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(54) Title: METHOTREXATE PHARMACEUTICAL COMPOSITION

(57) Abstract: Though oral liquid formulations of Methotrexate are advantageous as they can suitably be administered to the patients having swallowing difficulties such as pediatric patients, geriatric patients, stroke patients or patients who are unable to take solid oral therapy, they are not much explored in the prior art. Further, liquid formulations of Methotrexate known in the prior art have not been explored at higher pH and in the absence of additional solubilizing agents. An aim of the present invention is therefore to provide chemically and physically stable liquid pharmaceutical compositions of Methotrexate at higher pH and in the absence of solubilizing agents.

METHOTREXATE PHARMACEUTICAL COMPOSITION

CLAIM OF PRIORITY

This application claims priority to Indian Patent Application No. IN201821032299 filed on August 29, 2018 titled "METHOTREXATE PHARMACEUTICAL COMPOSITION" and is incorporated herein by reference.

FIELD OF THE INVENTION

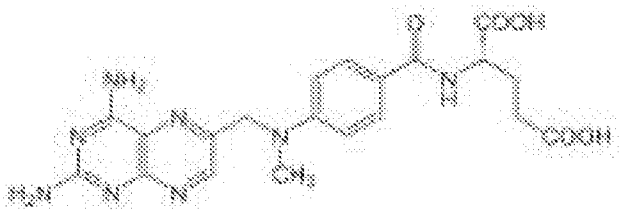
The present invention relates, in general to the pharmaceutical field, and more precisely it relates to the pharmaceutical compositions comprising folic acid antagonist. In particular, the present invention describes liquid pharmaceutical compositions suitable for oral administration comprising Methotrexate and process for the preparation thereof. The oral liquid pharmaceutical compositions comprising Methotrexate can be used for treating diseases or disorders where the administration of the therapeutic ally effective doses of Methotrexate has been found an effective therapy.

BACKGROUND OF THE INVENTION

Methotrexate (4-amino-10-methylfolic acid) is a structural analog of folic acid and inhibits dihydrofolate reductase. Methotrexate and its active metabolites compete for the folate binding site of the enzyme dihydrofolate reductase (DHFR). Folic acid must be reduced to tetrahydrofolic acid by DHFR for DNA synthesis and cellular replication to occur. Competitive inhibition of DHFR leads to blockage of tetrahydrofolate (THF) synthesis, depletion of nucleotide precursors, and inhibition of DNA, RNA and protein synthesis. Methotrexate is cell cycle phase-specific (S phase). Upon prolonged storage of methotrexate, methyl folic acid (also known as methyl folate, MFA) can form. If methyl folic acid builds up in the body, anemia can result, through a process called the folate trap.

Methotrexate having the systemic name of (2S)-2-[(4-{[2, 4-diaminopteridin-6-yl) methyl] (methyl) amino} benzoyl) amino] pentanedioic acid and molecular formula $C^{20}H^{22}N^8O^5$

has following structural formula:



Methotrexate is used as a folic acid antagonist, in the treatment of neoplastic disease, such as trophoblastic neoplasms and leukaemia and in the control of severe recalcitrant psoriasis which is not responsive to other forms of therapy. It is also used to treat a wide range of tumours, such as acute leukaemias, Non-Hodgkin's lymphoma, soft tissue and bone sarcomas, solid tumours like breast, lung, head, neck, bladder, cervical, ovarian and testicular cancer, as an immunosuppressant and as an anti-metabolite.

Formulations and drug delivery systems incorporating Methotrexate are known in the art. All prior art documents mentioned hereinafter are incorporated herein by references. US 4474752 discloses an injectable pharmaceutical composition, containing various drugs including Methotrexate, which is a liquid at room temperature and a semi-solid gel at body temperature. US 5472954 discloses a composition of various drugs, including Methotrexate in a solid or liquid co-complex with cyclodextrin. US 5770585 discloses Methotrexate, or other pharmaceuticals, in a water-in-perfluorochemical liquid dispersion, for treatment of the lung. US 5925669 discloses a composition including Methotrexate or other antineoplastic agents in a triglyceride, oil-rich in docosahexanoic acid. WO 1997/00670 & US 6083518 disclose a biologically active agent including Methotrexate, a glass-forming substance and a plasticizer. US 6309663 discloses a pharmaceutical composition containing

at least one hydrophilic surfactant, one hydrophobic surfactant and/or a hydrophilic therapeutic agent, including Methotrexate. US 6383471 discloses a pharmaceutical composition containing an ionisable hydrophobic therapeutic agent, including Methotrexate or other therapeutic agents, a carrier containing a surfactant and an ionizing agent, and a triglyceride.

Children generally reject taking medicine which does not have a favorable shape, taste, flavor, etc. However, if a child who needs to take a medicine, rejects taking it, he might never recover from his condition. When a child is unable to take medicine orally, it is intravenously administered, and he and his caregivers then may experience stress. Syrups and suspensions are considered as favorable types of dosage forms in which to orally administer medicine to infants and children. However, they may have disadvantages such as solubility, a bad taste, portability problems or required refrigerator storage. Palatability is one of the main elements of patient acceptability of an oral pediatric medicine. Palatability is defined as the overall appreciation of an oral medicinal product in relation to its smell, taste, aftertaste and feeling in the mouth. Design of the formulation of an oral pediatric medicine should be considered together with its palatability.

Use of Methotrexate containing compositions for oral administration in tablet form is known. Compared to the conventional tablets and capsules, oral liquid dosage forms including solutions, syrups, suspensions, elixirs, and concentrates offer unique advantages to many patients. For example, liquids may provide better patient compliance for those with swallowing difficulties and better dosage control versus a fixed tablet dose. Hence, liquid dosage forms are generally formulated for use in geriatric and pediatric patients. However, there are also a number of "challenges" surrounding the formulation and development of these forms.

Methotrexate in the form of solution for injection is also known. Although injections can be tolerated by pediatric populations, distraction techniques and local anesthetic to reduce pain may be required to encourage cooperation. Furthermore, muscle mass in children is variable, which may lead to nerve injury or other complications when administering intramuscular injections if the appropriate site of needle insertion, needle size and angle of injection are not selected.

In order to overcome above said problems, it would be beneficial to provide a Methotrexate containing composition as an oral solution which is palatable, as well as physically and chemically stable. However, Methotrexate has been found to precipitate out of the solution over a period of time at pH below 6.0. At pH values above 7.0 there is an increase in the degradation that will limit the shelf life of the final composition.

Literature survey reveals that although efforts have been put by the formulation scientists to prepare oral liquid formulations of Methotrexate and address above said problems, such efforts are limited in numbers, for example, US 9259427 & US 9855215 discloses an aqueous Methotrexate oral composition for oral administration consisting of a pharmaceutically acceptable salt of Methotrexate, purified water, one or more buffer agents to adjust the pH of the composition wherein the pH of the composition is 6.0 to 7.0, and at least one agent selected from the group consisting of preserving agents, flavouring compounds, and sweetening agents. US 2017/0312281 discloses a liquid pharmaceutical composition comprising Methotrexate free acid and a citrate buffer and one or more flavouring compounds and/or sweetening agents, wherein the pH of the composition is in the range of 6.6 to 7.0. US 2017/0312281 does not show any effect of the higher pH (e.g. 7.5 and above) on the physical stability of the formulations prepared therein. Further, the liquid compositions disclosed in US 2017/0312281 essentially teaches use of one or more co-

solvents such as polyethylene glycol and glycerol to increase the solubility of the active ingredient Methotrexate in the solution state and prevent precipitation.

US 2005/0101605 discloses an oral liquid pharmaceutical composition for gastrointestinal administration Methotrexate or a pharmaceutically acceptable salt or ester thereof, and a polyol such as glycerin, polyethylene glycol, sorbitol, propylene glycol etc.

From aforementioned prior art documents it can be seen that either the pH of the Methotrexate aqueous compositions is kept between 6.5 and 7.0 to control the degradation in the final product and to provide physical stability to the formulation or the solubility of Methotrexate in the solution state is increased by using one or more co-solvents (such as propylene glycol, polyethylene glycol, glycerin etc.). Further, when one or more co-solvents are used in the preparation of pharmaceutical compositions, amount of such co-solvents must be within the pharmaceutically acceptable limit to avoid any side effects or toxic effects thereof. Since, the principal aspect behind the development of liquid oral compositions is the administration thereof to the pediatric patient populations, extra care needs to be taken while choosing excipients of the pharmaceutical compositions. Thus, there is an increased need for the development of the liquid pharmaceutical compositions of Methotrexate which comprise less numbers of excipients and which are storage stable for prolonged time when stored under storage conditions.

In view of the existing need in the prior art, the inventors of the present application have now developed liquid pharmaceutical compositions of Methotrexate, suitable for oral administration which do not additionally comprise one or more co-solvents. Further, Methotrexate is used in the form of free acid and not in the salt form. The pH of the compositions of the present invention is also high i.e. between 7.5 and 9.0 than what is suggested in the prior art documents, i.e. below 7.0. Following the preparation of the compositions of the present invention, the inventors have surprisingly found that the active

ingredient Methotrexate does not get precipitate out and remains in the solution in the dissolved form even then, when Methotrexate salt form (such as disodium salt) is not used and even then, when one or more co-solvents are not used. Further, the present inventors also surprisingly found that the compositions of the invention does not contain higher amounts of impurities or related substances or degradation products when stored under storage conditions for prolonged time.

OBJECTS OF THE INVENTION

Because of their liquid character, liquid dosage forms represent an ideal dosage form for patients who have difficulty swallowing tablets or capsules. This factor is of particular importance in administration of drugs to children and aged patients. It is therefore principal object of the present invention to provide liquid pharmaceutical compositions of Methotrexate.

A yet another object of the present invention is to provide liquid pharmaceutical composition of Methotrexate suitable for oral administration. The oral liquid compositions of the present invention are useful for administering to the pediatric patients, the geriatric patients and other patients who are unable to take solid oral therapy.

A yet another object of the present invention is to provide liquid pharmaceutical compositions which are aqueous in nature and do not comprise one or more organic solvents/co-solvents. The liquid compositions according to the present invention comprise Methotrexate, one or more preservatives, one or more buffering agents and one or more sweeteners. The liquid compositions of the present invention may further comprise one or more flavouring agents.

According to a yet another object, the pH of the liquid compositions of the present invention is between about 7.5 and about 9.0.

A yet another object of the present invention is to provide liquid compositions of Methotrexate having palatability, prolonged stability and comparable bioavailability when compared to the marketed drug.

A yet another object of the present invention is to provide process for the preparation of liquid compositions of Methotrexate.

A yet another object of the present invention is to provide method of treating spondyloarthropathies, systemic dermatomyositis, severe, recalcitrant psoriasis, including psoriatic arthritis that is not adequately responsive to other forms of therapy, rheumatoid arthritis, seronegative arthritis, adult rheumatoid arthritis systemic dermatomyositis, Crohn's disease, multiple sclerosis, polyarthritic forms of severe, active juvenile idiopathic arthritis, resistant juvenile rheumatoid arthritis, graft versus host disease, lupus, morphea (also known as localized scleroderma), ankylosing spondylitis and other autoimmune diseases, and in the treatment of a wide range of neoplastic conditions, such as mycosis fungoides, haemoblastosis, trophoblastic neoplasms, acute lymphoblastic leukaemia, prophylaxis of meningeal leukaemia, Non-Hodgkin's lymphomas, osteogenic sarcoma, breast cancer, head and neck cancer, choriocarcinoma and similar trophoblastic diseases, lung cancer, bladder cancer, adult soft tissue sarcoma, and various other malignant tumours or any other condition wherein the patient requires Methotrexate therapy which comprises administration of an effective dosage amount of the liquid compositions of the present invention.

A yet another object of the present invention is to use the liquid compositions of the present invention in the treatment of spondyloarthropathies, systemic dermatomyositis, severe, recalcitrant psoriasis, including psoriatic arthritis that is not adequately responsive to other forms of therapy, rheumatoid arthritis, seronegative arthritis, adult rheumatoid arthritis systemic dermatomyositis, Crohn's disease, multiple sclerosis, polyarthritic forms of severe, active juvenile idiopathic arthritis, resistant juvenile rheumatoid arthritis, graft versus host

disease, lupus, morphea (also known as localized scleroderma), ankylosing spondylitis and other autoimmune diseases, and in the treatment of a wide range of neoplastic conditions, such as mycosis fungoides, haemoblastosis, trophoblastic neoplasms, acute lymphoblastic leukaemia, prophylaxis of meningeal leukaemia, Non-Hodgkin's lymphomas, osteogenic sarcoma, breast cancer, head and neck cancer, choriocarcinoma and similar trophoblastic diseases, lung cancer, bladder cancer, adult soft tissue sarcoma, and various other malignant tumours or any other condition wherein the patient requires Methotrexate therapy.

DETAILED DESCRIPTION OF THE INVENTION

Prior art review suggests that very limited numbers of efforts have been carried out for the preparation of liquid compositions of Methotrexate for oral administration. Such efforts themselves are abide by many limitations.

Methotrexate is almost insoluble in water, alcohol, chloroform and ether, and has been reported to be freely soluble in alkaline solution and slightly soluble in hydrochloric acid. For pharmaceutical solutions, it is essential that both the therapeutic agent and excipients are present in solution over the entire shelf life of the product. This is particularly challenging when there is limited aqueous solubility of the therapeutic agent.

It is common practice in the drug development, and in the re-formulation of known drugs, to use the salt forms of a drug substance. This is because salt forms of drug substance are known to have preferential properties. Known advantages include improved stability, solubility and improved processability. Therefore, in the development of stable formulations, salts are generally preferred. Like many other drugs, Methotrexate is also marketed as the salt form and various salt forms of Methotrexate are also available. A number of marketed products contain the sodium salt of Methotrexate, the choice of which is attributed to its higher solubility compared to the free acid.

Additionally, Methotrexate has a degree of chemical instability, particularly at very low and very high pH. The preferred range of the pH for attaining desired solubility of Methotrexate or salt thereof is suggested to have between 6.5 and 7.0. Further, generation of impurities/degradation products can be controlled by adjusting the final pH of the final Methotrexate compositions between 6.5 and 7.0. Instances have been seen where amount of impurities/degradation products increase over a period of time above pH 7.0.

A major challenge for formulation scientists is therefore to achieve the optimum pH of the final composition for chemical stability whilst also achieving acceptable solubility of the active pharmaceutical ingredient. Aqueous solubility is one of the key factors to consider when assessing the oral bioavailability of oral dosage forms. The most frequent causes of low oral bioavailability are attributed to poor solubility.

In order to satisfy aforementioned requirements, final pH of the final liquid compositions of Methotrexate is known to keep between 6.5 and 7.0 and in the interest to keep the Methotrexate or its salt dissolved in the solution state it is suggested that the pH of the liquid formulation must not go below 6.5. Further, stability is also an essential parameter in the case of Methotrexate liquid compositions which needs to be taken care of. In order to control the impurities or degradation products in the Methotrexate compositions, it is desirable to keep the final pH of the final formulation between 6.5 and 7.0 and not more than 7.0. Beyond 7.0 pH amounts of impurities/degradation products increase dramatically.

Solubility of the active ingredient Methotrexate or salt thereof can be increased upon increasing the pH. However, increased pH also raises the concern of the stability of the product over a period of time. Use of co-solvents such as polyethylene glycol, glycerin, propylene glycol etc. is therefore suggested and is evident in the prior art to increase the solubility of Methotrexate or salt thereof in the formulation so that Methotrexate does not get precipitate out from the solution even if the pH of the formulation drops down than 6.5.

Further, when organic co-solvents such as propylene glycol, polyethylene glycol, glycerin etc. are used in the liquid formulations, amount of such co -solvents must be within the pharmaceutically acceptable limit to avoid any side effects or toxic effects thereof. Since, the aim behind the development of liquid oral compositions is to increase the suitability of administration to the pediatric patient populations, extra care needs to be taken while choosing excipients of the pharmaceutical compositions.

In view of the above, the inventors of the present invention as a part of their extensive research have now come up with the liquid pharmaceutical compositions of Methotrexate which overcome problems detailed in the foregoing paragraphs. The liquid compositions of the present invention do not comprise use of Methotrexate salt to increase the solubility of Methotrexate in the formulation and uses Methotrexate in the form of a free acid instead.

The present invention also does not use one or more co-solvents to increase the solubility of Methotrexate free acid in the formulation. Here, to the inventors' surprise, even after using Methotrexate in the form of free acid and in the absence of one or more co-solvents, Methotrexate does not get precipitate out from the solution over a period of time when stored under storage conditions.

The pH of the liquid compositions prepared according to the present invention is between about 7.5 and about 9.0. Preferably, the pH of the compositions of the present invention is between about 7.8 and about 8.2. To the inventors' surprise, even at such a higher pH, total amount of the related substances (or impurities) present in the formulation is not more than about 5.0% when stored at 40°C for three months. At 25°C, the total amount of the related substances (or impurities) present is less than 1.0% after three months and at 2-8°C the total amount of the related substances (or impurities) present is less than 0.5% after three months.

Thus, the pharmaceutical compositions of the present invention comprise Methotrexate in the form of free acid and one or more pharmaceutically acceptable excipients. The liquid compositions of the present invention are aqueous in nature and comprise Methotrexate free acid, one or more preservatives, one or more buffering agents and one or more sweeteners, wherein the pH of the compositions is between about 7.5 and about 9.0, preferably between about 7.8 and about 8.2. Flavouring agents may also be added to the compositions of the present invention to provide patients pleasant smell, taste and great feeling in the mouth after administration.

The liquid compositions as disclosed herein comprise aqueous vehicle. Suitable examples of aqueous vehicle without limitation include water, purified water and the like. The purified water is the preferred vehicle for the preparation of the liquid compositions of the present invention.

Preservatives as used herein are the chemical substances which become inevitable to prevent the growth of microorganisms during the product's manufacture and shelf life. Most formulations require some kind of preservative to ensure no microbial growth. Non-limiting examples of preservatives include Alcohol, Ethanol, Chlorobutanol, Phenoxyethanol, Potassium benzoate, Benzyl alcohol, Benzoic acid, Potassium sorbate, Sorbic acid, Benzalkonium chloride, Benzethonium chloride, Cetrimonium bromide, Cetylpyridinium chloride, Bronopol, Chlorbutol, Chlorocresol, Cresol, Butylparaben (butyl 4-hydroxybenzoate) or salt thereof, Methylparaben (methyl 4-hydroxybenzoate) or salt thereof, Propylparaben (propyl 4-hydroxybenzoate) or salt thereof, Ethylparaben (ethyl 4-hydroxybenzoate) or salt thereof, Phenol, Thymol, Phenylethanol, Sodium benzoate, Antimicrobial solvents like Propylene glycol, Glycerin, Chloroform and the like or any combinations thereof. Two or more preservatives can be used for the preparation of the liquid compositions of the present invention. Preferably, preservatives used for the

preparation of the liquid compositions of the present invention are selected from the group consisting of methyl paraben (methyl 4-hydroxy benzoate), ethyl paraben (ethyl 4-hydroxy benzoate) and propyl paraben (propyl 4-hydroxy benzoate) or salt thereof such as sodium salt.

The pH of an oral liquid formulation is a key point in many regards. Control of the formulation pH, could prevent large changes during storage. Therefore, most formulations utilize a buffer to control potential changes in the solution pH. The selection of a suitable buffer should be based on (i) Whether the acid-base forms are listed for use in oral liquids, (ii) The stability of the drug and excipients in the buffer, and (iii) The compatibility between the buffer and container. A combination of buffers can also be used to gain a wider range of pH compared to the individual buffer alone. However, not all buffers are suitable for use in oral liquids. For example, a boric acid buffer may be used for optical and IV delivery but not in oral liquids because of its toxicity. The stabilizing effect of buffers that have multiple charged species in solution could also determine the potential reaction between excipients and API. For example, buffers that use carbonates, citrate, tartrate, and various phosphate salts may precipitate with calcium ions by forming sparingly soluble salts. However, this precipitation is dependent upon the solution pH. The activity of phosphate ions may be lowered due to interactions with other solution components.

There are a number of factors that may also affect the solution pH such as temperature, ionic strength, dilution, and the amount and type of co-solvents present. For example, the pH of acetate buffers is known to increase with temperature, whereas the pH of boric acid buffers decreases with temperature. Finally, the drug in solution may itself act as a buffer. If the drug is a weak electrolyte, such as salicylic acid or ephedrine, the addition of base or acid, respectively, will create a system in which the drug can act as a buffer.

Non-limiting examples of buffers/buffering agents are Acetic acid, Adipic acid, Ammonium carbonate, Ammonium hydroxide, Ammonium phosphate, Boric acid, Citric acid, Citric acid monohydrate, Diethanolamine, Fumaric acid, Hydrochloric acid, Malic acid, Nitric acid, Propionic acid, Potassium acetate, Potassium bicarbonate, Potassium chloride, Potassium citrate, Potassium metaphosphate, Potassium phosphate, Sodium acetate, Sodium bicarbonate, Sodium borate, Sodium carbonate, Sodium chloride, Sodium citrate, Sodium glycolate, Sodium hydroxide, Sodium lactate, Sodium phosphate, Sodium proprionate, Succinic acid, Sulfuric acid, Tartaric acid, Triethylamine, Triethanolamine, Tromethamine (Tris/Trometamol), Trolamine and the like or any combinations thereof. One or more buffering agents can also be used in the preparation of the liquid compositions of the present invention. Preferably, the present invention uses two buffering agents, *viz.* citric acid or hydrate thereof and tromethamine (tris/trometamol).

Palatability of oral medicines is an important factor in compliance. There are several components to palatability including flavor, mouth-feel and sweetness. Most patients prefer medicines that are not too bitter but may be slightly "tart" (acidic). Most APIs are bitter. However, for bitterness to develop, the drug must be sufficiently soluble to interact with taste receptors on the tongue. For insoluble APIs in the form of suspensions, components of the suspension are also bitter, e.g. preservatives, or very salty, e.g. buffer systems. However, a slight saltiness and a slight bitterness are desirable for palatability.

Traditionally, oral medicines were sweetened using Syrup (concentrated sucrose solution) or honey (contains fructose). However, these materials are inadequate for the formulation of many products because they simply are not able to adequately mask the very bitter taste of many pharmaceutical materials, including APIs and excipients. Several alternative sweetening agents have been developed over the years to better mask unpleasant tastes in both processed foods and pharmaceuticals.

Several of the materials classified as sweetening agents are sugar alcohols (also known as polyhydric alcohols, polyols and hydrogenated sugars). Several of the commonly used sweetening agents are ionic and have the potential to interact with other components of the suspension. Some sweetening agents are more stable than others in aqueous solution. These will be important factors in the final selection of the sweetening agent. Non-limiting examples of sweetening agents include Glucose, Sucralose, Trehalose, Fructose, Xylose, Dextrose, Galactose, Tagatose, Maltose, Sucrose, Glycerol, Dulcitol, Mannitol, Lactitol, Sorbitol, Xylitol, Saccharine or the corresponding sodium, potassium or calcium salt, Cyclamate or the corresponding sodium or calcium salt, Aspartame, or Acesulfame or the potassium salt thereof, Dulcin or Ammonium glycyrrhizinate, Alitame, Inulin, Isomalt, Neohesperidin dihydrochalcone, Thaumatin and the like or any combinations thereof. The preferred sweetening agent/sweetener for the preparation of the liquid compositions according to the present invention is sucralose.

Flavors may also be used to improve the palatability of oral medicines. One problem that can arise with oral formulations is that they may produce a “cloying” sensation in the mouth. While this is not the same as a bitter taste, it can nevertheless cause problems for the patient and affect compliance. This can be a particular problem with high levels of inorganic components. Flavors can help reduce this “cloying” taste and thereby improve palatability, and ultimately patient compliance.

There are many different flavors, and most flavors are complex mixtures of many components. Today most flavors are developed by specialist flavor houses, and typically the flavor is formulated for each individual application. Flavor development and compounding is a specialist discipline. Flavor preferences vary with age, but the citrus flavors appear generally acceptable to most age groups. Non-limiting examples of flavoring agents are synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from

plants leaves, flowers, fruits, and so forth and the like or any combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, oil of bitter almonds, and cassia oil and the like or any combinations thereof. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot, and so forth and the like or any combinations thereof. Solid forms, such as spray dried forms of flavoring agents, may also be useful.

Coloring agents may also be used in the preparation of the liquid compositions of the present invention. Pharmaceutical colors come in two types; soluble dyes and insoluble pigments.

The liquid compositions of the present invention are stable for prolonged time when stored under storage conditions. The term "storage conditions" as used herein without limitation include typical storage conditions such as 2°C-8°C, 40°C±2°C/75±5% RH, 30°C±2°C/65±5% RH, 25°C±2°C/40±5% RH, 25°C±2°C/60±5% RH, and 40°C±2°C/NMT 25% RH (NMT = not more than) and accelerated conditions such as 40°C±2°C/75±5% RH. The term "prolonged time" as used herein indicates that the liquid compositions of the present invention are stable for at least 1 month, at least 3 months, at least 6 months or at least 12 months when stored under storage conditions.

As used herein, the terms "stable" or "stability" encompass any characteristic of the liquid compositions which may be affected by storage conditions including, without limitation, potency, total impurities, degradation products, specific optical rotation, optical purity, water content, appearance, viscosity, sterility, and colour and clarity. The storage conditions which may affect stability include, for example, duration of storage, temperature, humidity, and/or light exposure.

The term “degradant”, “impurity”, “degradation impurity” and “related substance” as used herein represents the same meaning and can be used interchangeably.

In some of the aspects of the present invention, “stable” or “storage stable”, or “stability” when used with reference to the liquid compositions of the present invention or when used “stable liquid compositions” or “stability of the liquid compositions” all these terms/phrases refer to compositions of the present invention which refer to the compositions which retain at least about 90%, or about least about 95%, or at least about 96%, or at least about 98%, of the labelled concentration of Methotrexate contained in the said composition after storage under typical and/or accelerated conditions. In further aspects, stable liquid compositions or stability of the liquid compositions refer to less than about 15% (area percent), or less than about 10% (area percent), or less than about 7% (area percent), or less than about 5% (area percent), or less than about 2% (area percent) of Methotrexate-related impurities are present after storage under typical and/or accelerated conditions.

In some of the aspects, liquid compositions of the present invention contain no more than about 15% (area percent), or no more than about 10% (area percent), or no more than about 7% (area percent), or no more than about 5% (area percent), or no more than about 2% (area percent), or no more than about 1% (area percent), or no more than about 0.5% (area percent), or no more than about 0.2% (area percent), or no more than about 0.1% (area percent) any known or unknown single Methotrexate-related impurity or other impurity after storage under typical and/or accelerated conditions.

In some of the aspects, liquid compositions of the present invention contain no more than about 15% (area percent), or no more than about 10% (area percent), or no more than about 7% (area percent), or no more than about 5% (area percent), or no more than about 2% (area percent), or no more than about 1% (area percent), or no more than about 0.5% (area percent), or no more than about 0.2% (area percent), or no more than about 0.1% (area

percent) total Methotrexate-related impurities or other impurities after storage under typical and/or accelerated conditions.

Methods for determining the stability of the liquid compositions of the present invention with respect to a given parameter are well-known to those of skill in the art. For example, individual impurities and total impurities can be assessed by high-performance liquid chromatography (HPLC) or thin layer chromatography (TLC). Unless otherwise indicated to the contrary, a percentage amount of any individual impurities (known/unknown), or total impurities reported herein in the liquid compositions are determined by a peak area percent method using HPLC.

The term "comprise/comprises/comprising" as used herein mean that other ingredients, steps, etc. are optionally present. When reference is made herein to a method comprising two or more defined steps, the steps can be carried in any order or simultaneously (except where the context excludes that possibility), and the method can include one or more steps which are carried out before any of the defined steps, between two of the defined steps, or after all of the defined steps (except where the context excludes that possibility).

The term "about," as used herein, refers to any value which lies within the range defined by a variation of up to ±10% of the value.

The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context.

All percentages mentioned herein, unless otherwise indicated, are on a w/v basis, i.e. percentage ingredient (active/inactive) present in the total volume of the liquid composition.

In accordance with the methods of use and administration of medicinal products, packaging materials, closures and containers vary a great deal and have to meet a wide variety of different requirements. The liquid compositions of the present invention may be packaged within any type of pharmaceutically-acceptable package, containers, pumps, bottles with spray pump, bottles with dropper assembly, bottles, collapsible tubes, glass ampoules, stoppered vials, pre-filled syringes, low-density polyethylene (LDPE), high-density polyethylene (HDPE), polyolefin, polypropylene containers/bottles depending upon the quantity of the final dosage form. The bottles or containers without limitation include clear/transparent/opaque or amber colored glass bottles or containers and clear/transparent/opaque or amber colored plastic bottles or containers made from polyethylene, polyamide, polycarbonate, acrylic multipolymers, polypropylene, polyethylene terephthalate, polyvinyl chloride, polystyrene and the like. Depending upon the type of the containers or bottles, closures may have different shapes and sizes. The closure of the packaging material may be made from polyethylene, polyamide, polycarbonate, acrylic multipolymers, polypropylene, polyethylene terephthalate, polyvinyl chloride, polystyrene and the like.

Liquid compositions of the present invention may be packaged in a sterile/non-sterile single use/multi use bottle/container that contains a unit dose for administration to a patient. Suitable bottles/containers may contain volumes between 1-10 ml, 10-20 ml, 20-40 ml, and 40-100 ml, and even more. The container may typically comprise Methotrexate in an amount of between 10-40 mg, between 40-80 mg, between 80-130 mg, and even more. Thus, it may also be noted that the container may be a multi-use container (i.e., retains at least one more unit dose after a first unit dose is dispensed).

According to the invention, the amount of Methotrexate free acid in a composition of the invention ranges from 0.4 mg/ml to 20 mg/ml. Preferably, the

methotrexate free acid is present in a concentration of 1 mg/ml to 10 mg/ml. More preferably, the Methotrexate free acid is present in a concentration of 1 mg/ml to 5 mg/ml.

"Methotrexate" as used herein, unless the context requires otherwise, includes Methotrexate, its pharmaceutically acceptable salts and chemical derivatives thereof such as polymorphs, solvates, hydrates, anhydrous forms, amorphous forms, prodrugs, chelates, and complexes. "Methotrexate" as used herein also includes racemic or substantially pure forms.

The present invention also provides process for the preparation of the liquid compositions of the present invention. The process for the preparation of the liquid compositions of the present invention comprises various steps. In the said process, two or more preservatives may be added in the aqueous vehicle, followed by addition of one or more buffering agents to adjust the pH of the liquid compositions between about 8.0 and about 8.5. Methotrexate in the form of free acid may be added in the mixture obtained by the process mentioned above. One or more sweetening agents may be added in the sufficient quantity to make the compositions palatable. Remaining quantity of the aqueous vehicle may be added to adjust the final volume of the composition. The final composition is filtered through 10µ propylene filter and filled in the pharmaceutically acceptable container. In order to protect the degradation of the active ingredient Methotrexate, the preparation of the liquid compositions of the present invention may be carried out under continuous nitrogen purging and light protection.

The liquid compositions according to the present invention can be described by following general formula:

Sr No	Name of ingredient	Quantity
1	Methotrexate	0.1-20 mg/mL
2	One or more preservatives	0-10 mg/mL
3	One or more buffering agents	Q.S. to adjust the pH between about 7.5 and about 9.0
4	One or more sweetening agents	Q.S. to make the

		composition palatable
5	Vehicle	Q.S.
Q.S. = Quantity Sufficient		

The liquid pharmaceutical compositions prepared according to the present invention are suitable for administration to a subject to treat or prevent a disease or condition. Preferably, the subject is a mammal. More preferably, the mammal is a human. Preferably, the disease or condition is a disease or condition that is treatable by the administration of Methotrexate.

The present invention is also directed to the method of treating spondyloarthropathies, systemic dermatomyositis, severe, recalcitrant psoriasis, including psoriatic arthritis that is not adequately responsive to other forms of therapy, rheumatoid arthritis, seronegative arthritis, adult rheumatoid arthritis systemic dermatomyositis, Crohn's disease, multiple sclerosis, polyarthritic forms of severe, active juvenile idiopathic arthritis, resistant juvenile rheumatoid arthritis, graft versus host disease, lupus, morphea (also known as localized scleroderma), ankylosing spondylitis and other autoimmune diseases, and in the treatment of a wide range of neoplastic conditions, such as mycosis fungoides, haemoblastosis, trophoblastic neoplasms, acute lymphoblastic leukaemia, prophylaxis of meningeal leukaemia, Non-Hodgkin's lymphomas, osteogenic sarcoma, breast cancer, head and neck cancer, choriocarcinoma and similar trophoblastic diseases, lung cancer, bladder cancer, adult soft tissue sarcoma, and various other malignant tumours or any other condition wherein the patient requires Methotrexate therapy which comprises administration of an effective dosage amount of the liquid compositions of the present invention.

"Effective dosage amount" as used herein with respect to, for example Methotrexate liquid compositions shall mean that dosage that provides the specific pharmacological response for which Methotrexate administered in a significant number of subjects in need of such treatment. It is emphasized that "effective dosage amount",

administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a "effective dosage amount" by those skilled in the art.

The present invention also provides use of the liquid compositions of the present invention in the treatment of spondyloarthropathies, systemic dermatomyositis, severe, recalcitrant psoriasis, including psoriatic arthritis that is not adequately responsive to other forms of therapy, rheumatoid arthritis, seronegative arthritis, adult rheumatoid arthritis systemic dermatomyositis, Crohn's disease, multiple sclerosis, polyarthritic forms of severe, active juvenile idiopathic arthritis, resistant juvenile rheumatoid arthritis, graft versus host disease, lupus, morphea (also known as localized scleroderma), ankylosing spondylitis and other autoimmune diseases, and in the treatment of a wide range of neoplastic conditions, such as mycosis fungoides, haemoblastosis, trophoblastic neoplasms, acute lymphoblastic leukaemia, prophylaxis of meningeal leukaemia, Non-Hodgkin's lymphomas, osteogenic sarcoma, breast cancer, head and neck cancer, choriocarcinoma and similar trophoblastic diseases, lung cancer, bladder cancer, adult soft tissue sarcoma, and various other malignant tumours or any other condition wherein the patient requires Methotrexate therapy.

The liquid compositions of the present invention comprising Methotrexate, exhibit improved or comparable pharmacokinetic profiles as compared to known Methotrexate compositions. For example, the Cmax and/or AUC of the liquid compositions of Methotrexate of the present invention can be greater than or substantially equal to the Cmax and/or AUC for known Methotrexate compositions administered at the same dosage. In addition, the Tmax of the liquid compositions of Methotrexate of the present invention can be lower than or substantially equal to that obtained for a known Methotrexate compositions, administered at the same dosage. In addition, combinations of an improved or comparable Cmax, AUC and Tmax profile can be exhibited by the liquid compositions of Methotrexate

of the invention, as compared to known Methotrexate compositions. In further aspects, the liquid compositions of Methotrexate of the present invention may result in minimal different absorption levels when administered under fed as compared to fasting conditions.

In one of the aspects, a liquid composition comprising Methotrexate exhibits in comparative pharmacokinetic testing with Methotrexate marketed or known formulation, administered at the same dose, a Tmax not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the Tmax exhibited by the marketed or known Methotrexate formulation.

In one of the further aspects, the liquid composition comprising Methotrexate exhibits in comparative pharmacokinetic testing with Methotrexate marketed or known formulation, administered at the same dose, a Cmax which is at least about 50%, at least about 100%, or at least about 150% greater than the Cmax exhibited by the marketed or known Methotrexate formulation. In one of the further aspects, the liquid composition comprising Methotrexate exhibits in comparative pharmacokinetic testing with Methotrexate marketed or known formulation, administered at the same dose, a Cmax which is in the range between about 70% and about 150%.

In one of the further aspects, the liquid composition comprising Methotrexate exhibits in comparative pharmacokinetic testing with an Methotrexate marketed or known formulation, administered at the same dose, an AUC which is at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200% greater than the AUC exhibited by the marketed or known Methotrexate formulation. In one of the further aspects, the liquid composition comprising Methotrexate exhibits in comparative pharmacokinetic testing with Methotrexate

marketed or known formulation, administered at the same dose, an AUC which is in the range between about 80% and about 125%.

In one of the further aspects, the Tmax of Methotrexate, when assayed in the plasma of the mammalian subject, is less than about 6 to about 8 hours. In other aspects of the invention, the Tmax of Methotrexate is less than about 6 hours, less than about 5 hours, less than about 4 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or less than about 30 minutes after administration.

In some aspects, the liquid compositions of Methotrexate of the present invention exhibit improved or comparable bioavailability as compared to known Methotrexate compositions.

The present invention is further exemplified by the following non-limiting examples.

BEST MODE OF CARRYING OUT THE INVENTION EXAMPLES

The liquid compositions of the present invention are explained in more detail with reference to the following examples. These examples are provided by way of illustration only and should not be construed as to limit the scope or spirit of the claims in any manner.

Example-1: Preparation of Methotrexate Oral Solution

Sr No	Name of Ingredient	Function	Quantity (mg/ml)	
1	Methotrexate	Active ingredient	2.00	2.5
2	Methyl paraben sodium	Preservative	3.45	3.45
3	Propyl paraben sodium	Preservative	0.65	0.65
4	Tris (tromethamine)	Buffering agent	2.50	2.50
5	Citric acid-1-hydrate	Buffering agent	1.00	1.00
6	Sucralose	Sweetening agent	2.00	2.00
7	Purified Water	Vehicle	Q.S. to 1 ml	Q.S. to 1 ml

Method of preparation:

The process for the preparation of the Methotrexate oral solution comprises following steps:

1. Take required quantity of purified water to initiate the preparation process;
2. Add methyl paraben sodium and stir well to dissolve it;
3. Add propyl paraben sodium in step (2) and stir well to dissolve it;
4. Add Tris-citric acid buffer in step (3) under stirring to adjust the pH of the mixture between about 7.5 and about 9.0;
5. Add Methotrexate in the mixture obtained in step (4) and stir well to dissolve it;
6. Add sucralose in the mixture obtained in step (5) and stir well for complete solubilisation;
7. Adjust the volume of the mixture obtained in step (6) to the final volume of the total batch size with required quantity of the purified water; and
8. Filter the solution obtained in step (7) using 10µ propylene filter and fill in the pharmaceutically acceptable container.

The above mentioned process may be carried out under continuous nitrogen purging and by protecting from direct light.

Example-2: Stability study of the Methotrexate Oral Solution

The Methotrexate oral solution prepared according to the present invention as exemplified in Example-1 were tested for it physical stability. The Methotrexate oral solution was kept at various storage conditions such as 40°C±2°C and 25%±5% RH (relative humidity), 25°C±2°C and 40%±5% RH (relative humidity) and at 5°C±3°C. The amount of impurities (related substances or degradation products) present in the compositions were

tested by HPLC at initial level and after three months after stored the Methotrexate oral solution at above mentioned conditions. The results are summarized as under.

Parameters	Initial	40°C±2°C/25%±5% RH (3 months)	25°C±2°C/40%±5% RH (3 months)	2-8°C (3 months)
Description	Clear solution	Complies	Complies	Complies
Assay of Methotrexate	97.7%	97.6%	97.5%	97.1%
pH	7.8	8.0	8.1	8.1
Related Substances (by HPLC)				
Impurity-C	0.07%	2.56%	0.39%	0.06%
Impurity-E	BQL	BQL	BQL	BQL
Impurity-B	ND	0.09%	0.03%	0.02%
Impurity-H	ND	ND	ND	ND
Impurity-I	ND	ND	ND	ND
Single maximum unspecified impurity	BQL	0.06%	BQL	BQL
Total impurities	0.19%	2.87%	0.53%	0.16%

ND = Not detected
BQL = Below quantitation limit

From above it can be seen that even after storing the liquid formulation of the present invention at 25°C & 40°C for three months, precipitations of Methotrexate were not observed and the solution was clear.

From above, it can also be seen that the amount of Impurity-E present in the liquid formulation of the present invention is below quantitation limit at initial level and at 2-8°C, 25°C & 40°C. The prior art document, US 9259427, reveals that the amount of Impurity-E present in the liquid formulation disclosed therein is 0.00% at initial level and 0.13% at 25°C after 2 months (8 weeks) at pH 6.18 & 1.80% at 25°C after 2 months (8 weeks) at pH 7.17.

It can therefore be concluded that, in the liquid formulations of the present invention, the amount of Impurity-E does not increase over a period of three months at higher pH such as above 7.5 whereas in the Methotrexate liquid formulations disclosed in US

9259427, the amount of Impurity-E increases in just two months even at lower pH such as 7.17.

The liquid compositions of Methotrexate prepared according to the present invention as described herein are suitable for use in the industry.

It should be understood that various changes and modifications to the embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the subject matter of the present invention and without diminishing its intended advantages. It is therefore intended that such changes and modifications be covered within the scope of the present invention.

WE CLAIM:

1. A Methotrexate liquid composition, suitable for oral administration, comprising Methotrexate and one or more preservatives, one or more buffering agents, one or more sweetening agents and an aqueous vehicle, wherein the pH of the composition is between about 7.5 and about 9.0.

2. A Methotrexate liquid composition according to claim 1, wherein one or more buffering agents comprises any or any combination of Acetic acid, Adipic acid, Ammonium carbonate, Ammonium hydroxide, Ammonium phosphate, Boric acid, Citric acid, Citric acid monohydrate Diethanolamine, Fumaric acid, Hydrochloric acid, Malic acid, Nitric acid, Propionic acid, Potassium acetate, Potassium bicarbonate, Potassium chloride, Potassium citrate, Potassium metaphosphate, Potassium phosphate, Sodium acetate, Sodium bicarbonate, Sodium borate, Sodium carbonate, Sodium chloride, Sodium citrate, Sodium glycolate, Sodium hydroxide, Sodium lactate, Sodium phosphate, Sodium proprionate, Succinic acid, Sulfuric acid, Tartaric acid, Triethylamine, Triethanolamine, Tromethamine (Tris/Trometamol), Trolamine.

3. A Methotrexate liquid composition according to claim 1, wherein the composition comprises two or more buffer agents to form a buffer system.

4. A Methotrexate liquid composition according to claim 3, wherein the two or more buffer agents are Tris (Trometamol)-Citric Acid Monohydrate Buffer.

5. A Methotrexate liquid composition according to claim 1, wherein one or more preservatives are selected from the group comprising of Alcohol, Ethanol, Chlorobutanol, Phenoxyethanol, Potassium benzoate, Benzyl alcohol, Benzoic acid, Potassium sorbate, Sorbic acid, Benzalkonium chloride, Benzethonium chloride, Cetrimonium bromide, Cetylpyridinium chloride, Bronopol, Chlorbutol, Chlorocresol, Cresol, Butylparaben (butyl 4-hydroxybenzoate) or salt thereof, Methylparaben (methyl 4-hydroxybenzoate) or salt

thereof, Propylparaben (propyl 4-hydroxybenzoate) or salt thereof, Ethylparaben (ethyl 4-hydroxybenzoate) or salt thereof, Phenol, Thymol, Phenylethanol, Sodium benzoate, Antimicrobial solvents like Propylene glycol, Glycerin, Chloroform or any combinations thereof.

6. A Methotrexate liquid composition according to claim 1, wherein one or more sweetening agents are selected from the group comprising of Glucose, Sucralose, Trehalose, Fructose, Xylose, Dextrose, Galactose, Tagatose, Maltose, Sucrose, Glycerol, Dulcitol, Mannitol, Lactitol, Sorbitol, Xylitol, Saccharine or the corresponding sodium, potassium or calcium salt, Cyclamate or the corresponding sodium or calcium salt, Aspartame, or Acesulfame or the potassium salt thereof, Dulcin or Ammonium glycyrrhizinate, Alitame, Inulin, Isomalt, Neohesperidin dihydrochalcone, Thaumatin or any combinations thereof.

7. A Methotrexate liquid composition according to claim 1 optionally comprises flavoring agent selected from the group comprising of cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, oil of bitter almonds, cassia oil, vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot or any combinations thereof.

8. A Methotrexate liquid composition according to claim 1, wherein the pharmaceutically acceptable dosage of the Methotrexate used is 2.5 mg/5 ml, 5 mg/5 ml, 10 mg/5 ml or in the range of 0.05 mg/1 ml to 20 mg/1 ml.

9. A Methotrexate liquid composition according to claim 1 comprising:

a. 0.05-20 mg Methotrexate free acid;

b. Tris (trometamol)-Citric acid buffer system;

c. Sodium methyl 4-hydroxy benzoate;

d. Sodium propyl 4-hydroxy benzoate;

e. Sucralose; and

f. Purified water

10. A Methotrexate liquid composition according to claim 1, wherein the composition is stable for prolonged time when stored under typical storage conditions and/or accelerated conditions characterized in that any individual impurity present in the liquid composition is less than about 3.0% and the total impurities present in the liquid composition are less than about 5.0%.

11. A Methotrexate liquid composition according to claim 1, wherein the composition has:

(a) a Cmax for Methotrexate, when assayed in the plasma of a mammalian subject following administration that is at least about 50% to about 150% greater than the Cmax for Methotrexate marketed or known formulation, administered at the same dose;

(b) an AUC for Methotrexate, when assayed in the plasma of a mammalian subject following administration that is at least about 25% to about 200% greater than the AUC for Methotrexate marketed or known formulation, administered at the same dose;

(c) a Tmax for Methotrexate, when assayed in the plasma of a mammalian subject following administration that is less than about 6 hours to about 8 hours; or

(d) any combination of (a), (b), and (c).

12. A process for the preparation of the Methotrexate liquid composition according to claim 1 comprising following steps:

dissolve sodium methyl 4-hydroxy benzoate and sodium propyl 4-hydroxy benzoate in the required quantity of purified water;

add Tris-citric acid buffer in step (1) under stirring to adjust the pH of the mixture obtained in step (1) between about 7.5 and about 9.0;

dissolve Methotrexate in the mixture obtained in step (2);

dissolve sucralose in the mixture obtained in step (3); and

adjust the volume of the mixture obtained in step (4) to the total batch size with purified water.

13. A Methotrexate liquid composition according to claim 1 for use as a folic acid antagonist, as an anti-neoplastic agent, an immunosuppressant, an anti- metabolite, or for use in the treatment of at least one condition selected from the group comprising of spondyloarthropathies, systemic dermatomyositis, severe, recalcitrant psoriasis, including psoriatic arthritis that is not adequately responsive to other forms of therapy, rheumatoid arthritis, seronegative arthritis, adult rheumatoid arthritis systemic dermatomyositis, Crohn's disease, multiple sclerosis, polyarthritic forms of severe, active juvenile idiopathic arthritis, resistant juvenile rheumatoid arthritis, graft versus host disease, lupus, morphea (also known as localized scleroderma), ankylosing spondylitis and other autoimmune diseases, and in the treatment of a wide range of neoplastic conditions, such as mycosis fungoides, haemoblastosis, trophoblastic neoplasms, acute lymphoblastic leukaemia, prophylaxis of meningeal leukaemia, Non-Hodgkin's lymphomas, osteogenic sarcoma, breast cancer, head and neck cancer, choriocarcinoma and similar trophoblastic diseases, lung cancer, bladder cancer, adult soft tissue sarcoma, and various other malignant tumours or any other condition wherein the patient requires Methotrexate therapy.

14. A Methotrexate liquid composition according to claim 1 is packaged in the pharmaceutically acceptable packaging material selected from the group comprising of

containers, pumps, bottles with spray pump, bottles with dropper assembly, bottles, collapsible tubes, glass ampoules, stoppered vials, pre-filled syringes, wherein the bottles and containers are clear or transparent or opaque or amber colored glass bottles and containers or clear or transparent or opaque or amber colored plastic bottles and containers made from polyethylene, low-density polyethylene, high-density polyethylene, polyamide, polyolefin, polycarbonate, acrylic multipolymers, polypropylene, polyethylene terephthalate, polyvinyl chloride, polystyrene.