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(54) Title: A NOVEL SUSTAINED RELEASE COMPOSITION OF COMPOUNDS SELECTED FROM THE CLASS OF CENTRALLY ACTING MUSCLE RELAXANTS

(57) Abstract: The disclosed invention provides novel sustained release pharmaceutical preparations and process for making such compositions of Tolperisone and/or Eperisone and/or a pharmaceutically acceptable salt thereof. The present invention provides a sustained release formulation of Tolperisone and Eperisone either single or in combination or otherwise in combination with other drugs selected from the classes such as analgesic, antipyretic, neuroprotective agents, other muscle relaxants which can be formulated either in a fixed dose or as combination kit for oral administration. The composition is suitable for once a day administration into mammals and provides sustained and prolonged drug release till 24 hours which helps to reduce dosing frequency. The composition comprises therapeutically effective amount of active substance, release retarding polymers and other pharmaceutically acceptable excipients.

A NOVEL SUSTAINED RELEASE COMPOSITION OF COMPOUNDS SELECTED FROM THE CLASS OF CENTRALLY ACTING MUSCLE RELAXANTS

FIELD OF INVENTION

In the present invention, there is provided a preparation of sustained release formulations, more specifically sustained release tablets comprising of Tolperisone, Eperisone and alike drugs for oral administration useful for the symptomatic treatment of spasticity and muscle spasm. The present invention also relates to the preparation of sustained release dosage forms which contribute to reduced frequency of administration and side effects which are associated with repetitive administration of conventional dosage forms.

Present invention also relates to gastro retentive dosage forms comprising a skeletal muscle relaxant which remains buoyant in the stomach up to 24 hours to release the active medicaments into gastric contents over the period of 24 hours thereby achieving maximum absorption to provide enhanced therapeutic effect in the treatment of mucoskeletal disorders in the mammals.

BACKGROUND OF INVENTION

Tolperisone and its salts are muscle relaxants which are used for improving symptoms related to spastic paralysis, for improving muscle tone which arises from diseases or conditions such as inflammation of the joints, cervical syndrome and back pain.

Chemically Tolperisone is (RS)-2, 4' dimethyl-3-piperidinopropiophenone. An advantage of the treatment with Tolperisone is the fact that functional parameters e.g. the mobility of the patient, is also improved. Patients having long-term administration of Tolperisone have a good therapeutic relationship and the confidence basis necessary for therapeutic success by the absence of central side effects usually associated with the further employment of this medicine. The main indications for Tolperisone are illnesses, which are accompanied by painful muscle spasm, e.g. spinal column syndromes, muscular pain with degenerative

illnesses, sports, occupational repetitive motion syndromes and Fibromyalgia syndrome.

Chemical name of Eperisone hydrochloride is 1-(4-ethylphenyl)-2-methyl-3-(1-piperidyl) propan-1-one. It acts by relaxing both skeletal muscles and vascular smooth muscles, and demonstrates a variety of effects such as reduction of myotonia, improvement of circulation, and suppression of the pain reflex. The drug inhibits the vicious cycle of myotonia by decreasing pain, ischaemia, and hypertonia in skeletal muscles, thus alleviating stiffness and spasticity, and facilitating muscle movement. Eperisone also improves dizziness and tinnitus associated with cerebrovascular disorders or cervical spondylosis. Eperisone has a relatively low incidence of sedation in comparison of other anti-spasmodic drugs, therefore it becomes the drug of choice for anti-spasmodic therapy which does not show reduction in alertness.

The use of Tolperisone for treating neuropathic pain and pain associated with various nervous system disorders has also been suggested (U.S. Patent Application No. 2006/0004050).

The main drawback of using this drug in conventional formulation is the need of frequent administration because of rapid metabolism and clearance of the drug from the body. This is uneconomical and having compliance problems as it is very bothersome for patients and medical personnel. Several approaches have been described to eliminate the drawbacks associated with oral administration of Tolperisone due to its short circulating half-life.

Method and composition for preparation of different dosage form containing Tolperisone and Eperisone are known in the art.

U.S 6500455 describes various controlled release pharmaceutical preparations of Tolperisone, e.g., hydro-gel based formulations, coated tablets, and microcapsules. The active ingredient Tolperisone that is present as 50/50-racemate or as racemate with a preponderant content of the (-)-isomer or the (+)-

isomer is liberated from the preparation in the human body in a delayed manner and preferably in the intestinal canal. This invention provides delayed release which releases the medicament in the intestinal canal only. Further it does not claim the drug release up to 24 hours period.

U.S.2005/0196451 describes controlled release formulation in which Tolperisone is combined with a methacrylate based polymer such as Eudragit®. Pharmaceutically compatible material consists of polymers and/or copolymers selected from the group of acrylic and/or methacrylic acid esters, preferably methyl and/or ethyl (methyl) acrylate as well as mixtures thereof. This invention utilizes combinations of methacrylic acid polymers which may not be cost effective.

WO/2008/004127 discloses the method of oral administration of Tolperisone to prove that administration of Tolperisone to a subject in the fed state is effective to (i) increase the bioavailability of Tolperisone, as well as (ii) delay its absorption, in comparison to the conventional approach of oral administration of Tolperisone to a subject in the fasted state. The invention has given emphasis on the method of administration of Tolperisone in the fasted state but it does not give hint about sustained delivery of Tolperisone after administration.

WO/2004/032927 relates to transdermal preparations comprising Eperisone, Tolperisone or salts thereof. It contains adhesive layer which contains mixture of acrylic adhesives with or without hydroxy group. The use of this invention is limited to transdermal route only.

U.S 20040224012 is for topical application and methods for administration of active agents using liposome macro-beads which included various therapeutic class drugs which can be formulated by this process including Tolperisone. The use of this invention is limited to transdermal route only.

U.S 6733781 is for the fast dissolving tablets. The present invention relates to processes for the preparation of tablets which dissolve rapidly in the mouth. The

tablets of the invention comprise a compound which melts at about 37°C. or lower, have a low hardness, high stability and generally comprise few insoluble disintegrants which may cause a gritty or chalky sensation in the mouth. A non-limiting list of acceptable active ingredients which were included contains muscle relaxants such as Tolperisone and Eperisone. The invention is for fast dissolving tablets and there no emphasis given on sustaining the drug release.

U.S 6753011 relates to controlled delivery osmotic device which comprises an expandable-hydrophilic polymer-core located substantially in the center of the dosage form surrounded by a composition of the active agent(s) to be delivered. A novel dual function membrane permits delivery of the active agent(s) through a combination of diffusion and osmotic pumping mechanisms. The not limiting class of therapeutic agents also included muscle relaxant Tolperisone. The invention involves the use of complicated technology which is also expensive.

US 5252588 is for percutaneously absorbable crosslinked Eperisone or Tolperisone preparation. It comprises a pharmacologically effective amount of Eperisone or Toleprisone incoproated into a water-swellable crosslinked polyvinylpyrrolidone and a base carrier, and exhibits improved percutaneous absorption. The invention is for pecuataneous administration of drug, also there is no emphasis given on sustaining the drug release.

EP 0310259 is the Eperisone as a hypotensive agent which claims use of 4'-ethyl-2-methyl-3-piperidinopropiophenone or a pharmacologically acceptable salt thereof, for the preparation of a medicament with an anti-hypertensive action without inducing increased heart rate. The invention bounds to new therapeutic use of Eperisone but does not hint about sustained release preparations of Eperisone.

US 5498422 related to a sustained release capsule having good mucosa adhering property and stability. Capsules were filled with dispersion of drug in liquid paraffin and these capsules were coated with mucoadhesive polymers. Tolperisone and Eperisone under the class muscle relaxant are included in its

non limiting class of therapeutic ingredients. The use of this invention is limited to excipients of mucoadhesive category.

All the above cited prior arts however lacks in a technology to deliver the drugs over a period of 24 hours. Hence the inventors aimed at developing the formulation which can deliver the drug at sustained rate over the period of 24 hours and still serve the therapeutic need of the patient suffering from mukoskeletal disorders by reducing the dosing frequency.

OBJECTS OF INVENTION

Accordingly the prime objective of the present invention was to prepare a dosage form comprising of Tolperisone, Eperisone and alike drugs for the sustained drug delivery over a prolonged period of time.

SUMMARY OF INVENTION

The present invention is a sustained release oral formulation of Tolperisone, Eperisone or salts thereof for the treatment of muscular spasm resulting from various mucoskeletal disorders, various injuries and strains with the drug release profile of 24 hours. These dosage forms provide the drug release over a period of 24 hours, during which 20 to 80%, preferably between 25 to 75% of the active ingredient i.e. Tolperisone and or Eperisone or pharmaceutically acceptable salt thereof, is dissolved between 2 to 8 hours, and that of about 80% of active ingredient is dissolved between 8 and 24 hours.

BRIEF DESCRIPTION OF DRAWINGS

1) Fig 1: Drug release profile of Tolperisone SR tablets in different drug : polymer ratio
2) Fig 2: Drug release profile of Tolperisone SR tablets containing optimumdrug to release retardant polymer ratio
3) Fig 3: Dissolution profile of Eperisone controlled release floating tablets at different drug to release retardant polymer ratio

4) Fig 4: Dissolution profile of optimum formulation of controlled release Eperisone floating tablets
5) Comparative drug release profile of Tolperisone SR tablets versus Tolperisone immediate release tablets.
6) Comparative drug release profile of Eperisone controlled release Gastro retentive tablets versus Eperisone immediate release tablets.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions in the form of sustained release tablet formulations of Tolperisone or Eperisone or a pharmaceutically acceptable salt thereof, for treatment of muscle spasm, and mukoskeletal disorders. The present inventions also discloses the process for the preparation of the same.

According to another aspect of the present invention, there are provided pharmaceutical formulations comprising Tolperisone or Eperisone or a pharmaceutically acceptable salt thereof either alone or in combination with other muscle relaxants or analgesic drugs in therapeutically allowable doses along with suitable pharmaceutical excipients, particularly, diluents, binders, lubricants and rate controlling polymers.

The Tolperisone in conventional tablet format has various disadvantages like rapid metabolism, rapid clearance through body which leads to repeated administration of dosage for getting systemic effects and causes damage to the gastrointestinal tract.

The conventional, immediate release Tolperisone tablet releases 80% of drug content within 30 minutes and gets eliminated rapidly which is unlike the dosage for of the present invention.

The sustained release formulation helps to reduce these problems. A unit dosage form will sustain the drug release for 24 hours and ultimately reduce the dosage regime and associated side effects.

The combination of HPMC with other excipients like carbopol and ethyl cellulose in appropriate concentration only helps to release the drug from dosage form in sustained manner. The optimum concentration of these combinations of HPMC of different grades with carbopol and ethyl cellulose is given in the forthcoming examples below.

The drug to release retardant excipients ratio is a critical in the present invention, as the release retardant polymers used in the particular amount help to sustain the drug release up to 24 hours. The ratio of drug to total amount of release retarding polymers in Tolperisone sustained release tablets was particularly kept in the range of about 1:0.5 to 1:3. It was observed that increase in the drug to total amount of release retarding polymers beyond 1:3 resulted in the very poor release of the drug. The total amount of drug released at the end of 24 hours was only 57 %. Further it was also observed that Tolperisone sustained release formulations release the drug at very faster rate when the drug to total amount of the release retardant polymers were taken below the particular amount below the drug to total release retardant polymers ratio of 1:0.5. Here almost 90 % of drug was release within 4 hours.

The same is evident from the graphical representations of the comparative drug release profiles of Example 1 and 2 below.

The ratio of drug to total amount of release polymers in Eperisone sustained release tablets was in kept in the range of about 1:1 to 1:3. The ratio of drug to total amount of release retarding polymers in Eperisone sustained release tablets and Eperisone controlled release floating tablets was particularly kept in the range of about 1:0.5 to 1: 3. Here also it was observed that increase in the drug to total amount of release retarding polymers beyond 1:3 resulted in very retarded drug release than what was required. On the contrary when the drug to

total amount of the release retardant polymers were taken below 1: 0.5 the drug was found to release at rapid rate than what was desired. The same are evident from the graphical representations of the comparative drug release profiles of Example 3 and 4 below.

Present invention relates to a sustained release formulation of centrally acting muscle relaxant drugs, for the treatment of muscular spasm resulting from various mucoskeletal disorders, various injuries and strains with a drug release profile upto 24 hours. These dosage forms provide the drug release over a period of 24 hours, during which 20 to 80%, preferably between 25 to 75% of the active ingredient is dissolved between 2 to 8 hours; and that of about 80% of active ingredient is dissolved between 8 and 24 hours.

According to another aspect of the present invention, there is also provided gastro retentive dosage form comprising skeletal muslce relaxant which remains floated in the gastric medium upto 24 hours thereby providing sustained drug release of active ingredient in the stomach to provide maximum absorption to ultimately produce its desired therapeutic effect. Such formulation contains gas generating agent, mixture of excipients for producing effervescence, release retarding polymers and low density excipients. Gas generating agents are used in the gastro retentive dosage form to produce the gas. Such formed gas is trapped in the matrix of swelled polymers and thus maked the density of dosage form lower than the gastric fluid thereby making the dosage form to float on the surface of gastric fluid.

Low bulk density agents to formulate the gastro retentive dosage form may be selected from a mixture consisting of polymers selected from ethylcellulose or suitable enteric polymers of cellulose derivatives, hydrogenated oils, waxes, fatty acids either alone or in combination with suitable pharmaceutical additives.

Tolperisone / Eperisone can also be combined with other drugs such as tramadol or amtolmetin guacil or aceclofenac to formulate bilayer tablet dosage form. Such combination when appropriately mixed with the suitable excipients for the dermal

preparation may be used as a sustained release matrix for relieving the mucoskeletal pains. The same sustained release matrix may be used for the formulation of oral liquids using suitable excipients and the same matrix may be also filled in the capsules or sachets or as powder in the bottles. Additionally muscle relaxant spray of the above drugs can be used in the aerosol forms. The same can be prepared appropriately by incorporating into a suitable dispersing matrix.

According to another aspect of the present invention, Tolperisone or Eperisone or a pharmaceutically acceptable salt thereof either alone or in combination with other muscle relaxants or analgesic drug in therapeutically allowable can also be formulated into sustained release preparations such as granules, micorspheres, micorcapsules, micorbeads, nanoparticles, Solid lipid nanoparticles, liposomes. Such formulated preparations can be appropriately packed such as sachets which can be dispersed into sufficient amount of water before administeration. Moreover such sustained release granules of these drugs can also be dispersed into suitable liquid and can also be filled into capsules.

Tolperisone or Eperisone or its salts thereof may also be formulated in the form of bilayer tablets or multilayer tablets. Such bilayer or multilayer tablets may contain all the layer meant for sustained drug release profile or may contain one layer with sustained release drug profile and another layer having immediate release drug profile.

Tolperisone or Eperisone or its salts thereof or may also be fabricated in to transdermal drug delivery system to provide sustained drug delivery of the active medicaments to relieve the muscle spasm. Such system may be prepared by incorporating the active substance with rate controlling polymers and casting this drug reservoir on the impermeable backing membrane. Such muscle relaxant drugs can be combined with pain relieving agents and can be either dissolved or dispersed into suitable solvent to formulate the drug reservoir. Suitable adhesive can be applied on the other side of the drug reservoir to facilitate the application of device on to the skin. Such muscle relaxant drugs can be combined with pain

relieving agents and can be either dissolved or dispersed into suitable solvent to formulate the drug reservoir.

Tolperisone or Eperisone or its salts thereof or may also be formulated into sustained release granules which can be compressed later on into the tablets. Such granules meant for sustained release can also be dispersed into suspension to prepare the ready to use suspension to provide sustained drug release of medicaments.

Osmotic drug delivery device can also be developed comprising of Tolperisone or Eperisone to provide the extended drug release of these medicaments by using osmotic agents in combination with rate controlling excipients.

Tolperisone or Eperisone or its salts thereof can also be incorporated appropriately into rate controlling materials dispersed or dissolved into suitable vehicles to formulate depot preparation which can be administered via parenteral route to provide sustained delivery of the active substance.

Buccal or mucoadhesive compositions containing Tolperisone and Eperisone or salts thereof can also be prepared by incorporating these drugs with suitable mucoadhesive polymers. Such dosage form provides the drug delivery in the sustained manner by remaining adhered to the mucus wall of buccal cavity or gastrointestinal mucosa.

Tolperisone may also be combined with vinpocetine to prepare sustained release or immediate release tablets for the beneficial effect in the treatment of post stroke muscle spasm as this combination will provide relief in muscle spasm by action of Tolperisone and vinpocetine will improve the cerebral blood flow in the brain.

Tolperisone may also be combined with paracetamol or diclofenac to prepare sustained release or immediate release tablets for the beneficial effect in the management of spasm associated with severe pain.

Sustained release formulation of Tolperiosne or Eperisone or salts thereof can be prepared in combination with other muscle relaxants taken in a therapeutically effective amount. Examples of such muscle relaxants include but are not limited to Thiocolchicoside, Cyclobenzaprine, carisoprodol, chlorzoxazone, metaxolone, methocarbamol, orphenadrine, diazepam, baclofen, tizanidine, gabapentin, botulin toxin, tetradotoxin, Chlorphenesin carbamate, mephenesin, phenprobamate, chlormezanone, pridinol mesylate, afloqualone and dantrolene or combinations of the any of the foregoing in suitable form for administration into mammals via suitable routes.

Thiocolchicoside or Cyclobenzaprine or its salts can also be combined with other muscle relaxant drugs such as curare alkaloids and their derivatives to prepare sustained release compositions mentioned in the present invention in suitable form for administration into mammals via suitable routes. Examples of such muscle relaxant from this category include but are not limited to pancuronium, cisatracurium, rocuronium, vacuronium, doxacurium, cisatracurium, atracurium, mivacurium, rapacuronium, tubocuranine, pipecuronium and salts of these drugs and combinations of any of the foregoing.

The same formulation can be formulated containing Tolperisone or Eperisone or salts thereof either as sustained release dosage form or immediate release dosage form in combination with the drugs of therapeutic category like analgesic, antipyretic or NSAID's in suitable dose either as fixed dose or in combination or as bi-layer tablets. Non limiting examples of such categories of drugs includes analgesics, antipyretics which includes drug of aniline and p- Aminophenol analogues, salicylic acid analogues, quinoline derivatives, pyrazolones and pyrazolidones, N- arylanthranilic acid, Further drugs from the category NSAID's includes heteroacrylacetic acid analogues, arylacetic acid analogues, arylpropionic acid analogues, naphthalene acetic acid analogues, gold compounds, uricosuric agents, salicylic acid analogues, pyrazolones and pyrazolidones, lipo-oxygenase-2 (LOX2) inhibitors like licofelone and other classes of drugs. Pain relievers such as tropane alkaloids may also be combined

with Tolperisone or Eperisone or salts thereof to formulate the present composition.

These sustained release formulations are often referred in the art, as "matrix formulations" where by the drug is incorporated into a hydrated polymer matrix system and is released via diffusion or erosion mechanism.

Suitable release retarding excipients include release-retarding polymers, which may be swellable or form gel in contact with physiological fluid such as the GI tract contents. Polymers whose dissolution is pH dependant may be used either alone or with a plasticizer.

Release retarding polymers which may or may not be swellable include, inter alia, cellulose derivatives, cross- linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, hydroxyethylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide, potassium methacrylatedivinylbenzene co-polymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, hydroxyethyl cellulose high- molecular weight polyvinyl alcohols, polyethyleneoxides etc.

Release retarding gellable polymers includes methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, hydroxyethyl cellulose, low-molecular weight polyvinyl alcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone, acrylic acid derivatives, xanthan gum, isapgol husk, chitosan other such polymers which will release the drug in sustained manner.

Release retarding polymers simultaneously possessing swelling and gelling properties include acrylic acid derivative such as carbopol, medium-viscosity hydroxypropylmethylcellulose and medium-viscosity polyvinyl alcohols.

A preferred release-retarding polymer is one of the available grades of hydroxypropylmethyl cellulose or hydroxyethyl cellulose.

Examples of matrix forming polymers, which can be used, include various commercially available cellulose derivatives in different grades which differ in their viscosity, molecular weight and extent of cross linking. Some of the examples of such polymers are Methocel K4M, Methocel E50, Methocel K15M, Methocel K100M and Methocel KI00LV.

Other release-retarding polymers which may be incorporated include hydrocolloids such as natural or synthetic gums, cellulose derivatives other than those listed above, carbohydrate-based substances such as gum acacia, gum karaya, gum tragacanth, locust bean gum, guar gum, gums derived from Tamarindus indica, agar, pectin, carageenin, soluble and insoluble alginates, carboxypolymethylene, casein, zein, and the like, and proteinaceous substances such as gelatin.

Apart from the ingredients decribed above, tablet may also contain channeling agents which are used to modify the dissolution of the dosage form. Suitable pharmaceutically acceptable water soluble salts such as sodium chloride, potassium chloride, boric acid, sodium borate, and sugars such as sucrose, lactose can be used as channeling agents in the tablet. poly(ethylene glycol), poly(ethylene-co-propylene glycol), and poly(vinylpyrrolidone) can also be used as channeling agent. Apart form these, hydrophilic natural and modified polysaccharides such as dextran, arabinogalactan may be used. Synthetic polymers such as homo and copolymers of acrylic acid and vinyl alcohol can also be utilised as channeling agents.

The sustained release formulation may also include diluents/compression aids such as lactose, microcrystalline cellulose, dicalcium phosphate, sucrose, mannitol, xylitol, starches, and lubricants such as magnesium stearate, sodium stearyl fumarate and stearic acid. The sustained release formulation may further comprise binders such as povidone (polyvinylpyrrolidone); flow aids such as silicon dioxide or talc.

Sustained release tablets of Tolperisone hydrochloride and Eperisone Hydrochloride tablets were prepared using various grades of HPMC polymers differening in their viscosity in combination with other polymers like ethyl cellulose, carbopol, stearic acid, sodium alginate, microcrystalline cellulose and other release retarding polymers selected from the classes which are mentioned above.

In one embodiment of the present invention, comprises the process of preparing the sustained release matrix composition of Tolperisone hydrochoride/ Eperisone hydrochloride comprises dispensing of ingradients, mixing, granulation, sieving through mesh, drying, sifting, lubrication and finally compression. Such tablets can be prepared by wet granulation, dry granulation or direct compression. Further wet granulation may involve use of suitable aqueous as well as non aqueous solvents. Optionally tablets can be coated by using aqueous or nonaqueous coating materials and optionally using suitable approved colors.

In one of the preferred embodiment of the present invention, gastro retentive dosage forms of Tolperisone hydrochloride and Eperisone hydrochlorides were developed to provide sustained release of these drugs upto 24 hours for the treatment of mucoskeletal pain.

The below preferred embodiments are given to illustrate the scope of the present invention which are not exhaustive and not limiting. A person skilled in the art of pharmaceutics can formulate the similar kind of preparation which is obvious.

Example 1. Tolperisone sustained release tablets (Drug to total release retardant ratio more than 1:2.)

Sustained release tablets of Tolperisone were prepared wherein the ratio of drug to total amount of release retardant polymers was kept above 1:2. Tolperisone was taken in 30 % amount. Carbopol, ethyl cellulose and HPMC were taken in 10 %, 5%, and 53 % respectively. Wet granulation was carried out using isopropyl alcohol as a solvent. Lubrication was done using aerosil (1.5 %) and magnesium stearate (0. 5%). This blend was compressed into tablets. These tablets showed

very poor drug release. Only 57 % of drug was release after 24 hours period of in vitro drug dissolution studies.

Example 2. Tolperisone sustained release tablets (Drug to total release retardant ratio lower than 1: 0.5)

Sustained release tablets of Tolperisone were prepared wherein the ratio of drug to total amount of release retardant polymers was kept below 1:0.5. Tolperisone was taken in 77.15 % amount. Carbopol, ethyl cellulose and HPMC were taken in 3.2 %, 2.8 % and 14.85 % respectively. Wet granulation was carried out using isopropyl alcohol as a solvent. Lubrication was done using aerosil (1.5 %) and magnesium stearate (0. 5%). This blend was compressed into tablets. These tablets showed drug release at very faster rate. Almost 90 % drug was released within 4 hours of drug release studies.

Example 3. Eperisone controlled release floating tablets (Drug to total release retardant ratio more than 1:1.5.)

Controlled release Gastro retentive tablets of Eperisone were prepared wherein the ratio of drug to total amount of release retardant polymers was kept above 1:1.5. Eperisone was taken in 30 % amount. HPMC and K100M were added in 20 % and 35 % amount respectively.

This mixture was blended with 5 % amount of sodium bicarbonate and 2.5 % citric acid monohydrate to prepare the effervescent floating tablets. This mass was further blended 2 % lactose and finally the whole mass was granulated using 4 % PVP solution prepared in isopropyl alcohol. After drying the granules, they were mixed with 0.5 % magnesium stearate and 1% talc powder. The granules were finally compressed into tablets. The compressed tablets were evaluated for buoyancy, assay and drug release pattern for 24 hours period. The tablets were not able to float up to 24 hours and tablet provided very poor drug release. Only 51 % drug release was achieved within 24 hours period.

Example 4. Eperisone controlled release floating tablets (Drug to total release retardant ratio lower than 1:0.5)

Controlled release Gastro retentive tablets of Eperisone were prepared wherein the ratio of drug to total amount of release retardant polymers was kept below 1:0.5. Eperisone was taken in 54 % amount. HPMC and K100M were added in 8 % and 14 % amount respectively. This mixture was blended with 8 % amount of sodium bicarbonate and 4 % citric acid monohydrate to prepare the effervescent floating tablets. This mass was further blended 6.5 % lactose and finally the whole mass was granulated using 5 % PVP solution prepared in isopropyl alcohol. After drying the granules, they were mixed with 0.5 % magnesium stearate and 1% talc powder. The granules were finally compressed into tablets. The compressed tablets were evaluated for buoyancy, assay and drug release pattern for 24 hours period. The tablets were not able to float up to 24 hours and tablets showed drug release at very faster rate. Almost 95 % drug release was achieved within 4 hours period.

Example 5

The approach which was used in this example was non aqueous wet granulation method in which the drug Tolperisone hydrochloride (62.76%) and polymer HPMC (34.86%) were granulated using isopropyl alcohol as a solvent for binding. Other ingredient like talc (1.41%) and magnesium stearate (0.97%) were mixed with above prepared granules and then compressed to get the tablets. The tablets were evaluated for tablet physical parameters and release profile.

Example 6

Use of the ethyl cellulose by decreasing the concentration of hydroxypropylmethylcellulose was another approach. The concentration of hydroxypropylmethylcellulose was made up to 18.10 % and ethyl cellulose was added in concentration 16.2%. Tolperisone hydrochloride was added in 72.76 % amount to the polymers and tablets were prepared by wet granulation using isopropanol as a solvent. The process and other ingredients (talc 1.62% &

magnesium stearate 1.32%) kept same as that used in example 5. The tablets were evaluated for assay content and release pattern.

Example 7

The drug release was also controlled further by using hydroxypropyl cellulose alone in concentration of 39.11% with the active ingredient i.e. Tolperisone hydrochloride in 58%. Concentration of talc and magnesium stearate was kept 1.3 and 0.91% respectively. The granules were prepared by wet granulation technique using isopropyl alcohol as solvent. Granules were then compressed to get the tablets, which were evaluated, for various parameters and release pattern.

Example 8

The increase in concentration of hydroxypropyl cellulose up to 42.83% was another approach to modify the drug release. Tolperisone hydrochloride was added in 55.07%, the granules were prepared by wet granulation method using isopropanol as solvent. The lubrication was done by using 0.85% magnesium stearate, 1.22% talc. The granules were compressed to tablet using suitable compression force. The tablets were evaluated for drug content and release pattern. Tablets were coated by HPMC based film coating material optionally to improve further appearance

Example 9

The drug: release retarding polymer in 1:1 weight ratio was used. The 43.64 % drug Tolperisone was incorporated with equal proportions of HPMC polymer and binded with Polyvinyl Pyrrolidone (10 %) in isopropyl alcohol. The granules obtained were dried and compressed to get tablets. The tablets obtained by this approach have also shown the drug release up to 24 hours.

Example 10

The release pattern of Tolperisone hydrochloride over 24 hours of period was also achieved using ethyl cellulose alone in concentration of 35.59%. The drug

Tolperisone hydrochloride was used in 57.34 % concentration in the formulation. The granules were formulated using with 5% PVP K 30 using non-aqueous wet granulation technique. The granules were dried and talc (1.22%) and magnesium stearate (0.85%) were added for lubrication. The tablets were then evaluated for tablet physical parameters and the drug release pattern.

Example 11

The example involves the same procedure as that was used for example 6. Here the starch paste was used in place of PVP for wet granulation technique. The granules were prepared and compressed into tablets. Compressed tablets were evaluated various evaluation parameters like drug content and drug release pattern.

Example 12

The use of hydroxypropyl cellulose and ethyl cellulose in combination was another approach to control the drug release, in which they were added in concentration of 27.35 and 9.23% respectively. Tolperisone hydrochloride was added in 61.35%. The granules were prepared using the isopropyl alcohol as binding solvent. 1.22% talc and 0.85%magnesium stearate were added extra granularly for lubrication. The final blend was compressed into tablets which were evaluated for drug release pattern and other parameters such as hardness, friability and assay content.

Example 13

The sustained release tablet for Tolperisone hydrochloride was also prepared by using stearic acid by melt granulation technique. In this technique the various combinations of stearic acid with other fatty acid esters were tried, example of which are but not limiting to glyceryl monostearate, palmitic, behenic acid, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil or other natural waxes. Totality of stearic acid and other fatty acids added was 49.07% amount and drug was added in 49.07% proportions. The granules were prepared by melt granulation technique which was lubricated with talc (1.09%) and

magnesium stearate (0.76%). The tablets were compressed and evaluated. Tablets prepared by this method also showed drug release up to 24 hours.

Example 14

Tablets were also formulated using only stearic acid in concentration range 45% to 65%. The method involved melt granulation technique. Tolperisone Hydrochloride, magnesium stearate and talc were added in suitable amount. The granules obtained were compressed and evaluated for release pattern. Various combinations of stearic acid and Tolperisone hydrochloride released drug up to 24 hours.

Example 15

The use of carbopol, ethyl cellulose and HPMC as release retarding polymer in various concentration was another approach used to sustain the release of active ingredient up to 24 hours. The results revealed that tablet released the active ingredient depending on different polymer-to-polymer ratios. The non-limiting examples of such combination include the use of carbopol, ethyl cellulose and HPMC K100 in combination of 8.33%, 2.77% & 33.33% concentration respectively. The drug tolperisone was added in the concentration of 50%. Wet granulation was carried out using isopropyl alcohol as a solvent. Lubrication was done using aerosil (0.55 %), talc (0.72%) and magnesium stearate (0.33%). This blend was compressed into tablets. The tablets were coated with coating solution comprising HPMC based organic system with suitable coloring agent added such as titanium dioxide.

Example 16

Eperisone sustained release tablets were made using various grades of HPMC differing in the viscosity. Eperisone (23.07%) was mixed with HPMC K100 M (7.69%), HPMC K15M (7.69%), HPMC K4M (15.38%) and lactose (32.76%). To this mixture sodium chloride (11.54%) was added as a channeling agent. These were mixed uniformly and granulated using isopropyl alcohol. Granules were further mixed with magnesium Stearate (0.92%) and talc (0.92%) in similar

concentrations and finally compressed into tablets. Tablets were further tested for the different parameters like hardness, friability, drug content, weight variation and drug release pattern. Tablets were found to provide prolonged release of drug up to period of 24 hours.

Example: 17

Gastro retentive tablets of Eperisone and its salts thereof were prepared in one of the embodiment of present invention. The drug in 30% amount was mixed with 10% of HPMC K100 M and 20% amount of HPMC K4 M. This mixture was blended with 10% amount of sodium bicarbonate and 5% citric acid monohydrate to prepare the effervescent floating tablets. This mass was further blended 19% lactose and finally the whole mass was granulated using 5% PVP solution prepared in isopropyl alcohol. After drying the granules, they were mixed with 1% magnesium stearate and 1% talc powder. The granules were finally compressed into tablets. The compressed tablets were evaluated for buoyancy, assay and drug release pattern for 24 hours period. The tablets were found floating upto 24 hours period giving sustained drug release when tested in vitro.

Example: 18

Floating tablets of Eperisone and its salts thereof were also prepared in the same manner as described above but with replacement of HPMC K 100 M with HPMC K15 M in 20 % amount. The drug in 30% amount was mixed with 10% of HPMC K100 M and 20 % amount of HPMC K4 M. This mixture was mixed with 5 % sodium bicarbonate, 3 % citric acid monohydrate, 16% microcrystalline cellulose phosphate. This mass was granulated using 5 % PVP solution prepared in isopropyl alcohol. After drying the granules, they were mixed with 1% magnesium stearate and 1% talc powder. The granules were finally compressed into tablets. The compressed tablets were evaluated for buoyancy, assay and drug release pattern for 24 hours period. The tablets were found floating upto 24 hours period giving sustained drug release when tested in vitro.

Example: 19

Floating tablets of muscle relaxant drug were prepared using HPMC K 100 M and HPMC K 4 M each in 15% by weight amount. The drug in 30% amount was mixed with HPMC K100 M and HPMC K4 M. This mixture was mixed with 10 % sodium bicarbonate, 5% citric acid monohydrate and 19% microcrystalline cellulose phosphate. This mass was granulated using 5 % PVP solution prepared in isopropyl alcohol. After drying the granules, they were mixed with 1% magnesium stearate and 1% talc powder. The granules were finally compressed into tablets. The compressed tablets were evaluated for buoyancy, assay and drug release pattern for 24 hours period.

Example 20

Floating tablets of Tolperisone were prepared using HPMC K 100 M in 30 % by weight amount. Tolperisone in 30% amount was mixed with HPMC K100 M. This mixture was mixed with 10% sodium bicarbonate, 5% citric acid monohydrate and 19% microcrystalline cellulose phosphate. This mass was granulated using 5% PVP solution prepared in isopropyl alcohol. After drying the granules, they were mixed with 1% magnesium stearate and 1% talc powder. The granules were finally compressed into tablets. The compressed tablets were evaluated for buoyancy, assay and drug release pattern for 24 hours period.

Example 21

Tolperisone was formulated in combination with 50 mg Tramadol. The immediate release granules of Tramadol were prepared and incorporated in to sustained release granules of Tolperisone or its salts thereof. The so formed granules were filled in sachets. The sustained release matrix layer of Tolperisone was prepared according to same formula as employed in one of the examples above.

Example 22

Tolperisone was formulated in combination with 300 mg Etodolac. The immediate release granules of Etodolac were prepared and incorporated in to sustained release granules of Tolperisone or its salts thereof. The so formed granules were

filled in sachets. The sustained release matrix layer of Tolperisone was prepared according to same formula as employed in one of the examples above.

Example 23

Floating granules of Tolperisone were formulated in combination with 600 mg Amtolmetin guacyl.. The gastro retentive granules of Tolperisone were prepared as per the procedure given in example 18. These granules were incorporated into floating granules of Amtolmetin guacyl. Such granules were prepared as taste masked using suitable commercially available taste masking resins (e.g. Purolite C102DR, Purolite C115HMR, Purolite C100HMR, Purolite A430MR, Purolite C100MR) So prepared floating granules were filled in sachets.

In vitro drug release studies

In vitro drug release studies of Tolperisone hydrochloride Sustained release matrix tablets, controlled release gastro retentive tablets of Tolperisone and Eperisone sustained release tablets were performed in pH 1.2 buffer and simulated intestinal buffer to examine the release of the active ingredient from the formulated dosage form. Sustained release matrix tablets were kept in pH 1.2 buffer for first two hours and were kept in simulated intestinal fluid for the remaining 22 hours. Controlled release floating tablets were studied in pH 1.2 for 24 hours to mimic the conditions of gastric medium. The formulated compositions were found to deliver the drug at sustained rate over the period of 24 hours. The formulations were studied for stability testing at accelerated conditions of temperature and humidity for 6 months. The formulations were found to be stable in terms of description, active ingredient content, hardness, drug release profile, and buoyancy (for gastro retentive dosage tablets).

CLAIMS

1. A novel sustained release composition which comprises of therapeutically effective amount of active ingredient and further comprising pharmaceutical excipients including release retarding excipient(s) adapted to achieve not less than 80% of drug release in 24 hours when formulated in suitable dosage form, wherein the the active ingredient (s) and the release retarding excipient(s) are present in the ratio of 1: 0.5 to 1:3.
2. According to claim 1, an active ingredient is Tolperisone or pharmaceutically acceptable salt thereof.
3. According to claim 1, an active ingredient is Eperisone or pharmaceutically acceptable salt thereof.
4. A sustained release formulation according to claim 1, wherein the active is selected from Tolperisone and Eperisone and mixtures thereof in combination with therapeutically effective concentration of Tramadol or Etodolac or Amtolmetin or combination of any of these drugs or in combination with the drugs selected from therapeutic categories like muscle relaxants, analgesics, antipyretics or non steroidal anti inflammatory drugs.
5. A composition as claimed in claim 1, wherein said drug is in the form selected from the group consisting of a raw powder, dispersed in a suitable liquid, micro or nano particles, micro or a solvated powder, semisolid, a tablet, a capsule or a suitable specific two- or three-dimensional matrix composition.
6. A sustained release formulation according to claim 1, wherein the pharmaceutical excipients is selected from the group of pharmaceutical binders, diluents, release retarding excipients, lubricant, glidants, buffering agent, gas generating agents, coating systems, solvents, coloring agents.
7. A composition according to claim 1 comprising a pharmaceutical gastro-retentive delivery system containing Tolperisone or Eperisone or or salts thereof or other muscle relaxants or combinations thereof adapted to remain floated in the gastric medium up to 24 hours for controlled release of therapeutically active agent in stomach or upper part of gastrointestinal tract.

8. The delivery system as claimed in claim 7, further comprising at least one gas-forming agent.
9. A sustained release formulation according to claim 1, wherein the pharmaceutical excipients are used about 30 to 75% by weight.
10. A sustained release formulation according to claim 1 and claim 6, release retarding excipients are selected from group of hydrophilic and hydrophobic polymers selected from the below.
11. The sustained release composition as claimedin claim 10 wherein the release retarding excipients are selected from
    a) Cellulose derivatives including methylcellulose, ethyl cellulose, hydroxomethylcellulose, different viscocity grades of hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, carboxymethylcellulose;
    b) Hydrophilic polymer selected from the group consisting of a protein, a polysaccharide, a polyacrylate, a hydrogel, polyvinyl alcohol or polyvinyl pyrrolidone, carbopols, polyetylene oxides, magnesium aluminum silicate, modified starch derivatives or a derivative of such hydrophilic polymers and a combination thereof;
    c) Hydrophobic non-degradable polymer selected from the group consisting of ethylcellulose, a copolymer of acrylic acid and methacrylic acid esters, polyethylene, polyamide, polyvinylchloride, polyvinyl acetate or mixtures thereof;
    d) Natural gums like acacia, gum tragacanth, locust bean gum, guar gum, karaya gum, modified cellulosic, agar, pectin, carrageen, alginate, carboxypolymethylene, gelatin, casein, zein, bentonite,
    e) The water insoluble polymers selected from the group consisting of polyacrylic acids, acrylic resins, acrylic latex dispersions, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and a combination thereof;
    f) Stearic acid with other fatty acid esters of which are but not limiting to glyceryl monostearate, palmitic, behenic acid, glyceryl behenate,

glyceryl palmitostearate, hydrogenated castor oil or other natural waxes etc.

12. A sustained release formulation according to claim 1, wherein the ratio of drug to release retarding polymers is about 1:1.
13. A sustained release composition according to claim 7, wherein the ratio of gas generating agent sodium bicarbonate to citric acid is about 1:0.2 to 1: 1.
14. A sustained release composition according to claim 1, is formulated by wet granulation or non aqueous granulation using solvent & binder.
15. A sustained release composition according to claim 1 and 6, wherein formulation comprises of diluents/compression aids and disintegrants selected from lactose, microcrystalline cellulose, dicalcium phosphate, sucrose, mannitol, xylitol, starch; lubricants selected from magnesium stearate, sodium stearyl fumarate and stearic acid, talc and colloidal silica;. binders selected from natural gums, polyvinylpyrrolidone, starch preferably povidone flow aids such as silicon dioxide or talc.
16. The sustained release formulations according to claim 1, are in form selected from tablet, capsule, granules or a sachet, typically a tablet, with or without coating, bi-layered tablet in combination with other drugs, as a combination kit of sustained release dosage forms.
17. The sustained release formulations as claimed in claim 16 are in form selected from functional coated tablets or caplets, or time- release tablets or caplets, floating tablets, matrices containing wax or polymer, controlled release beads, granules, spheroids that are contained within a capsule or administered from a sachet or other unit dose powder device to mammals.
18. A process for preparing a sustained release formulation according to claim 1, wherein the tablets are optionally coated to get the elegant appearance by using suitable coating material such as titanium dioxide, shellac, carbowax, sugar, etc. using aqueous or non-aqueous solvents.

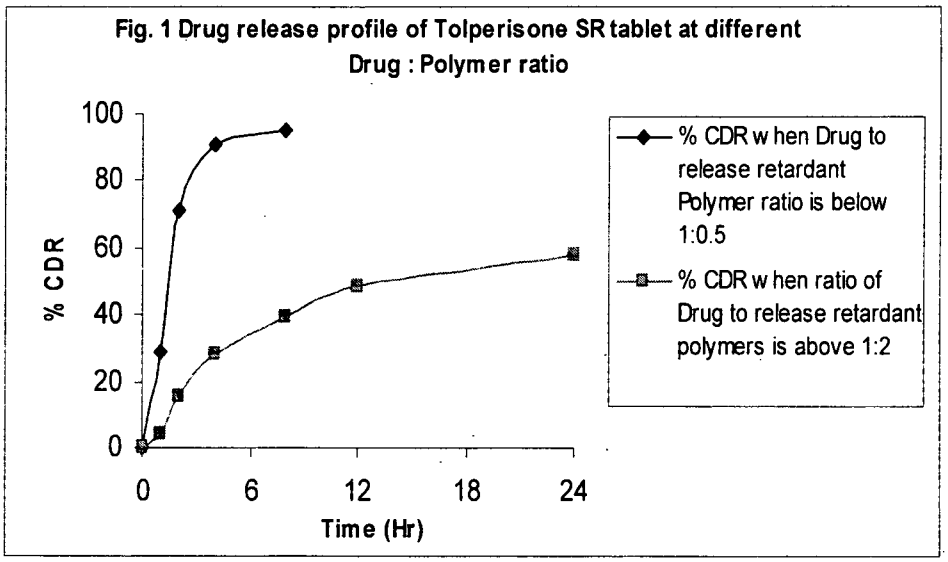

Figure 1

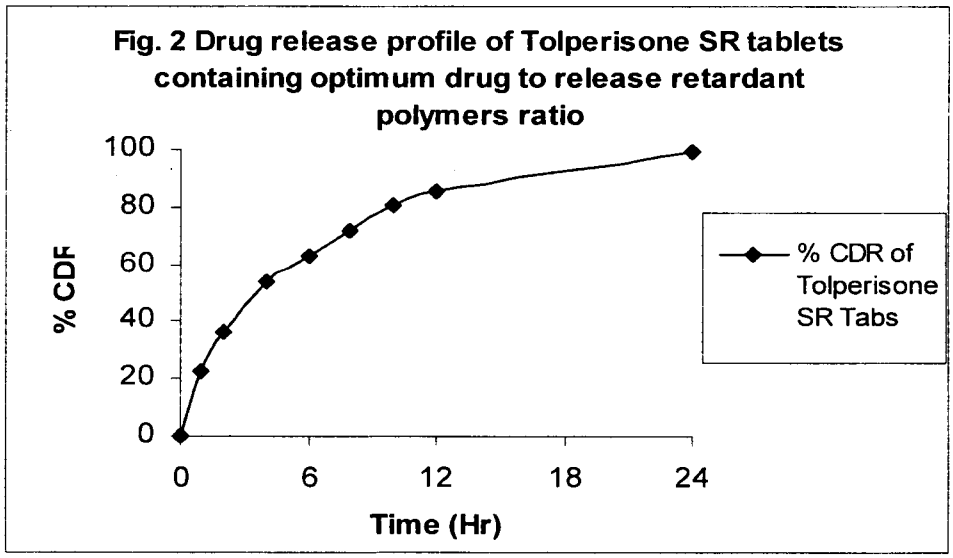

Figure 2

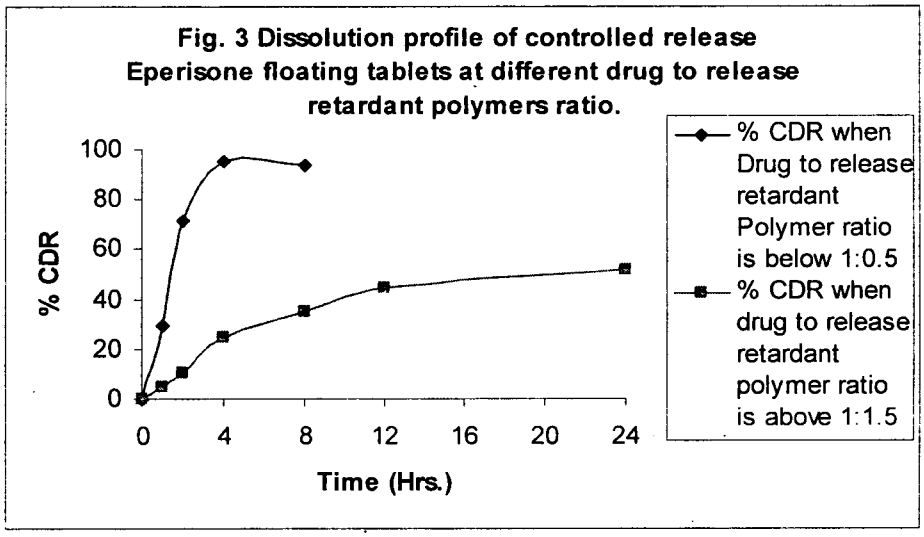

Figure 3

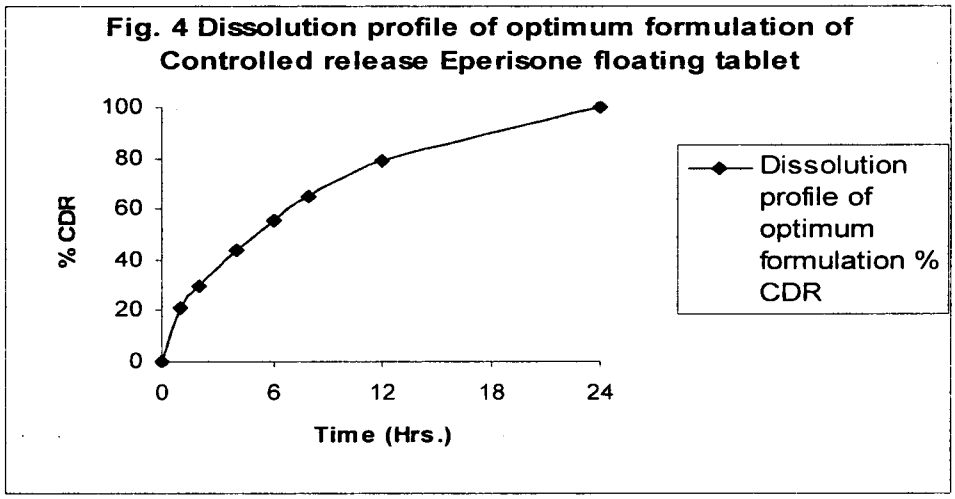

Figure 4

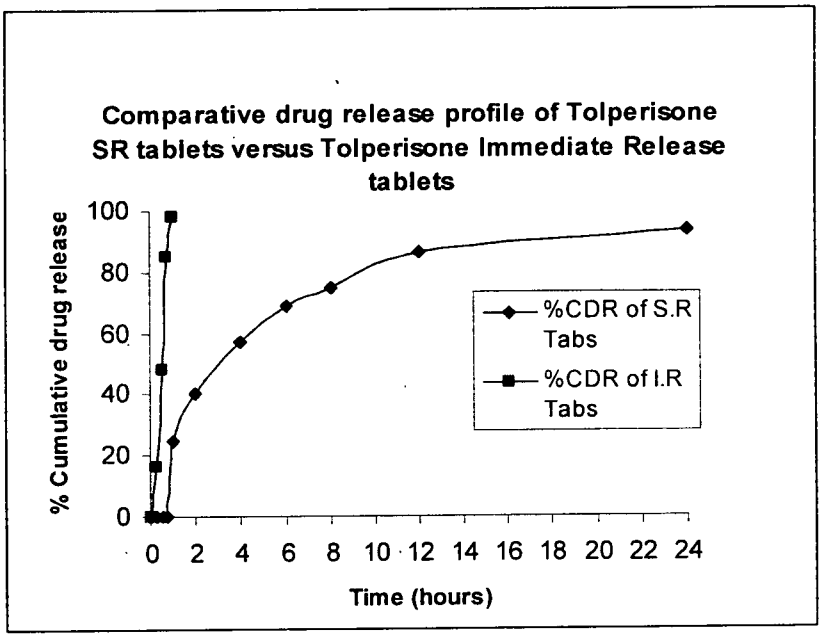

Figure 5

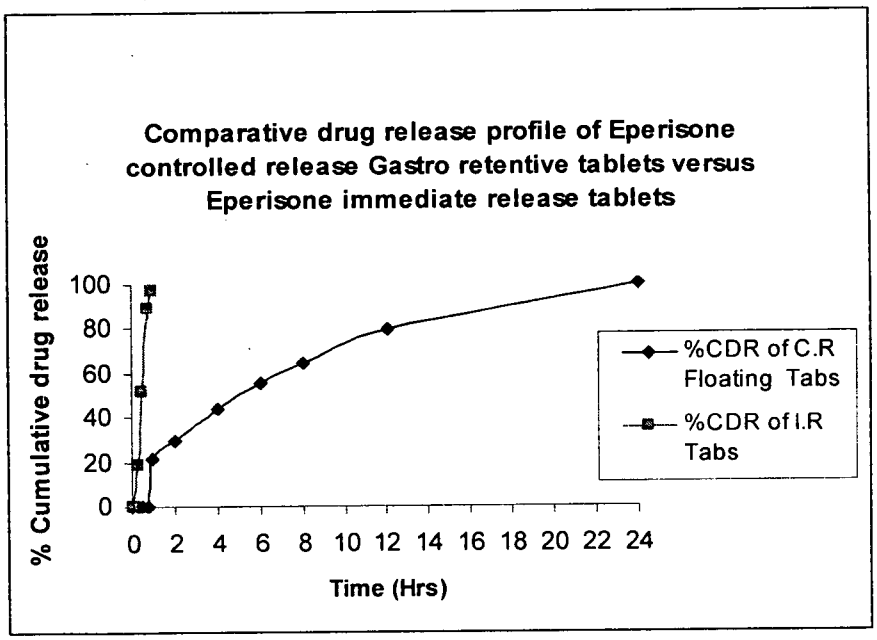

Figure 6