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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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(54) **Title**: AN INTRAVENOUS DRUG DELIVERY SYSTEM

(57) **Abstract**: The present invention is related to administer Paracetamol through Intra venous route through an aqueous vehicle. The Paracetamol is dissolved in Water for Injection with the help of Passive Ingredients responsible for Buffers, Isotonic, etc. The process is done at different temperatures. The activity of Paracetamol increases after dissolution in aqueous form & make the patient more comfortable.

COMPLETE SPECIFICATION

TITLE OF INVENTION: "AN INTRAVENOUS DRUG DELIVERY SYSTEM".

Field of Invention;

Filed of invention is related to the drug delivary system. More particulalry field is related to the pharamaceuical composition for the intravenous administration of a drug. Most particlaurly invention is related a pharameceutical composition for intravenous administartion containing paracetamol in an aqueous base.

Background of the invention;

In pharamacology and toxicology, a route of administration is the path by which a drug, fluid, poison or other substance is brought into contact with the body. Obviously, a substance must be transported from the site of entry to the part of the body where its action is desired to take place (even if this only means penetration through the into the skin). However, using the body's transport mechanisms for this purpose can be far from trivial. The pharmacokinetics properties of a drug (that is, those related to processes of uptake, distribution, and elimination) are critically influenced by the route of administration.

Routes of administration can broadly be divided into:

- *topical*: local effect, substance is applied directly where its action is desired
- *enteral*: desired effect is systemic (non-local), substance is given via the digestive route,
- *parenteral*: desired effect is systemic, substance is given by other routes than the digestive tract

Parenteral by injection;

- intravemous (into a vein), e.g. many drugs,
- intraarterial (into an artery), e.g. vasoloditor drugs in the treatment of vasospam and therobylotic drugs for treatment of embolisim,
- intramuscular (into muscle), e.g. many vaccines , antibiotics, and long-term psychoactive agents
- intracardiac (into the heart), e (no longer commonly performed)
- subcutaneous (under the skin), e.g. insulin
- intraosseous infusion (into the bone marrow) is, in effect, an indirect intravenous access because the bone marrow drains directly into the venous system. This route is occasionally used for drugs and fluids in emergency medicine and paediatrics when intravenous access is difficult.
- intradermal (into the skin itself) is used for skin testing some allergens and also for tattoos
- intrathecal (into the spinal canal) is most commonly used for spinal anesthesia and chemotherapy

Paracetamol or acetaminophen is a widely-used analgesic and antipyretic, Unlike aspirin it is not a very effective anti-inflammatory agent. It is well tolerated, lacks many of the side-effects of aspirin and is available over-the-counter so it is commonly used for the relief of fever headaches, and other minor aches and pains. Paracetamol is also useful in the management of more severe pain, where it allows lower dosages of additional non-steroidal anti-inflammatory drugs (NSAIDs) to be used, thereby minimizing overall side-effects. It is also used in combination with opioid analgesics It is a major ingredient in numerous cold and flu medicationsintraperitoneal (infusion or injection into the peritoneum) e.g. peritoneal dialysis.

There are different types of drug delivery modes are availbe for the non-steroidal anti-inflammatory drugs (NSAIDs) like paracetamol. Both patent and non patent litreture survey reveals,

WO2005115344 relates generally to formulations comprising paracetamol. More particularly, the present invention provides a swallow formulation comprising paracetamol which facilitates the rapid delivery of paracetamol into the circulatory system following oral administration. The present invention further relates to methods for inducing efficient pain relief including an analgesic effect by the administration of the paracetamol formulation.

WO/2005/115344 is relates to formulations comprising paracetamol. More particularly, the present invention provides a swallow formulation comprising paracetamol, which facilitates the rapid delivery of paracetamol into the circulatory system following oral administration. The present invention further relates to methods for inducing efficient pain relief including an analgesic effect by the administration of the paracetamol formulation.

U.S. Patent No. 6,316,025, Grattan describes a swallow tablet of paracetamol containing 300 mg to 1000 mg of sodium bicarbonate per tablet and a paracetamol to sodium bicarbonate ratio of between 0.74 and 1. Grattan et al. (2000 supra) subsequently reported that a formulation with 630 mg sodium bicarbonate gave a Tmax of 17.5 ± 4.95 minutes and a Cmax of 29.79 ± 9.06 *mg.L"1. It was suggested that this was due to an osmotic effect of sodium* bicarbonate, which would be isotonic when ingested with 100 mL of water.

U.S. Patent Application No. 20040204475 describes a formulation containing sodium bicarbonate and eletriptan. The sodium bicarbonate is administered in an amount to obtain a duodenal concentration approximately isotonic with serum (150 mmol). The formulations exemplified all contained 630 mg sodium bicarbonate

U.S. Patent Application No. 20040170681 describes a paracetamol formulation containing less than 100 mg sodium bicarbonate per tablet. About 90% of the paracetamol is described as being released from this formulation in 15 minutes using United States Pharmacopoeia (USP) dissolution apparatus 2 with 900 mL

0.05 N hydrochloric acid at 30 rpm and 370C. A formulation was exemplified which resulted in an area under the plasma concentration-time curve at 20 minutes after administration (AUC20) of πμg.min.mL"1 in fed subjects when given as a 1000 mg paracetamol dose.

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Object of the invention;

An object of the invetion is to design a direct injection method for the paracetamol. Another object of the invention is to formulate intraveous formulation of the paracetamol. Yet another object of the invention is to prepare water based formulation of intravenous adminstration of the paracetamol.

Summary of the invention;

Present invention is related to intravenous administration of the paracetamol. In this method paracetamol powder is directly dissolved in the aquesous base of the suitable pH and this solution is direcly administered in the patient's body though the direct injection.

The advantages of the direct delivary of the paracetamol in to blood flow and immediate relief form the suffering.

Detailed Description of the invention;

The subject in the methods described herein can be, e.g., a mammal, e.g., a human, mouse, rat, dog, cat, horse, cow, pig, or non-human primate. In some embodiments, the subject is a juvenile human, e.g., a subject less than 7 years of age.

The term "pharmacologically effective amount" as used herein means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician.

Administration to the subject in the methods described herein can be, e.g., intravenous, intramuscular, subcutaneous, sublingual, oral, rectal or via aerosol delivery. The inhibitor can be administered as a pharmaceutical composition that includes a safe and therapeutically effective of an inhibitor of xanthine oxidase and a pharmaceutically effective carrier. The compositions are preferably suitable for internal use and include an effective amount of a pharmacologically active compound of the invention, alone or in combination, with one or more pharmaceutically acceptable carriers. The compounds are especially useful in that they have very low, if any, toxicity.

In some embodiments, pharmaceutical compositions is water based formulation comprising the active ingredient together with a) diluents, e.g., mannitol, sorbitol, Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. The compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. The compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 0.1 to 50%, of the active ingredient.

Administration of the active compounds and salts described herein can be via any of the accepted modes of administration for therapeutic agents. These methods include systemic or local administration such as oral, nasal, parenteral, transdermal, subcutaneous or topical administration modes. The compositions will include an effective amount of active compound or the pharmaceutically acceptable salt thereof, and in addition, and may also include any conventional pharmaceutical excipients and other medicinal or pharmaceutical drugs or agents, carriers, adjuvants, diluents, etc., as are customarily used in the pharmaceutical sciences.

Parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection. One approach for parenteral administration employs the implantation of slow-release or sustained-released systems, which assures that a constant level of dosage is maintained, according to U.S. Pat. No. 3,710,795, which is incorporated herein by reference,

The method of administration of the paracetamol in the present invention is through the intravenous route through an aqueous vehicle. The paracetamol is dissolved in water for injection. The injection thus prepared also contains adjuvants, buffers isotonic.

Adjuvants are pharmacological or immunologicalagents that modify the effect of other agents (e.g., drugs, vaccines) while having few if any direct effects when given by themselves. In this sense, they are roughly analogous to chemical.

Chemically, mannitol is a sugar alcohol or a polyol; it is similar to xylitolor sorbitol However, mannitol has a tendency to lose a hydrogen in aqueous solutions, which causes the solution to become acidic For this, it is not uncommon to add a substance to adjust its pH such as sodium bicarbonate.

Phosphate buffered saline (abbreviated PBS) is a buffer solution commonly used in biochemistry and other branches of biological research. It is a salty solution containing sodium chloride and (in some formulations) potassium chloride and potassium phosphate. The buffer helps to maintain a constant pH The osmolarity and ion conc

The term isotonic may refer to;

- Isotonic muscle exercise
- Isotonic (exercise physiology) for the term associated with muscle contraction
- solutions that have equal osmotic pressure, such as the isotonic environment in cell biology
- to assist athletes rehydrate while balancing electrolytes

entrations of the solution usually match those of the human body (isotonic). The process is carried at the different temperatures. The activity increases after the direct administration of the paracetamol and patient gains immediate relief. Examples

1. Approximatly 5.0 ml of distilled water used for the preparation of the injection after purging with the nitrogen gas. Phamaceitically effective amount of the paracetamol is added in the container in addtion to this mannitol and sodium phosphate dibasic (unhydrous) is added. pH of the solution is adjsuted in between to 5.5 to 6.5 by usning acid or base.
2. Approximatly 10.0 ml of distilled water used for the preparation of the injection after purging with the nitrogen gas. Phamaceitically effective amount of the paracetamol is added in the container in addtion to this mannitol and sodium phosphate dibasic (unhydrous) is added. pH of the solution is adjsuted in between to 5.5 to 6.5 by usning acid or base.

Claims:

1. An intravenous drug delivary system comprising;
   (a) water;
   (b) pharamaceitically aceptable adjuvants/excipients;
   (c) isotonic soution /buffer solution
   (d) pharmaceitically effectve amount of active ingrident

   .Wherein, water used for the said system is purged with nitrogen gas.

2. An intravenous drug delivary system accodring to claim 1 wherein water is 1.0-1000 ml.
3. An intravenous drug delivary system accodring to claim 1 wherein pharamaceuitically aceptable adjuvants/excipients is maniitol.
4. An intravenous drug delivary system accodring to claim 1 wherein isotonic soution /buffer solution is phosphate buffer, sodium phospahte dibasic anhyrdous.
5. An intravenous drug delivary system accodring to claim 1 wherein active ingrident is paracetamol.
6. A method for preparation of intravenous drug delivary system comrising;
   (a) purging nitrogen gas thorugh water ;
   (b) adding pharamaceutically effective amount of the paracetamol,
   (c) addtion of appropriate amount of sodium phospahte dibasic anhydrous;
   (d) adjusting pH 5.5-6.5 by using acid or base;
7. An intravenous drug delivary system as described with refrence to description and example herein.

Signature: Sandip. D.

Applicant: **AKUMS DRUGS & PHARMACEUTICALS LTD.**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 08/00753

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M 5/14 (2009.01)
USPC - 604/80
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)
IPC(8) - A61M 5/14 (2009.01)
USPC - 604/80

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 604/80, 83, 85
(Text Search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, USOC, EPAB, JPAB); DialogPRO (Engineering) and Google Scholar.
Search Terms: intravenous, paracetamol, purg$, nitrogen, isotonic, PBS, phosphate, dibasic, mannitol, sodium, anhydrous, excipient, adjuvant, sodium phosphate.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 6,028,222 A (DIETLIN et al.) 22 February 2000 (22.02.2000) claim 19; col 1, ln 9-13; col 2, ln 36-38, 63-67; col 3, ln 16-23; 45-56; col 5, ln 24-27; col 6, ln5-13; col 15, ln 24-53.	1-3, 5 and 7 ---------- 4 and 6
Y	US 2006/0009469 A1 (WITCHEY-LAKSHMANAN et al.) 12 January 2006 (12.01.2006) Table 12; para [0168].	4 and 6

☐ Further documents are listed in the continuation of Box C. ☐

* 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
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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
"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	Date of mailing of the international search report
19 February 2009 (19.02.2009)	09 MAR 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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