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(54) **PHARMACEUTICAL DOSAGE FORM FOR PULSATILE DELIVERY OF METHYLPHENIDATE**

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(60) Provisional application No. 60/127,984, filed on Apr. 6, 1999.

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(58) **Field of Search** 424/451, 452, 424/457, 458, 459, 463, 464, 465, 468, 469, 474, 475, 481, 482

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(57) **ABSTRACT**

Novel pharmaceutical dosage forms provide for pulsatile delivery of methylphenidate, i.e., release encapsulated drug in spaced apart "pulses." The dosage forms are comprised of first, second and optionally third dosage units, with each dosage unit having a different drug release profile. The dosage forms may comprise capsules housing compressed tablets or drug-containing beads or particles, or may comprise a single tablet with the first, second and optionally third dosage units each representing an integral and discrete segment thereof. Methods of treatment using the pharmaceutical dosage forms are provided as well.

45 Claims, No Drawings

PHARMACEUTICAL DOSAGE FORM FOR PULSATILE DELIVERY OF METHYLPHENIDATE

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. Ser. No. 09/544,732, filed Apr. 6, 2000, now U.S. Pat. No. 6,340,476, which claims priority under 35 U.S.C. §119(e)(1) to U.S. Provisional Patent Application Serial No. 60/127,984, filed Apr. 6, 1999. The disclosures of the aforementioned patent applications are incorporated by reference in their entireties.

The present invention relates generally to drug delivery, and more specifically relates to novel pharmaceutical dosage forms that provide pulsatile delivery of methylphenidate. The invention additionally relates to methods for administering methylphenidate using the novel dosage forms.

BACKGROUND

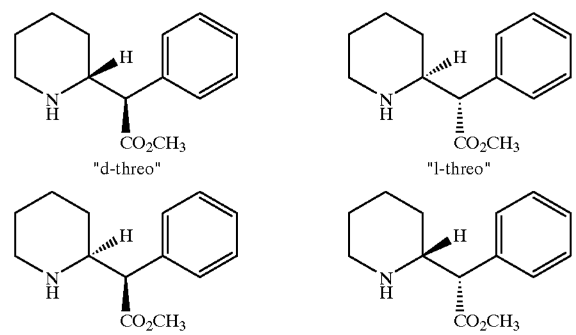
Pharmaceutical dosage forms are known which provide a variety of drug release profiles, including immediate release, sustained release, and delayed release. That is, it may be desirable, for a particular drug, to prevent drug release after drug administration until a certain amount of time has passed (so-called "timed release"), to provide substantially continuous release over a predetermined time period (so-called "sustained release") or to provide release immediately following drug administration (i.e., "immediate release"). For some types of drugs, it is preferred to release the drug in "pulses," wherein a single dosage form provides for an initial dose of drug followed by a release-free interval, after which a second dose of drug is released, followed by one or more additional release-free intervals and drug release "pulses." Pulsatile drug delivery is useful, for example, with active agents that have short half-lives and must be administered two or three times daily, with active agents that are extensively metabolized presystemically, and with active agents which lose the desired therapeutic effect when constant blood levels are maintained. These types of agents have pharmacokinetic-pharmacodynamic relationships that are best described by a clockwise "hysteresis loop." A drug dosage form that provides a pulsatile drug release profile is also useful for minimizing the abuse potential of certain types of drugs, i.e., drugs for which tolerance, addiction and deliberate overdose can be problematic.

Because a precise and effective pulsatile drug delivery system is difficult to formulate and manufacture, there are few such dosage forms that have been commercialized. There are, however, several patents and literature references pertaining to pulsatile drug delivery. See, for example, U.S. Pat. No. 5,413,777 to Sheth et al., directed to a pulsatile once-a-day delivery system for the administration of minocycline; U.S. Pat. No. 5,260,068 to Chen, directed to a multiparticulate pulsatile drug delivery system; U.S. Pat. No. 4,777,049 to Magruder et al., directed to an osmotic delivery system for constant release of a drug with intermittent release "pulses"; U.S. Pat. No. 5,391,381 to Wong et al., directed to a drug dispenser for delivering individual drug-containing units in a "pulsatile" manner; PCT Publication No. WO 98/32424, pertaining to pulsatile delivery of diltiazem hydrochloride; U.S. Pat. Nos. 5,472,708 and 5,260,069 to Chen; Ishino et al. (1992) "Design and Preparation of Pulsatile Release Tablet as a New Oral Drug Delivery System," *Chem. Pharm. Bull.* 40(11):3036–3041; Cohen et al. (1994), "Pulsatile Release from Microencapsulated Liposomes," *J. Liposome Res.* 349–360; and Gaz-

zaniga et al. (1994), "Chronotopic Drug Delivery Systems for Pulsatile and/or Site-Specific Release," 21[st]. *Proc. Int. Symp. Controlled Release Bioact. Mater.,* pp. 744–745.

The present invention is directed in part to a novel pulsatile drug delivery system which is straightforward to manufacture and provides precisely timed drug release "pulses" at desired intervals.

Methylphenidate hydrochloride (HCl), the hydrochloride salt of α-phenyl-2-piperidine-acetic acid methyl ester (available commercially as Ritalin®), is a central nervous system stimulant that is used in the treatment of Attention Deficit Disorder ("ADD"), a commonly diagnosed nervous system illness in children that is characterized by both distractability and impulsivity. Methylphenidate HCl is also used to treat a related disorder, Attention Deficit Hyperactivity Disorder ("ADHD"), in which symptoms of hyperactivity are present along with the symptoms of ADD. The drug is additionally used in the symptomatic treatment of narcolepsy, depression, and the cognitive decline associated with Acquired Immunodeficiency Syndrome ("AIDS") or AIDS-related conditions, as well as for mood elevation, particularly in terminally ill patients with diseases such as cancer. Methylphenidate exists as four distinct isomers, as follows:



"d-threo" "l-threo" "d-erythro" "l-erythro"

The drug as used in therapy is a racemic mixture of the d- and l-threo enantiomers, which have been acknowledged as more active than the erythro pair.

Because of its potential for tolerance (loss of clinical efficacy when constant blood levels are maintained), short-half life and potential for abuse, methylphenidate is a primary candidate for use in conjunction with the drug delivery systems of the invention.

Accordingly, the present invention provides novel pharmaceutical dosage forms for the administration of methylphenidate in its conventional form, i.e., as a racemic mixture of the d-threo and l-threo enantiomers. The novel dosage forms provide for pulsatile drug release, thereby maximizing efficacy (i.e., the loss of clinical efficacy over time), reducing the potential for abuse or noncompliance. The invention thus represents a significant advance in the art, particularly in the administration of drugs such as methylphenidate that have short half-lives, tend to be extensively metabolized presystemically, have pharmacokinetic-pharmacodynamic relationships which are best described by positive (clockwise) hysteresis loops (hence resulting in tolerance when constant blood levels are maintained), or are likely candidates for drug abuse. No art of which applicants are aware describes pulsatile drug delivery systems as now provided herein.

To the best of applicants' knowledge, the pharmaceutical dosage forms of the invention are previously unknown and completely unsuggested by the art.

SUMMARY OF THE INVENTION

Accordingly, it is a primary object of the invention to address the above-mentioned need in the art by providing a pharmaceutical dosage form for pulsatile delivery of methylphenidate.

It is another object of the invention to provide such a dosage form comprising at least two individual drug-containing dosage units, each of which has a different drug release profile.

It is another object of the invention to provide such a dosage form wherein the dosage units are housed in a closed capsule.

It is still another object of the invention to provide such a dosage form wherein the dosage units are compressed tablets.

It is yet another object of the invention to provide such a dosage form wherein the dosage units are drug-containing particles or beads.

It is a further object of the invention to provide such a dosage form comprised of a single tablet of which the drug-containing dosage units represent integral but discrete segments.

It is a further object of the invention to provide such a dosage form for administering methylphenidate optionally in combination with one or more other active agents such as CNS stimulants (including analeptic agents and psychostimulants), antidepressant drugs, antianxiety agents and the like.

It is an additional object of the invention to provide methods for administering methylphenidate using the novel dosage forms.

Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Nomenclature

Before the present formulations and methods of use are disclosed and described, it is to be understood that unless otherwise indicated this invention is not limited to specific pharmacologically active agents, specific pharmaceutical carriers, or to particular administration regimens, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" includes mixtures of active agents, reference to "a pharmaceutical carrier" includes combinations of two or more carriers, and the like.

In this specification and in the claims which follow, reference will be made to a number of terms which shall be defined to have the following meanings:

"Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not.

The terms "active agent," "drug" and "pharmacologically active agent" are used interchangeably herein to refer to a chemical material or compound which, when administered to an organism (human or animal, generally human) induces a desired pharmacologic effect. In the context of the present invention, the terms refer to a compound that is capable of being delivered orally.

The term "methylphenidate" as used herein refers to a racemic mixture of d-threo methylphenidate and l-threo methylphenidate, also referred to herein as "d,l-methylphenidate."

By the terms "effective amount" or "pharmaceutically effective amount" of an agent as provided herein are meant a nontoxic but sufficient amount of the agent to provide the desired therapeutic effect. The exact amount required will vary from subject to subject, depending on age, general condition of the subject, the severity of the condition being treated, and the particular active agent administered, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

By "pharmaceutically acceptable" carrier is meant a carrier comprised of a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with the selected active agent without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The term "carrier" is used generically herein to refer to any components present in the pharmaceutical formulations other than the active agent or agents, and thus includes diluents, binders, lubricants, disintegrants, fillers, coloring agents, wetting or emulsifying agents, pH buffering agents, preservatives, and the like.

Similarly, a "pharmaceutically acceptable" salt or a "pharmaceutically acceptable" ester of a compound as provided herein is a salt or ester which is not biologically or otherwise undesirable.

In the chemical structures drawn herein, the use of bold and dashed lines to denote particular conformation of substituents follows IUPAC convention. The symbols "α" and "β" indicate the specific stereochemical configuration of a substituent at an asymmetric carbon atom in a chemical structure as drawn. Thus "α," denoted by a broken line, indicates that the group in question is below the general plane of the molecule as drawn, and "β" denoted by a bold line, indicates that the group at the position in question is above the general plane of the molecule as drawn.

"Pulsatile Release" Dosage Forms

In a first embodiment, the invention features pharmaceutical dosage forms that provide for pulsatile delivery of methylphenidate. By "pulsatile" is meant that a plurality of drug doses are released at spaced apart time intervals. Generally, upon ingestion of the dosage form, release of the initial dose is substantially immediate, i.e., the first drug release "pulse" occurs within 1–2 hours of ingestion. This initial pulse is followed by a first time interval during which substantially no drug is released from the dosage form, after which a second dose is then released. Typically, the second dose is released on the order of 3–5 hours following ingestion of the dosage form. Preferably, release of the second dose is followed by a second non-release interval, which is again followed by a "pulse" of drug release. Ideally, release of a third dose occurs on the order of 7–9 hours following ingestion. In a preferred embodiment herein, either two or three release pulses are provided. However, the invention is also intended to encompass dosage forms that provide more than three pulses, with non-release intervals therebetween of approximately 2–6 hours, preferably 3–5 hours.

The aforementioned pulsatile release profile is achieved with dosage forms that, in one embodiment, are closed and preferably sealed capsules housing two or more drug-containing "dosage units." In a preferred embodiment, each dosage unit comprises a compressed or molded tablet, wherein each of the tablets within the capsule provides a different drug release profile. That is, for an exemplary dosage form, a first tablet releases drug substantially immediately following ingestion of the dosage form, while a second tablet in the capsule releases drug approximately 3–5 hours following ingestion, and an optional third tablet provides drug release after approximately 7–9 hours. While the dosage form will not generally include more than three tablets, dosage forms housing four or more tablets are within the scope of the present invention.

In an alternative embodiment, each dosage unit comprises a drug-containing particle or bead (drug-containing "beads" refer to drug-coated inert supports, e.g., lactose beads coated with drug). A first group of these particles or beads releases drug substantially immediately following ingestion of the dosage form, a second group releases drug approximately 3–5 hours following ingestion, and an optional third group provides drug release after approximately 7–9 hours.

In a further alternative embodiment, the individual dosage units are compacted in a single tablet, and represent integral but discrete segments thereof (e.g., layers). For example, drug-containing particles or drug-containing beads can be compressed together into a single tablet using conventional tabletting means.

As will be appreciated by those skilled in the art and as described in the pertinent texts and literature, a number of methods are available for preparing drug-containing tablets or other dosage units which provide a variety of drug release profiles. Such methods include coating a drug or drug-containing composition, increasing the drug's particle size, placing the drug within a matrix, and forming complexes of the drug with a suitable complexing agent.

The delayed release dosage units in the present capsules can be prepared, for example, by coating a drug or a drug-containing composition with a selected membrane coating material, typically although not necessarily a polymeric material. When a coating is used to provide delayed release dosage units, particularly preferred coating materials comprise bioerodible, gradually hydrolyzable and/or gradually water-soluble polymers. The "coating weight," or relative amount of coating material per dosage unit, generally dictates the time interval between ingestion and drug release.

Suitable membrane coating materials for effecting delayed release include, but are not limited to: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethyl cellulose phthalate, cellulose ester-ether phthalate, hydroxypropylcellulose phthalate, alkali salts of cellulose acetate phthalate, alkaline earth salts of cellulose acetate phthalate, hydroxypropylmethyl cellulose hexahydrophthalate, cellulose acetate hexahydrophthalate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, with a terpolymer of ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride (sold under the tradename Eudragit RS) particularly preferred; vinyl polymers and copolymers such as polyvinyl pyrrolidone, polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate.

In some cases, it may be desirable for the third tablet or bead or particle fraction to provide for release of the active agent in the colon, in which case polymeric or other materials are used that enable drug release within the colon. These may be selected from the aforementioned list, or other materials may be used as will be known to those skilled in the art of pharmaceutical formulation and drug delivery. For example, hydrocolloid gums may be effective to provide for colonic delivery, e.g., guar gum, locust gum, bena gum, gum tragacanth, and karaya gum (see, e.g., U.S. Pat. No. 5,656,294 to Friend). Other materials suitable for effecting colonic drug delivery include polysaccharides, mucopolysaccharides, and related compounds, e.g., pectin, arabinogalactose, chitosan, chondroitin sulfate, dextran, galactomannan, and xylan.

Combinations of different coating materials may also be used to coat a single dosage unit.

To bring about the desired pulsatile release profile for a dosage form comprised of encapsulated tablets, the first tablet is provided with little or no coating material, the second tablet is provided with some degree of coating material, the coating weight of a third tablet is still higher, and so on. Analogously, for encapsulated dosage forms in which the drug-containing dosage units are beads or particles, a first fraction of beads or particles is provided with little or no coating material, a second fraction is provided with some degree of coating material, the coating weight of a third fraction is still higher, etc. For example, when the dosage form contains three tablets (or, analogously, three groups of drug-containing particles or beads), the first tablet, which releases drug substantially immediately, may have a total coating weight of less than about 10%, preferably less than about 8%, the second tablet may have a total coating weight in the range of approximately 10% to 30%, preferably 15% to 25%, and the third tablet, if present, may have a total coating weight in the range of approximately 15% to 65%, preferably 20% to 65%. The preferred coating weights for particular coating materials may be readily determined by those skilled in the art by evaluating individual release profiles for dosage units prepared with different quantities of various coating materials.

Alternatively, the delayed release dosage units, i.e., tablets or particles, may be formulated by dispersing the drug within a matrix of a suitable material such as an insoluble plastic, a hydrophilic polymer, or a fatty compound. The insoluble plastic matrices may be comprised of, for example, polyvinyl chloride or polyethylene. Hydrophilic polymers useful for providing a matrix for a delayed release dosage unit include, but are not limited to, those described above as suitable coating materials. Fatty compounds for use as a matrix material include, but are not limited to, waxes generally (e.g., carnauba wax) and glyceryl tristearate. Once the active ingredient is mixed with the matrix material, the mixture can be compressed into tablets or processed into individual drug-containing particles.

The individual dosage units may be provided with colored coatings, with a single color used to identify a tablet or bead or particle fraction having a corresponding delayed release profile. That is, for example, a blue coating may be used for the immediate release tablet or bead or particle fraction, a red coating may be used for the "medium" release tablet or bead or particle fraction, and the like. In this way, errors during manufacture can be easily avoided. The color is introduced by incorporating a pharmaceutically acceptable colorant into the coating during coating preparation. The colorant may be either natural or synthetic. Natural colorants include pigments such as chlorophyll, anattenes, beta-carotene, alizarin, indigo, rutin, hesperidin, quercitin, carminic acid, and 6,6'-dibromoindigo. Synthetic colorants are dyes, including both acidic dyes and basic dyes, such as nitroso dyes, nitro dyes, azo dyes, oxazines, thiazines, pyrazolones, xanthenes, indigoids, anthraquinones, acridines, rosanilines, phthaleins, quinolines. e.g., a dye or pigment, during preparation of the coating solution.

For encapsulated tablets, the weight of each individual tablet in the capsule is typically in the range of about 10 mg to 150 mg, preferably in the range of about 25 mg to about 100 mg, and most preferably is in the range of about 40 mg to 80 mg. The individual tablets are prepared using conventional means. A preferred method for forming tablets herein is by direct compression of a powdered, crystalline or granular drug-containing composition, alone or in combination with diluents, binders, lubricants, disintegrants, colorants or the like. As an alternative to direct compression, compressed tablets can be prepared using wet-granulation or dry-granulation processes. Tablets may also be molded rather than compressed, starting with a moist material containing a suitable water-soluble lubricant. Preferred tablets herein are manufactured using compression rather than molding, however. Drug-containing particles or beads are also prepared using conventional means, typically from a fluid dispersion.

Conventional coating procedures and equipment may then be used to coat the dosage units, i.e., the drug-containing tablets, beads or particles. For example, a delayed release coating composition may be applied using a coating pan, an airless spray technique, fluidized bed coating equipment, or the like. For detailed information concerning materials, equipment and processes for preparing tablets, beads, drug particles, and delayed release dosage forms, reference may be had to *Pharmaceutical Dosage Forms: Tablets,* eds. Lieberman et al. (New York: Marcel Dekker, Inc., 1989), and to Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems,* 6^{th} Ed. (Media, Pa.: Williams & Wilkins, 1995).

Optional components present in the individual drug-containing dosage units include, but are not limited to, diluents, binders, lubricants, disintegrants, stabilizers, surfactants, coloring agents, and the like. Diluents, also termed "fillers," are typically necessary to increase the bulk of a tablet so that a practical size is provided for compression. Suitable diluents include, for example, dicalcium phosphate dihydrate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, hydrolyzed starches, silicon dioxide, titanium oxide, alumina, talc, microcrystalline cellulose, and powdered sugar. Binders are used to impart cohesive qualities to a tablet formulation, and thus ensure that a tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums, e.g., acacia, tragacanth, sodium alginate, polyvinylpyrrolidone, celluloses, and Veegum, and synthetic polymers such as polymethacrylates and polyvinylpyrrolidone. Lubricants are used to facilitate tablet manufacture; examples of suitable lubricants include, for example, magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, and polyethylene glycol, and are preferably present at no more than approximately 1 wt. % relative to tablet weight. Disintegrants are used to facilitate tablet disintegration or "breakup" after administration, and are generally starches, clays, celluloses, algins, gums or crosslinked polymers. Stabilizers are used to inhibit or retard drug decomposition reactions which include, by way of example, oxidative reactions. Surfactants may be anionic, cationic, amphoteric or nonionic surface active agents, with anionic surfactants preferred. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfonate and sulfate ions, associated with cations such as sodium, potassium and ammonium ions. Particularly preferred surfactants include, but are not limited to: long alkyl chain sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylhexyl)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate. If desired, the tablets may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, preservatives, and the like.

As noted earlier herein, the individual drug tablets, beads or particles are, in one embodiment, contained within a closed capsule. The capsule material may be either hard or soft, and as will be appreciated by those skilled in the art of pharmaceutical science, typically comprises a tasteless, easily administered and water soluble compound such as gelatin, starch or cellulose. A preferred capsule material is gelatin. The capsules are preferably sealed, such as with gelatin bands or the like. See, for example, *Remington: The Science and Practice of Pharmacy,* Nineteenth Edition (Easton, Pa.: Mack Publishing Co., 1995), which describes materials and methods for preparing encapsulated pharmaceuticals designed to dissolve shortly after ingestion.

The novel dosage forms are used to administer methylphenidate in a pulsatile release manner. As noted earlier herein, the drug is administered as a racemic mixture of the d-threo and l-threo enantiomers. For administration of racemic methylphenidate, a dosage form of the invention comprises a total of approximately 2 mg to 100 mg methylphenidate, preferably 2 mg to 50 mg methylphenidate, divided among the individual dosage units. Optimally, the first and second dosage units each contain approximately 2 mg to 20 mg methylphenidate, and preferably, the first and second methylphenidate doses are approximately the same. The third tablet should contain a lower dose of methylphenidate, preferably about half the dose in the first tablet, to avoid sleep disruption. Also, if an additional CNS stimulant such as d-amphetamine is incorporated into the dosage form, it will be included in the first, immediate release dosage unit, will optionally be present in the second dosage unit, (and if present, at a lower dose than in the first dosage unit), and will not be included in the third dosage unit.

It may be desirable to include one or more additional active agents in the dosage forms herein. These active agents may potentiate certain effects of methylphenidate, or vice versa. The additional active agent or agents may be combined with methylphenidate in a single dosage unit within the dosage form, or one or more dosage units within the dosage form may comprise the additional active agent without any methylphenidate. In the former case, the various active agents may be present as an admixture in a tablet, or

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