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Review Article

ADVANCEMENTS AND PATENTS IN PHARMACEUTICAL SUSPENSION TECHNOLOGIES

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Abstract

Suspensions are solid-liquid dispersion and defined as heterogeneous biphasic liquid dosage form of medicaments in which continuous or external phase is usually a liquid or semisolid and the dispersed or internal phase is made up of particulate matter that is essentially insoluble in, but dispersed through, the continuous phase. They require suspending agents to suspend the fine particles of dispersed phase**,** proper wetting agents (surfactants), viscosity increasing agents to improve the stability of preparation and suitable preservatives in preparation. Suspensions are generally taken orally or by parenteral route and also used for external applications. Suspension should have heterogeneous nature and product should be resistant to microbial contamination. Various types of suspension are available in pharmaceuticals like oral, parenteral, ophthalmic and suspension for external uses. Several advancements in suspension technologies viz nanosuspension, taste masked suspension, sustained release suspension, aqueous suspension etc. are discussed in detail. Patents related to these advancements are also mentioned in this article of previous 39 years (from 2012 to 1975). This article emphasise on the general introduction of suspension, their types, recent advancements and patents related to these advancements.

Keywords: Suspension, nanosuspension, taste masked suspension, sustained release suspension, aqueous suspension, patents.

INTRODUCTION

Suspensions are solid-liquid dispersion and defined as heterogeneous biphasic liquid dosage form of medicaments in which continuous or external phase is usually a liquid or semisolid and the dispersed or internal phase is made up of particulate matter that is essentially insoluble in, but dispersed through, the continuous phase. The dispersed phase may consist of discrete particles, ranging from 0.5 to 5.0 micrometer[1]. Suspensions are generally taken orally or by parenteral route and also used for external applications. The particle size of disperse phase is very important in formulation of suspension[2]. Suspensions for topical application should have very small particle size to avoid gritty feel on application and to provide greater coverage and protection to the area to which suspension is applied. In case, the solid substance is meant for skin penetration, its small size gives a quicker rate of dissolution and its penetration. In suspensions meant for introduction in to ophthalmic cavity (eye) particle size should be less than 10 micrometer, beyond this suspension gives feeling of pain and discomfort. Suspensions which are meant for parenteral administration (injectable suspension) should have a particle size that can easily pass thorough the syringe needle[3].

Merits and Demerits of Pharmaceutical Suspensions

If drug not stable in solution form i.e. Procaine Penicillin G and not soluble in water and non-aqueous solvent, e.g. corticosteroids suspension, then drugs administered in the form of suspension. They sustaining the effect of drug e.g. protamine zinc insulin and procaine penicillin G. These have a higher bioavailability compared to other dosage forms (except solution) due to its large surface area, higher dissolution rate[4]. They require suspending agents to suspend the fine particles of dispersed phase, proper wetting agents (surfactants), viscosity increasing agents to improve the stability of preparation and suitable preservatives in preparation.

Characteristics of pharmaceutical suspension

Suspension should be smooth and elegant appearance and physically and chemically stable. Rate of sedimentation of disperse phase should be slow. Sediment must be re dispersed upon gentle shacking of container. Particle size of disperse phase must remain fairly constant throughout shelf period of preparation. Flow of suspension must be uniform so that it is readily and evenly available from container. Parenteral suspension should not loose efficiency during sterilization and these should have aesthetic properties with regard to taste

and odour[5]. It should have acceptable colour and should be easy to apply and not run off and should not dry off too quickly. Suspension ingredients should not hydrolyse or degrade too rapidly or undergo change in polymorphic form. Suspension should have heterogeneous nature and product should be resistant to microbial contamination[6].

Types of Suspension
Based on Pharmaceutical use

Oral suspensions
Oral suspensions generally contain flavouring agent and sweetening agents to mask the bitter taste of the drug. They are also made palatable by using suitable derivatives of the drugs. Nowadays suspensions are available in the market in dry powder form and these are reconstituted by adding a specified quantity of freshly boiled and cooled water before use[2].

Parenteral suspensions
Parenteral suspensions are dispersed heterogeneous systems containing insoluble drug particles which are to be re suspended in either aqueous or vegetable oil vehicles before administering to a patient. They should be sterile, pyrogen free, stable, resuspendable, syringeable, injectable, isotonic and non-irritating[7].

Ophthalmic suspensions
These are prepared only in those cases, when the drug is insoluble in the desired solvent or unstable in liquid form. These suspensions should be sterilised, isotonic, desired viscosity and should be packed in a suitable container, so that it can be prepared for instil into the eye. The particle size of the eye-suspensions should be fine enough for being non irritating to the eye.

Suspension for external use
These suspensions contained very small particles to avoid grittiness. Lotion containing suspended particles evaporates when applied to skin leaving a light deposit of medicament on the surface. Lotions are easier to apply and less messy than other semi solid external preparations[2].

Based on proportion of solid particles
- Dilute suspension have solid content 2 - 10 %.
- Concentrated suspensions have solid content 10 - 50 %.

Based on electrokinetic nature of solid particles
- Flocculated suspension
- Deflocculated suspension

Flocculated suspension
In this system, particles aggregate themselves by chemical bridging. These flocs are light, fluffy conglomerates which are held together by weak vander Walls forces of attraction. Aggregation is achieved by adding flocculating agents. For instance, by the addition of more anions on to a positively charged deflocculated particle flocculation can be achieved. This system possesses better physical stability characteristics but its bioavailability is less when compared to deflocculated system because the dissolution of flocs is a prerequisite for drug absorption. In flocculated suspension, formed flocs (loose aggregates) will cause increase in sedimentation rate due to increase in size of sedimenting particles; thus the flocculated suspensions sediment more rapidly. Sedimentation depends not only on the size of the flocs but also on the porosity of flocs. In flocculated suspension the loose structure of the rapidly sedimenting flocs tends to preserve in the sediment, which contains an appreciable amount of entrapped liquid. The volume of final sediment is thus relatively large and is easily re dispersed by agitation.

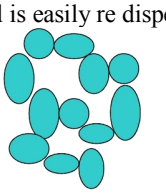


Figure 1: Flocs formation in pharmaceutical flocculated Suspension

Deflocculated Suspension
In deflocculated suspension, individual particles are settling, so rate of sedimentation is slow which prevents entrapping of liquid medium which makes it difficult to redisperse by agitation. This phenomenon also called 'cracking' or 'claying'. In deflocculated suspension larger particles settle fast and smaller remain in supernatant liquid so supernatant appears cloudy whereby in flocculated suspension, even the smallest particles are involved in flocs, so the supernatant does not appear cloudy. These systems have a shorter shelf life, but have greater bioavailability when compared to flocculated systems.

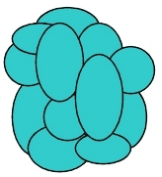


Figure 2: Cake formation in pharmaceutical deflocculated suspension

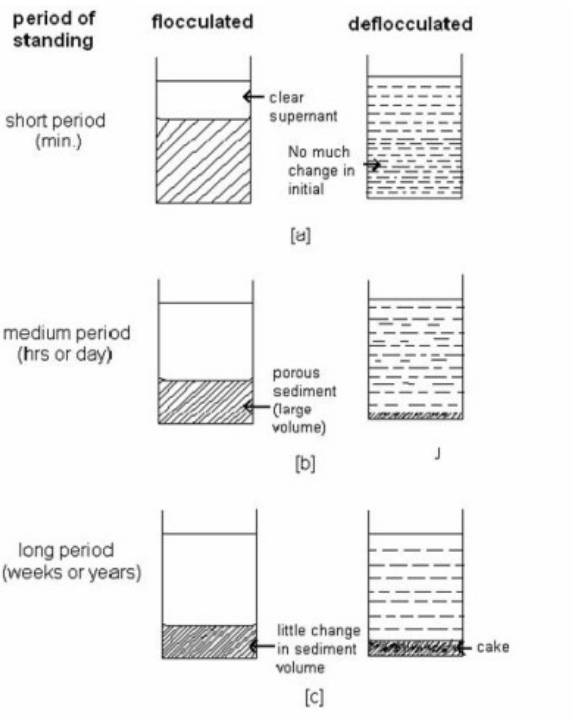


Figure 3: Sedimentation behaviour of flocculated and deflocculated suspensions

Based on size of solid particles

- Colloidal suspensions have particle size less than1 micrometer.
- Coarse suspensions have particle size greater 1 micrometer.
- Nanosuspensions have particle size 10 mg[8].

Formulation of Suspension

Following additives are used in preparation of suspensions:

- Flocculating agents
- Suspending agents
- Wetting agents
- Dispersants
- Preservatives
- Organoleptic additives
- Thickening agents[3].

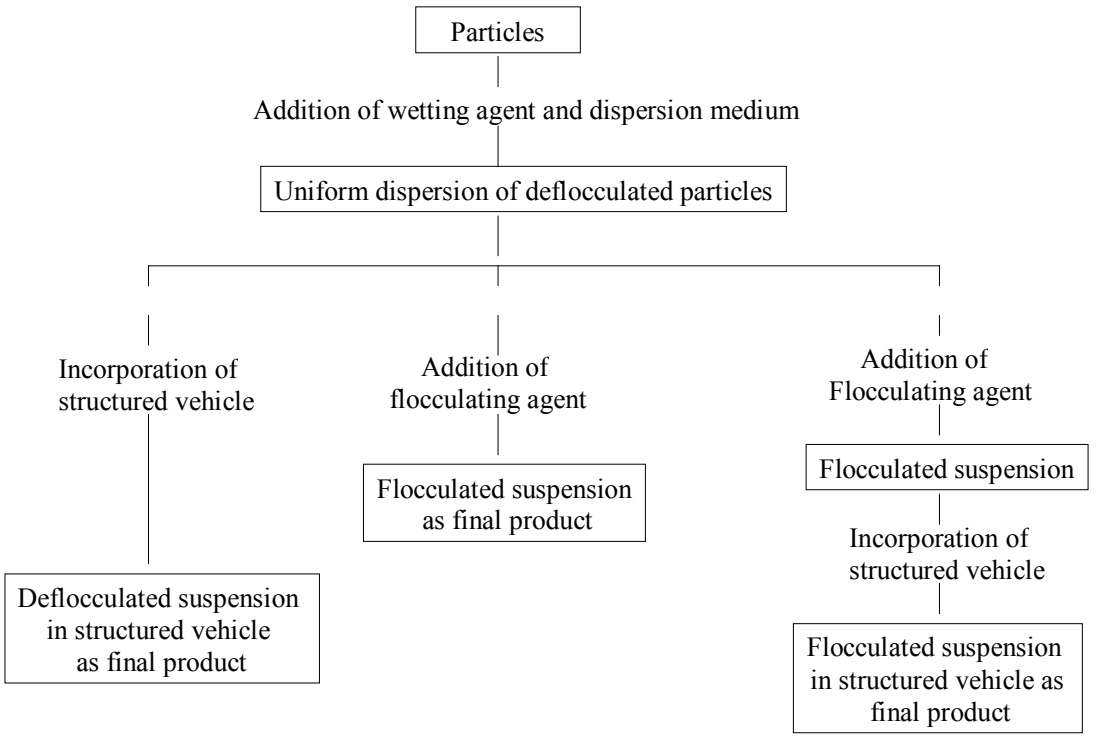


Figure 4: The approaches used in the formulation of suspensions[8].

Recent Advancements of Suspension and their Patents

- Nano Suspension
- Taste Masked Suspension
- Sustained Release Suspension
- Aqueous suspension

Nano Suspension

Nano, 10^{-9} or one billionth, is a Greek word means 'dwarf'[9]. Nanosuspensions are biphasic system consisting of pure drug particles dispersed in an aqueous vehicle. These are colloidal dispersions of nanosized drug particles stabilized by surfactants. Reduction of drug particles to nanometer range leads to an enhanced dissolution rate not only because of increased surface area but also because of saturation solubility. The increase in the saturation solubility and solution velocity of nanoparticle is due to increase of vapour pressure of the particles. 'Bottom up technology' and 'Top down technology' are two methods for preparation of nanosuspension[10]. Nanosuspensions differ from nanoparticles, not difference concerning diameter. There are differences concerning the method of preparation, nature of material, etc. Nanoparticles are polymeric colloidal carriers of drugs (Nanospheres and Nanocapsules), and solid-lipid nanoparticles (SLN) are lipidic carriers of drug. Conventionally the drugs that are insoluble in water but soluble in oil phase system are formulated in liposome, emulsion systems but these lipidic formulation (liposome and emulsion) approaches are not applicable to all drugs due to formulation and stability problems. In these cases nanosuspensions are preferred. In case of drugs that are insoluble in both water and in organic media instead of using lipidic systems, nanosuspensions are used as a formulation approach. This formulation approach is most suitable for the compounds with high log P value, high melting point and high dose[9]. Nano-suspension of potent insoluble active pharmaceutical ingredient will become improved drug delivery formulations when delivered to at sizes less than 50 nm. When delivered I.V. at sizes less than 50 nm. the suspension particles avoids the normal reticulo-endothelial system filtration mechanisms and circulates for long periods. The suspension particles may be insoluble active pharmaceutical ingredient (API) particles or Nano-particle polymeric carriers of soluble or insoluble drugs and may be useful in delivering genetic therapeutic materials targeted to the cells. For oral delivery, nanometre size particles may allow delivery of API through the intestinal wall into the

blood stream, at desired rates and with minimal degradation in the GI tract. Insoluble particles at these sizes may be designed to be transportable across this barrier. Another strategy involves encapsulation of active drugs in Nano-particulate degradable polymer structures[8]. Nanosuspensions offer enhancement in the solubility and bioavailability of drugs, suitability for hydrophilic drugs, higher drug loading, dose reduction and increase in the physical and chemical stability of drugs[11].

Patents Related to Nano Suspensions

Homar M, *et al* 2011 described an aqueous nanosuspension formulation comprising a drug possessing low intrinsic water solubility, e.g. amiodarone. It also provides a method for the preparation of intravenous formulation comprising amiodarone, with markedly decreased adverse effects[12]. Chen M J, *et al* 2011 described the compositions and methods for preparation and administration of an oral nanosuspension of a poorly soluble drug with improved bioavailability. The method is optimized through microfludization processwith water soluble polymeric excipients in the absence of surfactants[13]. Rundfeldt C, *et al* 2010 described the new nanosuspensions of antifungal azole derivatives, particularly itraconazole, with improved impurity profile optimized for inhaled administration for the prevention, reversal and medical treatment of fungal infections of the respiratory tract including adjacent lymph nodes. The new formulation which is devoid of particulate inorganic contamination can be safely administered by inhalation. This administration route results in an improved therapeutic effect and reduced side effect profile as compared to the previously used clinical administration route, i.e. oral or parenteral (intravenous) administration[14]. Rainer M, *et al* 1997 described systems with strongly increased saturation solubility (Cs) which is obtained by preparing nanosuspensions of medicaments. The saturation solubility of medicaments with low bioavailability may thus be increased. This additional increase of the saturation solubility increase the speed of dissolution beyond what can be achieved by simply enlarging the surface of the medicament. Extremely stable nanosuspensions are obtained by using very low surfactant and stabiliser concentrations. Surfactant-free nanosuspensions may be prepared. Large scale production of nanosuspensions with a very low content of micrometric particles is made possible by cavitation, with its accompanying advantages. The preparation of nanosuspensions by cavitation was thought to be impossible because the powdered medicament particles were expecting the above principles of optimum stabilisation or surfactant-free preparation[15]. Georg W H, *et al* 1996 using the pharmaceutical composition for intravenous administration of staurosporin derivative (A) with low solubility in water comprises (A); a polyoxyethylene - polyoxypropylene block copolymer (B); ethanol and water as transport materials; and obtained a phospholipid of formula (I) or its salts, and/or other adjuvants[16].

Table 2: Patents Related to Nanosuspension

Patent number	Title of patent	Drug / Polymers used	Reference
WO 2011080148 A2	An aqueous intravenous nanosuspension with reduced adverse effects	Amiodarone	Homar M, *et al* 2011
US 2011/0124702 A1	Nanosuspension of a poorly soluble drug via micro fluidization process	Water soluble polymeric excipients	Chen M J, *et al* 2011
EP 2254562 A1	Nanosuspension with antifungal medication to be administered via inhalation with improved impurity profile and safety	Itraconazole	Rundfeldt C, *et al* 2010
EP0790821	Process for the preparation of pharmaceutical nanosuspension	-	Rainer M, *et al* 1997
EP0733358	Nanosuspension for intravenous application	Polyoxyethylene-polyoxypropylene block copolymer	Georg W H, *et al* 1996

Taste Masked Suspension

Taste is an important parameter in administering drugs orally. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs orally with acceptable level of palatability is a key issue for health care providers. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals. Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter-tasting components. Various chemical and physical methods are involved for achieving taste masking that prevents the drug substance from interaction with taste buds[17]. Taste masking is defined as a perceived reduction of undesirable taste that would otherwise exist. Taste masking of liquid formulation present a major challenge because the majority of paediatric preparations are syrups and suspensions[18].

Taste Masking Technologies

Various methods are available to physically mask the undesirable taste of drugs, such as: taste masking with flavours, sweeteners, and amino acids, by polymer coating of drug, by the formation of inclusion complexes, by ion exchange resin complexes, solid dispersion, microencapsulation, mass extrusion, multiple emulsions, by the development of Liposome, prodrug concept, by using spray drying technique, by adsorption, etc[17].

Table 3 - Some examples of taste masked suspension

Name of the drug	Taste masking approach
Risperidone	pH control and polymer coating (with Eudragit RS). The coating drug is suspended in water based liquid constituted at an optimum pH.
Roxithromycin-I and Roxithromycin-II	Polymer coating with Eudragit RS 100
Diclofenac	Polymer coating with Eudragit RS 100
Levofloxacin	Polymer coating (Eudragit 100 : cellulose acetate, 60:40 or 70:30)

(http://www.pharmainfo.net/free-books/pharmaceutical-suspensionsa-review)

Patents Related to Taste Masked Suspension

Badhe G U, *et al* 2012 described a dry taste masked powder composition comprising a steroid or its salts or derivatives and pharmaceutically acceptable excipients. The taste-masked powder may be used for suspension compositions suitable for use as a liquid suspension for children and elderly patients[19]. Chen S, *et al* 2012 described a preparation method of taste-masked suspension granules of Gegenqinlian decoction. The preparation method comprises the following steps: 1) taking appropriate amounts of dispensing granules of three traditional Chinese medicines comprising radix puerariae, coptis chinensis and scutellaria baicalensis and respectively carrying out coating processes in a fluidized bed through adopting one or more polymers as coating materials to obtain coated granules for next use, 2) taking an appropriate amount of at least one suspending agent, mixing uniformly the at least one suspending agent and radix glycyrrhizae preparation dispensing granules, then adding an appropriate amount of an adhesive into the mixture to prepare into granules by a wet method, drying the prepared granules in an oven, and then spraying an appropriate amount of an ethanol solution as an aromatic to obtain suspending agent-containing radix glycyrrhizae preparation dispensing granules after ethanol is volatilized, and 3) weighing appropriate amounts of the suspending agent-containing radix glycyrrhizae preparation dispensing granules and the coated granules containing radix puerariae, coptis chinensis and scutellaria baicalensis, mixing well, and carrying out sub-packaging to obtain the taste-masked suspension granules of Gegenqinlian decoction, wherein the one or more polymers as coating materials are selected from enteric-coated polyacrylic resin, hypromellose acetate succinate and hydroxypropyl methylcellulose phthalate. The invention provides the preparation method of the taste-masked suspension granules of Gegenqinlian decoction[20]. Kassotakis 2010 described a pharmaceutically acceptable composition in the form of suspension for oral delivery of dexamethasone acetate in which the active ingredient is homogenously dispersed in a pharmaceutically acceptable aqueous carrier-vehicle. The present invention relates to a method for taste masking the bad taste of dexamethasone, provide a pharmaceutical composition comprising a specific ester of dexamethasone (dexamethasone acetate), in a therapeutically effective amount in an aqueous, compatible, stable media vehicle and a suspending agent. The inventive formulation comprising dexamethasone acetate dispersed in an aqueous, compatible, between about 0.4 mg/ml to about 40 mg/ml, more preferably between 0.4 mg/ml to about 10 mg/ml, more preferably 4 mg/ml. The aqueous vehicle may further consist of glycerine and propylene glycol. The inventive composition comprises more than one pharmaceutical excipient[21]. Yu HZ 2007 describes a taste-masking typed children-influenza dry mixing suspension and making method, which is characterized by the following: adopting acetamidophenol, ephedrine hydrochloride, hydrobromic acid dextromethorphan and auxiliary drug material as raw material; cladding drug through glyceride compound to mask taste[22]. Davies J, *et al* 2005 described a taste-masked resinate that contains a water-insoluble active substance complexed to an ion exchange resin in a taste-masking effective amount. The taste-masked resinate resin is useful in the manufacture of a dosage form such as a rapid disintegrating film, an effervescent tablet, a chewable tablet, a chewing gum, a suspension like preparation thereof[23]. Ulrich S A, *et al* 2004 described a taste masked liquid pharmaceutical composition comprising a pharmaceutically active agent and a taste masking composition. In particular the taste masking composition comprises a taste masking effective amount of an artificial sweetener[24]. Ulrich S, *et al* 2002 described a taste masked pharmaceutical composition comprising a microcapsule, wherein the microcapsule comprises a pharmaceutically active agent core coated with a taste masking effective amount of a water in-soluble enteric coating, wherein the coating comprises a weakly acidic methacrylic acid-ethyl acrylate copolymer[25]. Morella A M, *et al* 2001 described a taste-masked pharmaceutical composition. In particular the invention relates to suspensions of microcapsules taste-masked as a function of a polymer coating and the pH of a suspending medium. Surprisingly, a polymer considered permeable maintains taste masking in this media whereas a polymer considered impervious by the industry does not. There is provided a taste masked oral pharmaceutical composition including: a pharmaceutically active ingredient having a pH-dependent solubility; a polymer encapsulating said pharmaceutically active ingredient, said polymer having a quaternary ammonium functionality; a suspending medium for suspending the encapsulated pharmaceutically active ingredient, said medium adjusted to a predetermined pH at which the pharmaceutically active ingredient remains substantially insoluble; and wherein the pharmaceutically active ingredient is taste masked by the combination of the polymer and suspending medium[26]. Tustian A, *et al* 1995 described Acetaminophen composition in which the taste of the acetaminophen is effectively masked by suspending the drug in a suspension medium containing suspension agent and additive agents that decrease the solubility of the acetaminophen in aqueous solution. The additive agents preferably include sweetening agents. The concentration of the sweetening agent is preferably at least about 25 weight percent of the acetaminophen composition[27].

Table 4: Patents Related To Taste Masked Suspension

Patent number	Title of patent	Drug / Polymers used	Reference
WO2011101724 A3	Taste-masked powder for suspension compositions of methylprednisolone	Methyl-prednisolone	Badhe G U, *et al* 2012
CN 102309562 (A)	Preparation method of taste masked suspension granules of gegenqinlian decoction	Hypromellose acetate succinate and Hydroxypropyl methyl cellulose phthalate	Chen S, *et al* 2012
WO2010119300	Oral suspension of dexamethasone acetate -taste masking composition of dexamethasone	Dexamethasone acetate, propylene glycol	Kassotakis, 2010
CN1969850 (A)	Taste masked suspension prescription for treating infant cold and method for preparing same	Acetamidophenol	Yu H Z, 2007
US20050036977 A1	Taste-masked resinate and preparation thereof	-	Davis J, *et al* 2005
US6806256 B2	Taste masked liquid pharmaceutical compositions	-	Ulrich S A, *et al* 2004
US 2002/0197327 A1	Taste masking pharmaceutical compositions	Weakly acidic methacrylic acid-ethyl acrylate copolymer	Ulrich S A, *et al* 2002
US 6197348 B1	Taste masked liquid suspensions	-	Morella A M, *et al* 2001
WO 1995000133 A1	Taste-masked acetaminophen suspensions and methods	Acetaminophen	Tustain A, *et al* 1995

Sustained Release Suspension

Sustained release is a method to increase only the duration of action of drug being formulated without affecting onset of action. In suspension sustained release affected by coating the drug to be formulated as suspension by insoluble polymer coating. The polymer coating provides sustained release and also masks the taste of the bitter drug. The polymer used for sustained release in suspension is enlisted as follows as Ethyl cellulose, Eudragit, Cellulose acetate, etc. The main advantage of sustained release suspension is decrease in dosing frequency[8].

Patents Related to Sustained Release Suspension

Cheng Q, *et al* 2012 described a montmorillonite combined propranolol sustained-release dry suspension, a preparation method thereof and a preparation method of Sodium montmorillonite used in the propranolol sustained-release dry suspension. The propranolol sustained-release dry suspension comprises montmorillonite-propranolol compound, an outer coating sustained-release material, a flavouring agent and a suspending aid. The preparation method comprises the following steps: firstly, preparing the montmorillonite-propranolol compound; secondly, coating partial montmorillonite-propranolol compound; and finally, mixing the montmorillonite-propranolol compound, the montmorillonite-propranolol compound coating, the flavouring agent and the suspending aid. The propranolol sustained-release dry suspension provided by the invention has good compliance to a patient who has oral administration difficulty, utilizes particle exchange carrier namely montmorillonite, and can stay in a human body for longer time[28]. Juan A U, *et al* 2012 described a parenteral pharmaceutical formulation or composition, in suspension, having sustained release, containing suspended particles of estradiol and progesterone for hormonal replacement in female mammals in low and ultralow dosage; the formulation consists of an 10 injectable suspension comprising particles of estradiol, particles of progesterone, a surfactant agent, an isosmotic agent, a thickening agent, and one or more preservation agents, wherein the estradiol is in particles having a size between 1 and 100 micrometers and the progesterone is in particles having a size between 1 and 100 micrometers, for application thereof in parenteral, intramuscular, subcutaneous or intradermal pharmaceutical form[29]. Ge H, *et al* 2011 using a gliclazide oral sustained-release dry-mixed suspension, which comprises the following components in percentage by weight: 30 percent of gliclazide, 40 to 45 percent of suspending aid, 15 to 20 percent of filler, 5 to 10 percent of bonding agent, 2 to 5 percent of flow aid, 0.1 to 1.0 percent of flavouring agent and 0.1 to 1.0 percent of colouring agent. The invention also discloses a preparation method for the gliclazide oral controlled-release dry-mixed suspension. The gliclazide oral sustained-release dry-mixed suspension can maintain plasma concentration required by treatment for a long time and keep the plasma concentration stable, and reduces the peak-valley change of the plasma concentration and the incidence and severity of toxic and side effect simultaneously so as to give full play to the treatment effect of gliclazide. The method has simplicity of operation and high repeatability, and contributes to the realization of mass production[30]. Mohan G, *et al* 2011 described a stable, sustained release oral liquid suspension dosage form of pharmaceutical active ingredients, which is easy to administer and particularly beneficial for the paediatric and geriatric patients. The suspension dosage form comprises sustained release pellets comprising inert pellets, surrounded by seal coating, drug layer comprising pharmaceutically active ingredient with one or more pharmaceutically acceptable excipients surrounding said seal coated inert pellets, and coating layer comprising rate controlling polymer surrounding said drug layer, such that the sustained release pellets are suspended with suitable suspending agent, in addition to other pharmaceutically acceptable excipients in a suspending media at a suitable pH. A process for preparation of the suspension dosage form is also provided[31]. Zhang *et al* 2008 described pharmaceutical compositions for long-term sustained release of bisphosphonate drugs. In one embodiment, the composition includes an aqueous suspension of a solid which includes a salt of a bisphosphonate drug and a salt of pentavalent phosphorus oxoacid. The compositions can be used to treat a variety of bone diseases, including osteoporosis[32]. Eichel H J, *et al* 1992 described a sustained release pH independent pharmaceutical preparation having multi units of microparticles comprising granular drug which is less soluble at low pH and more soluble at high pH. The granular drug is surrounded by or admixed with a pH controlled material formed from at least one polymer that is hydrophilic at low pH and hydrophobic at higher pH and is in a ratio with the granular drug such that the resulting sustained release pharmaceutical preparation is independent from the pH environment. The resulting sustained release pH independent

pharmaceutical preparation allows a uniform release of drug for a period of at least 12 to 24 hours. In an alternative embodiment, the drug may be more soluble at low pH and less soluble at higher pH and the pH controlled material formed from at least one polymer that is hydrophobic at low pH and hydrophilic at higher pH[33]. Grim W M, *et al* 1991 described a method for the preparation of the sustained release pharmaceutical composition comprising forming a fluidized ring of said particles and contacting said particles maintained suspended in said ring with a liquid composition containing a pharmaceutically active material and an alkali soluble material[34]. Koyama I, *et al* 1989 described a method of preparing a sustained release pharmaceutical preparation, which comprises a solution of binder in water or alcohol and a fine powder of a hydrophobic solid material which does not easily dissolve within the stomach and intestines to the surface of solid particles containing a drug while the solid particles are being tumbled, thereby to coat the solid particles with the binder and the hydrophobic solid material[35]. Ikura H, *et al* 1988 described an oral sustained release pharmaceutical preparation which is prepared as a pharmaceutical preparation comprising lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt, and active drugs or a pharmaceutical preparation comprising lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt and active drug together with a forming agent, so that it may release the active drugs by such slow degrees in the stomach or the intestinal tract as to make it possible to provide an adequate supply of active drugs in enough concentration to display their therapeutic value for many hours[36].

Table 5: Patents Related to Sustained Release Suspension

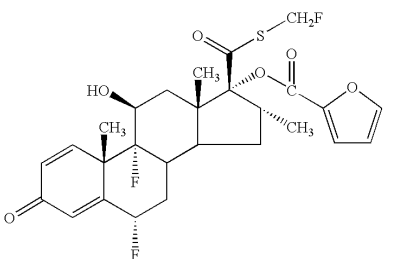
Patent number	Title of patent	Drugs / polymers used	Reference
CN102406616 (A)	Montmorillonite combined propranolol sustained release by suspension, preparation method thereof and preparation method of Na-montmorillonite used in propranolol sustained release dry suspension	Propranolol	Cheng Q, 2012
EP 2 520 301 A2	Parenteral pharmaceutical formulation in suspension, having sustained release, in low and ultralow dosage, in hormonal therapy in the climateric syndrome	Estradiol	Juan A. U. *et al*, 2012
CN102028660 (A)	Gliclazide oral sustained release dry mixed suspension and preparation method thereof	Gliclazide	Ge H. *et al*, 2011
WO2011107855 (A2)	Sustained release oral liquid suspension dosage form	-	Mohan G. *et al*, 2011
WO2008085281 (A1)	Long term sustained release pharmaceutical composition containing aqueous suspension of bisphosphonate	Bisphosphonate	Zheng *et al*, 2008
US 5,102,668	Sustained release pharmaceutical preparation using diffusion barriers whose permeabilities change in response to changing pH	-	Eichel H. J. *et al*, 1992
US 5,026,709	Method for the preparation of a theophylline sustained release pharmaceutical composition and the composition prepared thereby	Theophylline and derivatives	Harwood R. J. *et al*, 1991
US 4,853,249	Method of preparing sustained release pharmaceutical preparation	Hydroxypropylmethylcellulose and polyvinylpyrolidone	Koyama I. *et al*, 1989
US 4,777,033	Oral sustained release pharmaceutical preparation	Alkyl ether of cellulose and Polyacrylic acid	Ikura H. *et al*, 1988

Aqueous Suspension

Aqueous suspension is defined as a particle suspension whose suspending phase is composed of water[37].

Patents Related to Aqueous Suspension

Biggadike K, *et al* 2005 described a pharmaceutical formulation comprising an aqueous suspension of particulate compound of formula or a solvate thereof[38].



Yasueda S, *et al* 2002 described an aqueous suspension can be prepared by incorporating, in an aqueous suspension of a hardly soluble drug, a water soluble polymer within the concentration range from the concentration at which the surface tension of the aqueous suspension of the drug begins to decrease up to the concentration at which the reduction in surface tension ceases. The resulting aqueous suspension shows ready redispersibility and will not undergo aggregation of dispersed particles or caking. Because of its good redispersibility, the suspension is useful as a parenteral suspension, eye drops, nasal drops, a preparation for oral administration, a lotion or the like[39].

Tiongson A 2002 describes a high dosage calcium carbonate aqueous antacid pharmaceutical suspension for oral use, and methods of preparation[40].

Kim S 1999 provide an aqueous pharmaceutical composition which is capable of being sprayed into the nasal cavity of an individual and which comprises: (A) a pharmaceutically effective amount of solid particles of medicament which is effective in treating a bodily condition by virtue of its being present on the mucosal surfaces of the nasal cavity; and (B) a suspending agent in an amount effective to maintain said particles dispersed uniformly in the composition and to impart to the composition the following thixotropic properties: (i) the viscosity of the position in un sheared form is relatively high, with the composition being in gel-like form; (ii) as the composition is subjected to shear (shaken) in preparation for spraying, the viscosity of the composition becomes relatively low and such that the composition in the form of a mist flows readily into the nasal passages for the deposit on the mucosal surface of nasal cavity; and (iii) in deposited form of mucosal surfaces, the viscosity of composition is relatively high and such that it resist being cleared from the mucosal surfaces by the inherent

mucocilliary forces which are present in the nasal cavity, a method of use of the composition and a method for preparation of the composition, including in preferred form the use of anti-inflammatory steroid, for example, triamcinolone acetonide, and an odourless form of the composition[41].

Ratnaraj S M, *et al* 1997 described an aqueous pharmaceutical suspension composition containing suspended acetaminophen and at least one additional pharmaceutical active, a suspension system containing xanthan gum, a mixture of microcrystalline cellulose and sodium carboxymethylcellulose and an auxillary suspending agent selected from the group consisting of hydroxyethylcellulose and a pharmaceutically acceptable salt of carboxymethylcellulose an effective amount of a taste-masking composition; and water, as well as a process for producing such aqueous pharmaceutical suspensions[42].

Gowan W J, 1997 describe an aqueous pharmaceutical suspension composition comprising: from about 0.2 % to 20 % of a substantially water insoluble pharmaceutical active, e.g. ibuprofen; a suspension stabilizing effective amount of xanthan gum, pre gelatinized starch and polyoxyethylene sorbitan monooleate; an effective amount of taste masking composition; and water, as well as a process for producing such aqueous pharmaceutical suspensions[43].

Ratnaraj S M, *et al* 1996 describes an aqueous pharmaceutical suspension and methods of making same. The suspension comprises a therapeutic amount of controlled release acetaminophen powder, the powder being suspended in a suspending system comprising a suspension stabilizing effective amount of xanthan gum, hydroxyethyl cellulose and pregelatinized starch, an effective amount of taste masking composition, and water[44].

Blase C M, *et al* 1993 describe an aqueous pharmaceutical suspension composition comprising from about to 0.2 % to 20 % of a substantially water soluble pharmaceutical active; e.g. Acetomenophen[45].

Burdick C L, 1989 describe an aqueous suspension comprising at least 8 %, by the weight of total suspension, of water soluble carboxymethyl cellulose dispersed in an aqueous solution comprising at least 33 %, by weight of the total salt and water, of potassium carbonate, a process for preparing the same, and use of the same in a variety of applications, are disclosed[46].

Ohno Y, *et al* 1975 described an aqueous suspension consisting basically of pharmaceutically active ingredient(s) which is insoluble or sparingly soluble in water and a suspending agent consisting of 1) crystalline cellulose, 2) at least one component selected from the group consisting of cellulose ether, polyvinyl alcohol and copolymer of polyvinyl alcohol with polyvinyl pyrolidine, and 3) at least one component selected from the group consisting of polyvinyl pyrolidine, vegetable mucilage and derivative protein, in which said active ingredient(s) can satisfactorily be suspended for administration[47].

Table 6: Patents Related to Aqueous Suspension

Patent number	Title of patent	Drug / Polymers used	Reference
US20050164996 A1	Pharmaceutical formulation comprising an aqueous suspension of an androstane derivative for the treatment of inflammatory and allergic conditions	androstane derivative	Biggadike K, *et al* 2005
US6,448,296 B2	Aqueous suspension with good redispersibility	Water soluble polymer	Yasueda S, *et al* 2002
US6,368,638 B1	Process of making an aqueous calcium carbonate suspension	calcium carbonate	Tiongson A, 2002
US5,976,573	Aqueous based pharmaceutical compositions	Triamcinolone acetonide	Kim S, 1999
US5,658,919	Aqueous pharmaceutical suspension and process for preparation thereof	Acetomenophen, Xanthan gum	Ratnaraj S M, *et al* 1997
US5,374,659	Aqueous pharmaceutical suspension for substantially water insoluble pharmaceutical actives	Ibuprofen, Xanthan gum	Gowan W J, 1997
EP 0717992 A2	Aqueous suspension formulations for pharmaceutical applications	Acetaminophen, Xanthan gum	Ratnaraj S M, *et al* 1996
US,5,272,137	Aqueous pharmaceutical suspension for pharmaceutical actives	Acetomenophen, Xanthan gum	Blase C M, *et al* 1993
US4,883,537	Aqueous suspension of Carboxymethylcellulose	Carboxymethyl cellulose	Burdick C L, 1989
US3,927,205	Aqueous suspensions of pharmaceuticals	Polyvinylpropyline	Ohno Y, *et al* 1975

CONCLUSION

Suspensions are solid-liquid dispersion and generally taken orally or by parenteral route and also used for external applications. Several advancements in suspension technologies viz nanosuspension, taste masked suspension, sustained release suspension, aqueous suspension etc. are available today. The suspension technology, thus emphasized, has vast applications in pharmaceutical industry.

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