | CN 1634087 (ZHEJIANG HAILISHENG PHARMACEUTICALS CO LTD) 5 April 2006<br>-see Abstract | 1-31 |
| Y | Rowe R et al, Handbook of Pharmaceutical Excipients 5th Ed$^{n}$ published 2006 by Pharmaceutical Press and American Pharmacists Association<br>-see pages 371-373, 553-560, 892, 897, 905 | 1-31 |
| | AU 758299 B, US 4980170 B, WO 2002/060385 A2, US 2004/0166157 and CN 1511524 may be combined with CN 1634087 or with CN 1634087 and Rowe R et al for claims 1-31 | |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
**PCT/IN2007/000530**

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX